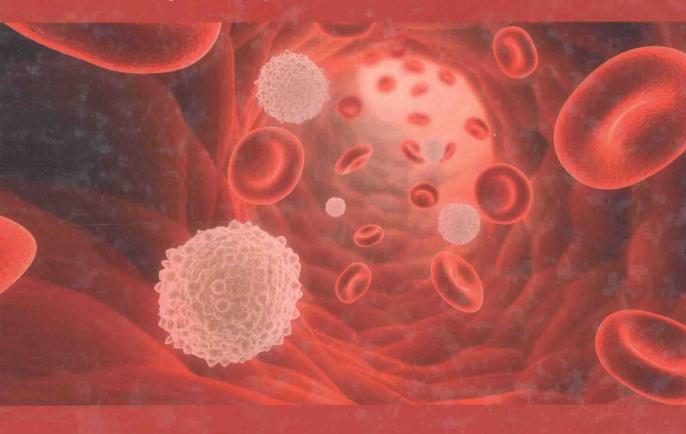
Inflammatory Diseases of Blood Vessels

Second Edition

Edited by

Gary S. Hoffman Carol A. Langford Cornelia M. Weyand Jörg J. Goronzy



Inflammatory Diseases of Blood Vessels

EDITED BY

Gary S. Hoffman MD, MS

Professor of Medicine
Department of Rheumatic and Immunologic Diseases
Center for Vasculitis Care and Research
Cleveland Clinic
Lerner College of Medicine
Cleveland, OH, USA

Cornelia M. Weyand MD, PhD

Professor of Medicine Department of Medicine Stanford University School of Medicine Stanford, CA, USA

Garol A. Langford MD, MHS Di letter Contention Vasculitis Care and Resourch Department of Rheymotic and International Directors Cloveland Clinic Letner College Medicine Cloveland Mary SA Jorg J. Goronzy MD, PhD

Professor of Medicine
Department of Medicine
Stanford University School of Medicine
Stanford, CA, USA

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Editorial offices: 9600 Garsington Road, Oxford, OX4 2DQ, UK

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List of Contributors

Ahmet Ruchan Akar MD, FRCS (CTh)

Professor of Cardiovascular Surgery
Department of Cardiovascular Surgery
Ankara University School of Medicine
Deputy Director of Ankara University Stem Cell Institute
Ankara, Turkey

Daniel S. Alam MD FACS

Section Head, Facial Aesthetic and Reconstructive Surgery Head and Neck Institute Cleveland Clinic Cleveland, OH, USA

Turki Albacker MD, MSc, FRCSC, FACS, FACC

Assistant Professor of Cardiac Sciences Consultant Cardiac Surgeon King Fahad Cardiac Center College of Medicine, King Saud University Riyadh, Saudi Arabia

Nezam Altorok MD

Resident
Division of Rheumatology and Immunology
University of Toledo Medical Center
Toledo, OH, USA

Moshe Arditi MD

Professor of Pediatrics Division of Infectious Diseases and Immunology Burns and Allen Research Institute, Cedars-Sinai Medical Center and David Geffen School of Medicine at UCLA Los Angeles, CA, USA

Claire E. Barber MD

Rheumatology Resident University of Toronto Toronto, ON, Canada

Thorsten Alexander Bley MD

Associate Professor of Radiology Department of Interventional and Diagnostic Radiology University Medical Center Hamburg-Eppendorf Hamburg, Germany

Patrice P. Cacoub MD

Professor of Medicine National Referral Center for Autoimmune and Systemic Diseases Department of Internal Medicine Hópital la Pitié Salpêtrière Paris, France

Leonard H. Calabrese DO

Professor of Medicine, Cleveland Clinic Lerner College of Medicine RJ Fasenmyer Chair of Clinical Immunology Department of Rheumatic and Immunologic Diseases Cleveland, OH, USA

