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Cover illustration: Early formation of the coronary vascular arterial tree represented by a coronary cast formed by injection of a plastic polymer. The cast is from a stage HH 33 quail which is about 1 day after the two main coronary arteries attach to the aorta. The scanning electron microscopic micrograph is from the laboratory of Robert Tomanek.

Library of Congress Cataloging-in-Publication Data

Assembly of the vasculature and its regulation / edited by Robert J. Tomanek.

p. cm.—(Cardiovascular molecular morphogenesis)

Includes bibliographical references and index.

ISBN 978-1-4612-6616-7 ISBN 978-1-4612-0109-0 (eBook)

DOI 10.1007/978-1-4612-0109-0

1. Neovascularization—Regulation. 2. Blood-vessels—Growth—Regulation.

I. Tomanek, Robert J. II. Series.

[DNLM: 1. Blood Vessels—embryology. 2. Blood Vessels—physiology.

3. Endothelium, Vascular—embryology. 4. Endothelium, Vascular—physiology.

5. Morphogenesis. WG 101 A844 2001]

QP106.6.A85 2001

612.1'3—dc21

2001025378

Printed on acid-free paper.

© 2002 Springer Science+Business Media New York

Originally published by Birkhäuser Boston in 2002

Softcover reprint of the hardcover 1st edition 2002

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ISBN 978-1-4612-6616-7 SPIN 10838366

Production managed by Michael Koy, manufacturing supervised by Jeffrey Taub.

Typeset by SNP Best-set Typesetter Ltd., Hong Kong.

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Series Preface

The overall scope of this new series will be to evolve an understanding of the genetic basis of (1) how early mesoderm commits to cells of a heart lineage that progressively and irreversibly assemble into a segmented, primary heart tube that can be remodeled into a four-chambered organ, and (2) how blood vessels are derived and assembled both in the heart and in the body. Our central aim is to establish a four-dimensional, spatiotemporal foundation for the heart and blood vessels that can be genetically dissected for function and mechanism.

Since Robert DeHaan's seminal chapter "Morphogenesis of the Vertebrate Heart" published in *Organogenesis* (Holt Rinehart & Winston, NY) in 1965, there have been surprisingly few books devoted to the subject of cardiovascular morphogenesis, despite the enormous growth of interest that occurred nationally and internationally. Most writings on the subject have been scholarly compilations of the proceedings of major national or international symposia or multiauthored volumes, often without a specific theme. What is missing are the unifying concepts that can make sense out of a burgeoning database of facts. The Editorial Board of this new series believes the time has come for a book series dedicated to cardiovascular morphogenesis that will serve not only as an important archival and didactic reference source for those who have recently come into the field but also as a guide to the evolution of a field that is clearly coming of age. The advances in heart and vessel morphogenesis are not only serving to reveal general basic mechanisms of embryogenesis but are also now influencing clinical thinking in pediatric and adult cardiology.

Undoubtedly, the Human Genome Project and other genetic approaches will continue to reveal new genes or groups of genes that may be involved in heart development. A central goal of this series will be to extend the identification of these and other genes into their functional role at the molecular, cellular, and organ levels. The major issues in morphogenesis highlighted in the series will be the local (heart or vessel) regulation of cell growth and death, cell adhesion and migration, and gene expression responsible for the cardiovascular cellular phenotypes.

Specific topics will include the following:

- The roles of extracardiac populations of cells in heart development.
- Coronary angiogenesis.
- Vasculogenesis.
- Breaking symmetry, laterality genes, and patterning.
- Formation and integration of the conduction cell phenotypes.
- Growth factors and inductive interactions in cardiogenesis and vasculogenesis.
- Morphogenetic role of the extracellular matrix.
- Genetic regulation of heart development.
- Application of developmental principles to cardiovascular tissue engineering.

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Preface

In 1983 Ciba Foundation Symposium 100, entitled *Development of the Vascular System* (London: Pitman), was published, in which the chairman's introduction noted that this was "the first meeting to be recorded on the development of the cardiovascular system." The chairman also stated that it was "surprising that such an important subject has been so neglected." Since that time, considerable progress has been made regarding vascular formation and the molecular mechanisms that regulate the process. Although much of the work has focused on angiogenesis in disease states, such as tumors, retinopathy, and ischemic models, our understanding of vasculogenesis and angiogenesis during development has advanced. Progress in this field has been facilitated by the rapid advances in the field of growth factor biology, as well as new discoveries concerning adhesion molecules, various extracellular components, and signaling pathways.

Considering the expanding literature in this area, it is obvious that a comprehensive book addressing the major areas of vessel formation during development is long overdue. Accordingly, *Assembly of the Vasculature and Its Regulation* addresses key topics in the field of vessel formation during development. In the first section of the book major issues regarding vessel formation and its regulation (growth factors and their receptors, extracellular matrix, adhesion molecules, and smooth muscle differentiation) are detailed. The second section addresses vascular development in a number of organs (heart, central nervous system, kidney, lung, and placenta). The rationale for the book is to provide a reference treatise that covers the events and regulatory factors characterizing vessel formation during the prenatal and perinatal periods. In aggregate, this book addresses the proliferation, migration, and differentiation of angioblasts, their assembly into vascular tubes, the subsequent growth of these structures, and the addition of medial and adventitial components to form a functional network, i.e., the vascular system.

