PREFACE

The field of angiogenesis continues to rapidly evolve in many different directions. Initial discoveries of a few angiogenic growth factors, such as vascular endothelial growth factors (VEGF), fibroblast growth factors (FGF) and angiopoietins, gave an impression of a relatively uncomplicated system with a few straightforward regulatory mechanisms revolving around hypoxia and inflammation. However, failures of therapeutic approaches based on brute force stimulation or inhibition of vessel growth combined with discoveries in fields as diverse as developmental biology, signal transduction and neurosciences began painting a much more nuanced and complex system. The existence of a great number of checks and balances involved in growth and maintenance of the vasculature, a great diversity of angiogenic growth factors and inhibitors, and in particular the concepts of vascular guidance and participation of numerous proteins capable of modifying growth factor activities were some of the more prominent discoveries of the last decade.

It would be utterly impossible to summarize all these developments in one volume. Therefore, we have chosen to focus on a few select developments in the field of therapeutic angiogenesis that have significantly altered our understanding of vascular biology and pathology.

The first part of the book deals with key components of the angiogenic cascade. Semaphorins, plexins and neuropilins have emerged as important regulators of vascular growth by both providing guidance clues and transmitting signaling to the endothelium. The diversity of these families, their structure and interactions, as well as our current understanding of their roles are discussed in Chapter 1 by G. Neufeld and colleagues. Ephrins and their Eph receptors play an important

and still poorly understood bidirectional signaling function in various cell-cell interactions that regulates processes as diverse as vascular sprouting, blood and lymphatic vessel morphogenesis and remodeling as well as arterial-venous fate decisions. These and other roles played by numerous members of this family are addressed in Chapter 2 by E. Pasquale.

FGF were the first angiogenic growth factors isolated, yet their function in the vasculature still remains mysterious and poorly appreciated. New insights into FGF biology are presented in Chapter 3 by P. Auguste and A. Bikfalvi. The discovery of various ways in which the nervous system participates in regulation of angiogenesis has been one of the most intriguing recent developments in vascular biology. In Chapter 4, J. Kitlinska and Z. Zukowska address the role of neuropeptide Y (NPY) in regulation of blood vessel growth. The extracellular matrix (ECM) plays a critical role in modulating signaling of various growth factors. One relatively little studied component of the ECM is the heparan sulfate matrix that affects signaling of various heparin-binding growth factors. Recent advances in this field are addressed in Chapter 5 by N. Shworak.

The second part of the book deals with various processes that affect the angiogenic cascade. The concept of arterial guidance is addressed in Chapter 6 by A. Horowitz. The chapter addresses various guidance systems starting with semaphorins, neuropilins and plexins, and progressing to ephrins/Eph receptors, and then to netrins. New development in our understanding of the role of HIF signaling are discussed in Chapter 7 by G. Semenza.

The reactive oxygen species have long been studied in terms of their contribution to vascular wall injury. But new discoveries in this field demonstrate an important role of ROS in regulation of various aspects of endothelial signaling. These and other new ideas about ROS function are examined in Chapter 8 by M. Ushio-Fukai and W. Alexander. The growth of new vessels may affect normal organ function and, conversely, organ growth *per se* can apparently induce an angiogenic program in the absence of hypoxia by using mechanical stretch as a stimulus. These new insights are discussed in the context of myocardial hypertrophy by R. Tomanek and E. Dedkov. The growth of new

vessels may affect microvascular milieu in a number of ways, including changes in microvasculature response to various agonists and antagonists. These microvascular physiological aspects of angiogenesis are addressed in Chapter 10 by F. Sellke and colleagues.

The third part of the book deals with new insights into therapeutic applications of discoveries in the field of angiogenic biology. Perhaps one of the most anticipated applications has been the development of various tyrosine kinase inhibitors. This side of therapeutic anti-angiogenesis is discussed in Chapter 11 by K.-H. Thierauch. To date, application of angiogenic therapies to cardiovascular diseases have not fulfilled lofty expectations of the past decade. The reasons for this lack of progress and potential paths forward are addressed in Chapter 12 by M. Murakami and M. Simons. Perhaps some of the more exciting recent therapeutic applications in the angiogenic growth factor field have involved the hepatocyte growth factor (HGF). HGF biology and biological role as well as its therapeutic applications are discussed in Chapter 13 by R. Morishita and T. Ogihara. Nitric oxide, a recent *Science* magazine molecule of the year, has always been at the center of endothelial biology. New advances in the NO field and their potential therapeutic applications are discussed in Chapter 14 by G. Rubanyi.

The composition of a multi-author monograph is never a simple process and many thanks are due. First, we would like to thank all the contributors for a thorough review of their respective areas. The editors at the Imperial College Press and especially Joy Quek have been highly professional and patient in dealing with us and helping us to put together the best book possible. Finally, we would like to thank our colleagues for their support and advice in this project.

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