Jeffrey P. Callen MD, FACP, FAAD

Professor of Medicine (Dermatology) Chief, Division of Dermatology University of Louisville School of Medicine Louisville, KY, USA

Simon Carette MD, MPhil, FRCPC

Professor of Medicine Division of Rheumatology Toronto Western Hospital and Mount Sinai Hospital Toronto, ON, Canada

Shuang Chen MD, PhD

Assistant Professor Division of Infectious Diseases and Immunology Burns and Allen Research Institute Cedars-Sinai Medical Center Los Angeles, CA, USA

Maria C. Cid мр

Senior Consultant
Vasculitis Research Unit, Department of Systemic Autoimmune
Diseases
Hospital Clínic;
Associate Professor
University of Barcelona
Institut d'Investigacions Biomèdiques August Pi i Sunyer
(IDIBAPS)
Barcelona, Spain

viii List of Contributors

Jan Willem Cohen Tervaert MD, PhD

Chairman, Division of Clinical and Experimental Immunology Professor of Medicine and Immunology Department of Internal Medicine Maastricht University Medical Center Maastricht. The Netherlands

Marc Corbera-Bellalta BA

PhD Student

Vasculitis Research Unit, Department of Systemic Autoimmune Diseases,

Hospital Clínic

Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS)

Barcelona, Spain

Enrico Crivellato MD

Associate Professor Department of Medical and Morphological Research Anatomy Section University of Udine Medical School Udine, Italy

Kirsten de Groot MD

Chief, 3rd Medical Department, Section of Nephrology and Rheumatology Klinikum Offenbach, GmbH KfH Nierenzentrum Offenbach Offenbach/Main, Germany

Serkan Durdu MD, PhD

Consultant Cardiovascular Surgeon Department of Cardiovascular Surgery Ankara University School of Medicine Ankara University Stem Cell Institute Ankara, Turkey

Georgina Espígol-Frigolé MD Visiting Fellow

Cellular and Molecular Biology Section, Laboratory of Cellular Oncology National Cancer Institute National Institutes of Health Bethesda, MD, USA; Associate Professor University of Girona

Girona, Spain

George E. Fragoulis MD

PhD Candidate Pathophysiology Department School of Medicine University of Athens Athens, Greece

Ricardo Garcia MD

Rheumatology Fellow Division of Rheumatology State University of New York Upstate Medical University Syracuse, NY, USA

Ana García-Martínez MD

Senior Specialist
Department of Emergency Medicine
Hospital Clínic
Institut d'Investigacions Biomèdiques August Pi i Sunyer
(IDIBAPS)
Barcelona, Spain

Jörg J. Goronzy MD, PhD

Professor of Medicine Department of Medicine Stanford University School of Medicine Stanford, CA, USA

Loïc Guillevin MD

Professor and Director, French Vasculitis Study Group National Referral Center for Rare Systemic and Autoimmune Diseases, Necrotizing Vasculitides and Systemic Sclerosis Department of Internal Medicine Hôpital Cochin University Paris-Descartes Paris, France

Rula A. Hajj-Ali MD

Assistant Professor of Medicine Center for Vasculitis Care and Research Department of Rheumatic and Immunologic Diseases Cleveland Clinic Cleveland, OH, USA

David G. Harrison MD

Betty and Jack Bailey Professor of Medicine and Pharmacology Director of Clinical Pharmacology Vanderbilt University School of Medicine Nashville, TN, USA

Philip J. Hashkes MD, MSc

Head, Pediatric Rheumatology Unit Shaare Zedek Medical Center Jerusalem, Israel; Associate Professor of Medicine and Pediatrics Cleveland Clinic Lerner Medical School of Case Western Reserve University Cleveland, OH, USA List of Contributors ix

José Hernández-Rodríguez MD

Senior Specialist

Vasculitis Research Unit, Department of Autoimmune and Systemic Diseases

Hospital Clínic, University of Barcelona

Insititut d'Investigacions Biomèdiques August Pi i Sunver (IDIBAPS)