Assembly of the Vasculature and Its Regulation is dedicated to the memory of Werner Risau (1953–1998) whose work has had profound impact on the field of vascular development. His contributions are many and will long be quoted and appreciated. Drs. Breier and Flamme provide a tribute to Dr. Risau on the following pages.

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Werner Risau (1953–1998)

Werner Risau, who died in December 1998, will be remembered for his outstanding work on the development of the vascular system in the vertebrate embryo and on the mechanisms of tumor angiogenesis.

Werner Risau was born in Rheine, Germany, in 1953, and educated in his native city. In 1973 he began to study chemistry in the nearby city of Münster; three years later he moved to Tübingen, Germany, and focused on biochemistry. His first appointment was at the Max Planck Institute for Developmental Biology in Tübingen, where he finished his Ph.D. thesis on ribonucleoprotein particles in *Drosophila* in the department of Prof. Friedrich Bonhoeffer in 1983. In parallel, Risau also studied medicine. During this time, his interest in biochemistry, developmental biology, and medicine amalgamated and he became fascinated by the question of how blood vessels develop and grow in the vertebrate embryo.

The defining period in Risau's scientific life was his postdoctoral time in Prof. Judah Folkman's laboratory at the Children's Hospital, Harvard University, in Boston from 1983 to 1984. There he learned endothelial cell biology and became familiar with angiogenic growth factors. Inspired by Folkman's brilliant concept of tumor angiogenesis, Risau had the vision that angiogenic growth factors not only might be involved in the vascularization of tumors, but also might regulate the development of the vascular system. This idea opened a new era in vascular biology and became a dominant research theme during the 1990s.

After having returned to the Max Planck Institute in Tübingen, Risau founded his own laboratory and initiated vigorous and creative research on the molecular mechanisms of endothelial cell growth and differentiation in the vertebrate embryo. He considered the brain to be an ideal organ in which to investigate the regulation of embryonic angiogenesis. By using biochemical methods, he showed that angiogenic growth factors of the fibroblast growth factor family are present in the embryonic chick brain. On the other hand, he put forward the hypothesis that the locally produced endogenous inhibitors of angiogenesis would counteract angiogenic growth factors and induce blood vessel regression in the embryo, for example in the limb bud. Risau's analyses of blood-brain barrier induction and function founded his reputation as an internationally recognized expert in endothelial cell biology. During his period, he also became interested in the ques-

tion of how endothelial cells differentiate from their mesodermal precursor cells. He put forward the concept of vasculogenesis as the principal mechanism by which the primary vascular system is established, as a mechanism distinct from angiogenesis, the blood vessel formation from preexisting vessels.

In 1988, Risau's interest in the vasculature of the brain led him and his group to the Max Planck Institute of Neurobiology in Martinsried (the former Max Planck Institute of Psychiatry). There he increasingly utilized molecular approaches to address the problems of vascular biology. This period was characterized by studies on the function of vascular endothelial growth factor (VEGF). In several papers published in 1992 and 1993, he laid down the basis for the work of many other researchers. These studies included the first identification of VEGF and the high-affinity VEGF receptor, Flk-1, as a critical signaling system involved in the development of the vascular system, and the first identification of the VEGF as tumor angiogenesis factor in malignant glioma and its regulation by hypoxia. Of the many fruitful collaborations from this time, two stand out—that with Dr. Erwin Wagner (Vienna), using the polyoma middle T oncogene in the study of endothelial cell growth and transformation, and that with Dr. Axel Ullrich (Martinsried) in the functional analysis of the Flk-1 receptor tyrosine kinase.

In 1992, Risau was appointed director at the Max Planck Institute for Physiological and Clinical Research in Bad Nauheim. In his department, he combined expertise in various research areas, including vasculogenesis, endothelial cell differentiation and blood-brain barrier development, endothelial cell signaling, endothelial cell-specific transcriptional control, mechanisms of hypoxia-induced expression, and endothelial cell apoptosis. He extended the investigation of the molecular players that cooperate to regulate endothelial cell growth and differentiation. These studies included other endothelial receptor tyrosine kinases such as Tie2 and its role in vascular remodeling and angiogenesis, endothelial phosphatases, hypoxia-inducible factors, and other transcription factors involved in blood vessel growth and development.

Werner Risau was a generalist interested in many areas of vascular biology. He was not only an excellent researcher, but also had a rare sense of community. This is documented by the large number of scientific collaborations that were initiated on the basis of his enthusiastic will to understand the biology of the vascular system.

*Georg Breier
Ingo Flamme*

Werner Risau