

Preface

Angiogenesis is an important natural process of new blood vessel growth that occurs in the body, both in health and in disease. It is essential for embryonic development, reproduction, and repair or regeneration of tissue during wound healing. Shifts in the finely balanced equilibrium between angiogenic stimulators and inhibitors that regulate angiogenesis are linked to a broad range of angiogenesis-dependent diseases, including both cancer and non-neoplastic diseases such as atherosclerosis, age-related macular degeneration, and rheumatoid arthritis. Angiogenesis is now recognized as one of the critical events required for tumor progression, where cancerous growth is dependent on vascular induction and the development of a neovascular supply.

The idea of targeting angiogenesis to inhibit tumor growth was proposed more than three decades ago, and since then several approaches to block or disrupt tumor angiogenesis have been explored. Regulation of vascular growth involves complex interactions of the cellular signaling network that govern the angiogenic process communicating with the extracellular matrix proteins. Each step in the angiogenic regulatory pathway represents a potential target for therapeutic development. Perhaps the best validated antiangiogenic approach involves blockade of the vascular endothelial growth factor (VEGF) and its signaling pathway. Indeed, inhibitors that block the VEGF pathway have shown extensive pruning of the rapidly growing tumor vasculature, decreasing microvessel density and normalizing the remaining blood vessels, thereby improving the delivery of chemotherapy and radiation treatments. As such, antiangiogenesis has become an important component of cancer treatment and recognized as a fourth modality of anticancer therapy. However, despite the positive results seen with VEGF inhibitors, clinical resistance remains an issue as these compounds block only one proangiogenic protein (e.g., VEGF) whereas many human tumors produce multiple proangiogenic proteins, which allows the tumor to evade angiogenic blockade. Therefore, additional targets and pathways are exploited to broaden the antiangiogenic spectrum. More recently, the discovery of novel molecular signaling pathways involved in regulating angiogenesis during development

has further expanded the therapeutic potential of this complex angiogenic network. A thorough understanding of the finely balanced interplay of various signalling pathways will help define a molecular signature of angiogenesis that can then be used to develop into potential targets or therapeutic strategies for angiogenesis-dependent diseases.

The original hypothesis postulating that inhibition of angiogenesis by means of holding tumors in a nonvascularized dormant state has proven to be an effective strategy in cancer treatment, and has laid the groundwork for the concept behind the development of “antiangiogenic” drugs. This has resulted in the US Food and Drug Administration’s approval of bevacizumab, the first antiangiogenic drug, along with the approval of several other angiogenesis inhibitors in recent years, and in the generation of a variety of antiangiogenic therapies that are currently in the drug development pipeline. The field of angiogenesis has grown exponentially, with some of the most impressive advances occurring in the last decade. Over the past 25 years, the number of MEDLINE publications dealing with angiogenesis has risen in a nonlinear fashion with more than 4300 publications in the year 2006 (that included “angiogenesis” as a key word).

This book was undertaken to compile and discuss the biological processes and molecular mechanisms involved in angiogenesis, and to discuss those agents that have shown clinical promise to inhibit (or stimulate) angiogenesis across various disciplines. It is divided into six sections, preceded by an introduction that outlines the history of angiogenesis and a concluding remark that addresses the future direction of this field. Part I describes the biology of the angiogenic process and of endothelial growth in physiological and pathological conditions, as well as the major components of the vascular architecture and the surrounding extracellular matrix. Part II introduces the key regulatory proteins involved in the angiogenic switch, including both proangiogenic and antiangiogenic molecules. Part III continues by discussing the molecular and cellular mechanisms of the angiogenic process, with a focus on the regulation of angiogenesis during tumor growth and factors that contribute to this process in the tumor microenvironment.

After looking at the overall angiogenic landscape, the next section of the book, Part IV, evaluates the functional assessments of angiogenesis, including the normalization process of the vasculature, targeted drug delivery, angiogenic models, imaging of angiogenesis, and surrogate markers for monitoring this process. In Part V, the clinical translation of angiogenesis inhibitors is presented. An overview is provided on the clinical applications of VEGF and protein tyrosine kinase inhibitors as antiangiogenic agents, followed by examples of key agents in clinical development and a discussion of the recent advances in the angiogenesis drug development scene. The combination approach of antiangiogenic therapy with other anti-cancer treatments, or immunotherapy, is also discussed, including the challenges involved with this new therapeutic strategy. As personalized medicine gains precedence, understanding the pharmacogenetics of antiangiogenic therapy becomes essential as a means for clinicians to better guide therapy. Finally, the last section of the book, Part VI, looks at angiogenesis in health and disease, highlighting the importance of this process in angiogenesis-dependent disease states. As such, this book is a comprehensive, concise summary of angiogenesis and is broad enough to elicit interest from readers in a number of settings and across various fields. The chapters describe state-of-the-art information that will be appropriate for a wide audience, including graduate students, physicians in

training, physicians, scientists, and members of the pharmaceutical industry.

Advances in understanding the biological basis of these angiogenesis-dependent diseases is critical, with these advances playing to the scientists' greatest strengths as they try to translate the biology into new therapies. As the search for angiogenic factors, regulators of angiogenesis, and antiangiogenic/proangiogenic molecules continue over the next decades, novel discoveries that provide insight into the angiogenic process will shed light on angiogenesis as an important therapeutic target for the treatment of cancer and other diseases. By viewing angiogenesis as an organizing principle, we have attempted to interconnect various health disciplines and disease states into one comprehensive volume unifying the field of angiogenesis research.

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