Barcelona, Spain

Gary S. Hoffman MD, MS

Professor of Medicine

Department of Rheumatic and Immunologic Diseases

Center for Vasculitis Care and Research

Cleveland Clinic

Lerner College of Medicine

Cleveland, OH, USA

Georg Jung

Department of Pharmacology

Max-Planck-Institute for Heart and Lung Research

Bad Nauheim, Germany;

Department of Vascular and Endovascular Surgery

Goethe-University

Frankfurt am Main, Germany

Bashar Kahaleh MD

Professor and Chief

Division of Rheumatology and Immunology

University of Toledo Medical Center

Toledo, OH, USA

Omar R. Kahaly BSc

Medical Student

Division of Rheumatology and Immunology

University of Toledo Medical Center

Toledo, OH, USA

Cees G.M. Kallenberg MD, PhD

Professor of Medicine

Department of Rheumatology and Clinical Immunology

University Medical Center Groningen

University of Groningen

Groningen, The Netherlands

Vikram S. Kashyap MD, FACS

Professor of Surgery, Case Western Reserve University; Chief, Division of Vascular Surgery and Endovascular Therapy;

Co-Director, Harrington-McLaughlin Heart & Vascular

Institute

University Hospitals Case Medical Center

Cleveland, OH, USA

Tanaz A. Kermani MD

Assistant Professor of Medicine

Division of Rheumatology

College of Medicine

Mayo Clinic

Rochester, MN, USA

Atul Khasnis MD, MS

Center for Vasculitis Care and Research

Department of Rheumatic and Immunologic Diseases

Cleveland Clinic

Cleveland, OH, USA

Paul Kubes, PhD

Director, Snyder Institute of Infection, Immunity and Inflammation

Professor, Department of Physiology and Pharmacology

Faculty of Medicine, University of Calgary

Health Research Innovation Center

Calgary, Canada

Carol A. Langford MD, MHS

Director, Center for Vasculitis Care and Research Department of Rheumatic and Immunologic Diseases

Cleveland Clinic

Lerner College of Medicine

Cleveland, OH, USA

Lawrence Leung MD

Chief of Staff

VA Palo Alto Health Care System

Palo Alto, CA, USA;

Maureen Lyles D'Ambrogio Professor of Medicine

Associate Dean for Veterans Affairs

Stanford University School of Medicine

Stanford, CA, USA

Kimberly P. Liang мр

Assistant Professor of Medicine

Department of Medicine and Division of Rheumatology and Clinical Immunology

University of Pittsburgh

Pittsburgh, PA, USA

C. David Lin MD

Associate Professor of Clinical Rehabilitation Medicine Weill Cornell Medical College

New York, NY, USA

Ester Lozano PhD

Visiting Fellow

Department of Neurology

Yale School of Medicine, University of Yale

New Haven, CT, USA

X List of Contributors

Kathleen Maksimowicz-McKinnon

Assistant Professor of Medicine Director, UPMC and University of Pittsburgh Center for Vasculitis

Division of Rheumatology and Clinical Immunology Pittsburgh, PA, USA

Eric Matteson MD, MPH

Professor of Medicine Consultant, Divisions of Rheumatology and Epidemiology Chair, Division of Rheumatology Mayo Clinic College of Medicine Rochester, MN, USA

Rex M. McCallum MD. FACP. FACR

Vice President, Chief Physician Executive Professor of Medicine/Rheumatology Department of Medicine, Division of Rheumatology University of Texas Medical Branch Galveston, TX, USA

Braedon McDonald BSc(Hon)

MD/PhD Candidate Department of Physiology and Pharmacology Faculty of Medicine, University of Calgary Health Research Innovation Center Calgary, Canada

Peter A. Merkel MD, MPH

Chief, Division of Rheumatology Professor of Medicine and Epidemiology University of Pennsylvania School of Medicine Philadelphia, PA, USA

