Preface

During development, the first blood vessels are formed by the de novo assembly of angioblasts, endothelial cell precursors, in a process called vasculogenesis. All subsequent sprouting of blood vessels from preexisting vessels is termed angiogenesis and is a process that continues throughout our life span during physiological processes such as wound healing as well as in a number of pathological conditions, such as tumor growth and age-related macular degeneration. The circulatory system pumps blood from the heart out to the organs through arteries and delivers oxygen and nutrients via capillaries to tissues and cells and returns carbon dioxide and waste products back through veins. Each organ varies in its blood vessel patterning, reflecting specialization to accomplish diverse functions including vascular permeability, filtration, immune trafficking, and hormone regulation. Approximately 90% of the fluid extravasated into the interstitium is recycled back to the circulatory system via the unidirectional lymphatic system. Lymphatic capillaries drain fluid, proteins, and cells from tissues and transport this lymph fluid through collecting lymphatic ducts toward lymph nodes. Eventually lymphatic fluid from the right and left lymphatic ducts joins the subclavian veins and recirculates throughout the circulatory system. These two intricate vascular systems, working in cooperation, help to maintain essential bodily functions such as fluid dynamics, tissue homeostasis, blood pressure, metabolism, and immunity. However, dysfunction of these systems is associated with a host of pathological conditions, including cardiovascular diseases, obesity, retinopathy, hypoxia, necrosis, and vascular malformations.

This Second Edition of *Angiogenesis: Biology and Pathology* includes 34 chapters covering many different aspects of angiogenesis and lymphangiogenesis from developmental to physiological to pathological. Each chapter is written by experts in the field of vascular biology and covers major advances in the field made over the last 12 years. It is our hope that the dissemination of knowledge regarding the biology of angiogenesis and lymphangiogenesis that has been acquired since the first edition of this volume will continue to advance translational research and result in improved therapies for vasculature-dependent diseases.

As an overview to the scientific topics covered in this volume, we have organized the chapters into ten major areas. **Progenitor Cells:** These chapters cover the early stages of embryogenesis and vasculogenesis with an emphasis on differentiation, specification, and cell fate determination. The importance of the Notch pathway in vessel formation will be highlighted, and human endothelial progenitor cells (or colony-forming cells) and their use in model systems will be discussed. **Patterning:** Content in this section explores vascular patterning and endothelial heterogeneity, plasticity, and regression. The role of extracellular matrix molecules in vessel morphology, stability, and maturity will be addressed. Organ-specific vascular patterning in the brain, skin, heart, kidney, pancreas, and lung as well as pathologies resulting from defective patterning will be reviewed. **Genesis:** This next set of chapters focuses on factors influencing angiogenesis and lymphangiogenesis including the role of endothelial connexins and prostanoids. The important role that platelets play in developmental lymphangiogenesis and adult pathological angiogenesis is examined. Lymphatics-on-a-chip and using lymphangiogenesis in tissue engineering is covered. **Permeability:** In the next section, authors delve into the regulation of microvascular permeability in blood vessels and the consequences of lymphatic vessel permeability. An in-depth discussion on lymphatic endothelial cell junctions called buttons and zippers, which function to modulate lymphatic fluid drainage, is included. **Molecular Regulation:** The next five chapters focus on a variety of mechanisms that modulate vascular function including proteins in the Notch pathway, S1P, and epsin endocytic adaptor

proteins. Mechanical stiffness and fluid sheer stress can affect microRNA expression to perturb mechanical homeostasis in the cardiovascular system. Furthermore, loss-of-function or gain-of-function mutations in specific genes can drive primary lymphedema or lymphatic anomalies. **Endothelial Cell–Smooth Muscle Cell Interactions and Pumping:** Two chapters in this section focus on the role of mural cell interactions with blood vessels. One deals with the role of Notch signaling and the cross talk between endothelial cells and pericytes, while the other focuses on these interactions in the context of cerebral cavernous malformations. Two other chapters concentrate on the role of smooth muscle pumping surrounding lymphatic collectors and ducts and their functional importance for lymphatic clearance and drainage. **Blood–Brain Barrier:** The chapters under this topic center around the cellular interactions and key molecular regulators that maintain the blood–brain barrier and changes in this barrier function during disease. An additional chapter considers in vitro systems for modeling immune interactions with the brain endothelium. **Inflammation and Immune Trafficking:** Consecutive chapters deal with leukocyte trafficking in blood vessels and lymphatic vessels. A review on the cross talk between angiogenesis and the resolution of inflammation via specialized pro-resolving mediators such as resolvins and their role in chronic inflammation is presented. Lastly, the effects of COVID-19 infection on the endothelium are discussed. **Lipids and Obesity:** Contributions in this area focus on endothelial cell lipid uptake, metabolism, and transport during homeostasis and genesis. Another chapter draws attention to lymphatics in cardiovascular disease, and a third sheds light on obesity-induced lymphedema. **Aging and Microbiome:** The last two chapters center on the effects of aging on the vasculature and methods to model aging in vitro. Finally, the impact of the microbiome on the microvasculature and its function is reviewed.

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