Dianna M. Milewicz MD, PhD

President George H.W. Bush Chair of Cardiovascular Medicine Director, Division of Medical Genetics Department of Internal Medicine University of Texas Health Science Center at Houston Houston, TX, USA

Frederick W. Miller MD, PhD

Chief, Environmental Autoimmunity Group Program of Clinical Research National Institute of Environmental Health Sciences National Institutes of Health Clinical Research Center Bethesda, MD, USA

Eli M. Miloslavsky MD

Rheumatology Fellow Division of Rheumatology, Allergy and Immunology Massachusetts General Hospital Boston, MA, USA

Eamonn S. Molloy MD, MS, MRCPI

Consultant Rheumatologist Department of Rheumatology St Vincent's University Hospital Dublin, Ireland

Larry W. Moreland MD

Margaret Jane Miller Endowed Professor of Arthritis Research Chief, Division of Rheumatology and Clinical Immunology University of Pittsburgh Pittsburgh, PA, USA

Matthew David Morgan MB, ChB, PhD

Senior Lecturer Renal Immunobiology College of Medical and Dental Sciences University of Birmingham Birmingham, UK

John Morser PhD

Senior Research Scientist Division of Hematology, Department of Medicine Stanford University School of Medicine and VA Palo Alto Health Care System Stanford, CA, USA

Haralampos M. Moutsopoulos MD, FACP, FRCP(hc), Master ACR

Professor and Director Pathophysiology Department School of Medicine University of Athens Athens, Greece

Jan Nilsson MD

Professor Experimental Cardiovascular Research Unit Department of Clinical Sciences Malmö Lund University Skåne University Hospital Malmö, Sweden

Masato Nose MD, PhD

Emeritus Professor Department of Pathogenomics Ehime University Graduate School of Medicine Proteo-Medicine Research Center Ehime University Ehime, Japan List of Contributors xi

Chester V. Oddis MD

Professor of Medicine

Director, UPMC and University of Pittsburgh Center for Myositis

Division of Rheumatology and Clinical Immunology University of Pittsburgh School of Medicine Pittsburgh, PA, USA

Christian Pagnoux MD, MPH, MSc

Vice-Director, Canadian Vasculitis Research Network (CanVasc) (Past) Vice-President, French Vasculitis Study Group Division of Rheumatology Mount Sinai Hospital and University Health Network Toronto, ON, Canada

Andras Perl MD, PhD

Professor of Medicine, Microbiology and Immunology, Biochemistry and Molecular Biology Chief, Division of Rheumatology State University of New York Upstate Medical University Syracuse, NY, USA

Ester Planas-Rigol BA

PhD Student

Vasculitis Research Unit, Department of Systemic Autoimmune Diseases Hospital Clínic Institut d'Investigacions Biomèdiques August Pi i Sunyer

(IDIBAPS)

Barcelona, Spain

Charles Pusey DSc, FRCP

Professor Renal Section Department of Medicine Imperial College London London, UK

Ravi R. Rajani мо

Assistant Professor of Surgery Division of Vascular Surgery and Endovascular Therapy, Department of Surgery Emory University School of Medicine Atlanta, GA, USA

Amy J. Reid BA

MD/PhD Candidate Division of Medical Genetics Department of Internal Medicine University of Texas Health Science Center at Houston Houston, TX, USA

Domenico Ribatti MD

Professor of Human Anatomy Department of Basic Medical Sciences, Anatomy and Histology Section University of Bari Medical School Bari, Italy

James T. Rosenbaum MD

Professor of Ophthalmology, Medicine, and Cell Biology Edward E. Rosenbaum Professor of Inflammation Research Chair, Division of Arthritis and Rheumatic Diseases Oregon Health & Science University Portland, OR, USA

Abraham Rutgers MD, PhD

Assistant Professor of Clinical Immunology
Department of Rheumatology and Clinical Immunology
University Medical Center Groningen
University of Groningen
Groningen, The Netherlands

Jan S.F. Sanders MD, PhD

Assistant Professor Department of Nephrology University Medical Center Groningen University of Groningen Groningen, The Netherlands

Caroline O.S. Savage PhD, FRCP, FMedSci

Honorary Professor of Nephrology Renal Immunobiology College of Medical and Dental Sciences University of Birmingham Birmingham, UK

Wolfgang Schaper MD, PhD

Director Emeritus Department of Arteriogenesis Research Max-Planck-Institute for Heart and Lung Research Bad Nauheim, German

Thomas Schmitz-Rixen MD, PhD

Professor of Vascular Surgery
Director, Department of Vascular and Endovascular Surgery
Goethe-University
Department of Wound Care
Goethe University Hospital
Frankfurt am Main, Germany

xii List of Contributors

Marta Segarra PhD

Postdoctoral Investigator Cellular and Molecular Biology Section, Laboratory of Cellular Oncology National Cancer Institute National Institutes of Health Bethesda, MD, USA

Rahul Seth, MD

Resident Physician
Section of Facial Aesthetic and Reconstructive Surgery
Head and Neck Institure
Cleveland Clinic
Cleveland, OH, USA

Prediman K. Shah MD

Director
Division of Cardiology/Heart Institute
Oppenheimer Atherosclerosis Research Center
Burns and Allen Research Institute
Cedars-Sinai Medical Center and David Geffen School of
Medicine at UCLA
Los Angeles, CA, USA

Ismail Simsek MD

Associate Professor Department of Medicine Division of Rheumatology Gülhane School of Medicine Ankara, Turkey

Raj Sindwani MD FACS

Section Head, Rhinology, Sinus and Skull Base Surgery Head and Neck Institute Cleveland Clinic Cleveland, OH, USA

Ulrich Specks MD

Division of Pulmonary and Critical Care Medicine Mayo Clinic Pulmonary and Critical Care Medicine Rochester, MN, USA

E. William St. Clair MD

Chief, Division of Rheumatology and Immunology Professor of Medicine and Immunology Department of Medicine, Division of Rheumatology and Immunology Duke University Medical Center Durham, NC, USA

Coen A. Stegeman MD, PhD

Professor of Nephrology Department of Internal Medicine, Division of Nephrology University Medical Center Groningen Groningen, The Netherlands

John H. Stone MD. MPH

Director, Clinical Rheumatology; Associate Professor Massachusetts General Hospital Boston, MA, USA

Lars Svensson MD, PhD, FACS

Cleveland Clinic Thoracic and Cardiovascular Surgery Cleveland, OH, USA

Benjamin Terrier MD

Consultant Department of Internal Medicine Hôpital la Pitié Salpêtrière Paris, France

Christian Troidl PhD

Head of Laboratory Franz-Groedel-Institute Kerckhoff Heart and Thorax Center Bad Nauheim, Germany

Kerstin Troidl PhD

Department of Pharmacology Max-Planck-Institute for Heart and Lung Research Bad Nauheim, Germany; Department of Vascular and Endovascular Surgery Goethe-University Frankfurt am Main, Germany

Carl Turesson MD, PhD

Associate Professor Department of Rheumatology Skåne University Hospital, Lund University Malmö, Sweden

Dimitrios Vassilopoulos MD

Associate Professor of Medicine – Rheumatology 2nd Department of Medicine Athens University School of Medicine Hippokration General Hospital Athens, Greece List of Contributors xiii

Alexandra Villa-Forte MD, MPH

Staff

Center for Vasculitis Care and Research Department of Rheumatic Diseases Cleveland Clinic Cleveland, OH, USA

Kenneth J. Warrington MD

Consultant, Division of Rheumatology Associate Professor of Medicine College of Medicine Mayo Clinic Rochester, MN, USA

Cornelia M. Weyand MD, PhD

Professor of Medicine Department of Medicine Stanford University School of Medicine Stanford, CA, USA

Hasan Yazici MD

Professor of Medicine Department of Medicine Division of Rheumatology Cerrahpasa Medical Faculty University of Istanbul Istanbul, Turkey

Yusuf Yazici MD

Assistant Professor of Medicine New York University School of Medicine NYU Hospital for Joint Diseases New York, NY, USA

Steven Yeh MD

Assistant Professor Uveitis, Vitreoretinal Diseases and Surgery Department of Ophthalmology Emory University School of Medicine Atlanta, GA, USA

Rae S.M. Yeung MD, PhD, FRCPC

Associate Professor
Departments of Pediatrics, Immunology and Medical Science
University of Toronto;
Senior Scientist and Staff Rheumatologist
The Hospital for Sick Children
Toronto, ON, Canada

Preface

Inflammatory Diseases of Blood Vessels (IDBV) is intended to provide a comprehensive overview of the science and clinical consequences of vascular inflammation in health and disease. Vascular diseases have many different topographic, microscopic and pathogenic phenotypes. This observation implies variability in disease-determining factors such as vascular substrate, cell trafficking, immune response, causes of injury and capacity for repair.

It is often not recognized that vessels are as heterogeneous as the organs they perfuse and that these differences are further modified during our lifetimes and experiences. Territorial differences are relevant to the study and care of patients with congenital vascular diseases, coronary artery disease, aortic aneurysms, infection-induced vascular injury and autoimmune vasculitis. Recognizing that vascular disease may occur in any organ, we have provided content that is designed to satisfy readers who are either generalists or come from many specialties.

For the clinician, there is also a need to recognize degrees of mimicry between different vascular diseases. At the bedside, distinguishing between congenital and acquired metabolic, infectious, malignant and autoimmune etiologies is critical for subsequent treatment decisions.

We have been fortunate to engage leading clinicianscientists whose appreciation of mechanisms of vascular injury is clinically relevant. Other authors are recognized for their work in epidemiology, disease classification, outcomes, clinical investigation and surgery. Our surgical colleagues have vital roles in repair of permanent damage, offering interventions that are life-changing for many seeking our help. We have admired and thank all contributors, not only for their chapters, but also for moving this field so far in such a short time.

The work behind a book like this goes beyond conception, recruiting the right authors and editing. The second edition of IDBV would not have been possible without Maria Khan and Jennifer Seward at Wiley-Blackwell. Maria believed in the project and Jennifer walked us through each step. Their understanding of process, layout and budget kept us out of trouble and greatly enriched our final product. They could not have been more supportive and professional.

Gary S. Hoffman Cornelia M. Weyand Carol A. Langford Jörg J. Goronzy

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PART I

Biology of Blood Vessels and Mechanisms of Vascular Inflammation



CHAPTER 1

Vascular Development

Domenico Ribatti¹ and Enrico Crivellato²

- ¹Department of Basic Medical Sciences, Anatomy and Histology Section, University of Bari Medical School, Bari, Italy
- ²Department of Medical and Morphological Research, Anatomy Section, University of Udine Medical School, Udine, Italy

Overview

- Vascular formation appears early during embryo development and entails both genetic and epigenetic factors.
- Two fundamental mechanisms are recognizable: vasculogenesis and angiogenesis, the latter including sprouting angiogenesis and intussusceptive microvascular growth.
- During the development of the vascular tree, blood vessels express a precise spatial and temporal hierarchy and form organ- and tissue-specific vascular beds.
- Several cytokines and signaling mechanisms are implicated in arterial, capillary and venous specification, a process which involves endothelial cells (EC) interfacing with pericytes, mural cells and tissue-borne elements.
- Structural and molecular heterogeneity of EC is believed to contribute to the generation of vascular bed diversity.

Development of the cardiovascular system

The circulatory system consists of the heart and an interconnected network of blood vessels which differ in size, structure and function. The heart develops from the precardic lateral folds to form the primitive heart tube. This consists of an inner endothelium, which is separated from the outer myocardial tube by the elastic cardiac jelly. Emergence of cardiac endothelium and cardiomyocytes occurs almost concomitantly and, at first, they develop rather independently from one another [1]. The endocardium is continuous with the endothelium of the major blood vessels, the axial vein and the dorsal aorta.

Blood vessels first appear as the result of vasculogenesis, i.e. the formation of capillaries from endothelial cells (EC) differentiating from groups of mesodermal cells (Figure 1.1). The vascular plexus is established before the onset of heart beat. Vasculogenesis leads to the formation of the first major intraembryonic blood vessels and to the set up of the primary vascular plexus in the yolk sac. Development of the vascular network of certain endodermal organs, including liver, lung, pancreas, stomach, intestine and spleen, occurs by vasculogenesis. Otherwise, in the developing brain and kidney the formation of the vascular tree occurs by angiogenesis.

Several factors are critical for vasculogenesis. Angioblasts begin to differentiate into EC and assemble into tubes, principally as the result of a series of inductive cues:

- 1 Vascular endothelial growth factor (VEGF)
- 2 Signals from surrounding tissues, and
- 3 The expression of intercellular and cell-matrix adhesion molecules.

EC tubes are soon stabilized by pericytes recruited from the surrounding mesenchyme to form early capillaries. In microvessels, platelet-derived growth factor (PDGF) and transforming growth factor $\beta 1$ (TGF- $\beta 1$) signals are involved in the recruitment of pericytes. In larger vessels, arterioles and venules, the vascular wall is made up of EC and smooth muscle cells, which are recruited mainly through the Tie-2 and angiopoietin-1 (Ang-1)

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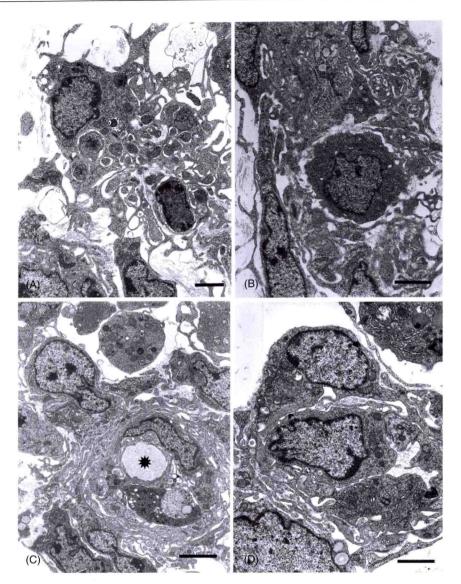


Figure 1.1 Electron micrographs of vasculogenic areas in the chick embryo chorioallantoic membrane (CAM). Poorly differentiated mesenchymal cells exhibiting highly irregular surface profiles and cytoplasmic processes closely interdigitating with similar projections of neighboring cells are documented at day 8 of incubation. In C, an initial vascular lumen (asterisk) is observable. Micrograph in A is taken from an erythropoietin-stimulated CAM. Part A reproduced from Crivellato et al. [21] with permission from Nature. Bars $= 2 \mu m$.

receptor-ligand pair, although neuropilins and the Notch pathway are also involved in mural cell formation.

VEGF-A deficient embryos die *in utero* between days 8.5 and 9.5 postcoitum and their primitive vascular structures are severely defective, while VEGF receptor-2 (VEGFR-2) deficient mice die early as a result of blocked

migration of angioblasts to the initial sites of vasculogenesis. Embryos lacking VEGFR-2 die *in utero* between days 8.5 and 9.5 postcoitum and show no development of any blood vessels or hematopoietic cells. The loss of both lineages suggests that VEGFR-2 is required for hemangioblast development.