Inflammatory Diseases of Blood Vessels provides a comprehensive overview of the science and clinical consequences of vascular inflammation in health and disease. In recent years, considerable progress has been made in understanding different forms of vasculitis. Investigation of pathogenesis of vascular inflammation has led to improved treatments and outcomes. Surgical and transplant procedures have improved in parallel with medical therapies. These areas are extensively examined in this new edition.

Inflammatory Diseases of Blood Vessels is an excellent resource for a broad readership, including clinicians, investigators and their support teams in numerous specialties e.g., rheumatology, immunology, cardiology, cardiovascular surgery, pulmonary medicine, nephrology, pathology, vascular biology, embryology and imaging.

Titles of related interest
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Inflammatory Diseases of Blood Vessels
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

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

Jörg J. Goronzy MD, PhD
Professor of Medicine
Department of Medicine
Stanford University School of Medicine
Stanford, CA, USA

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Contents

List of Contributors, vii
Preface, xiv

Part I Biology of Blood Vessels and Mechanisms of Vascular Inflammation

1 Vascular Development, 3
   Domenico Ribatti and Enrico Crivellato
2 Vascular Repair, 15
   Christian Troidl, Kerstin Troidl, Georg Jung, Thomas Schmitz-Rixen and Wolfgang Schaper
3 Leukocyte Trafficking, 28
   Braedon McDonald and Paul Kabes
4 Dendritic Cells and Vascular Inflammation, 39
   Cornelia M. Weyand
5 T Cells and Vascular Inflammation, 50
   Jörg J. Goronzy
6 Autoantibodies and Vascular Inflammation, 61
   Abraham Rutgers, Jan S.F. Sanders, Jan Willem Cohen Tervaert and Cees G.M. Kallenberg
7 Neutrophils and Vascular Inflammation, 71
   Matthew David Morgan and Caroline O.S. Savage
8 Cytokines and Vascular Inflammation, 82
   Maria C. Cid, Marc Corbera-Bellalta, Ester Planas-Rigol, Ester Lozano, Georgina Espígol-Frigolé, Ana García-Martínez, José Hernández-Rodriguez and Marta Segarra
9 Oxidative Stress and Vascular Inflammation, 94
   David G. Harrison
10 Hemostasis and Vascular Inflammation, 105
   Lawrence Leung and John Morser
11 Animal Models of Vasculitis, 115
   Masato Nose
12 Arteries, Smooth Muscle Cells and Genetic Causes of Thoracic Aortic Aneurysms, 126
   Amy J. Reid and Dianna M. Milewicz
13 Innate Immunity in Atherosclerosis, 136
   Shuang Chen, Prediman K. Shah and Moshe Arditi
14 Adaptive Immunity in Atherosclerosis, 147
   Jan Nilsson

Part II Primary Autoimmune Vascular Disease

15 Historical Perspectives of Vasculitis, 161
   Eric Matteson
16 Approach to the Differential Diagnosis of Vasculitis, 170
   Eamonn S. Molloy and Carol A. Langford
17 Imaging of Medium and Large Vessels (CT/MR/PET), 184
   Thorsten Alexander Bley
18 Kawasaki Disease, 194
   Rae S.M. Yeung
19 Henoch–Schönlein Purpura, 205
   Philip J. Hashkes and Alexandra Villa-Forte
20 Polyarteritis Nodosa, 217
   Eli M. Miloslavsky and John H. Stone
21 Microscopic Polyangiitis, 227
   Coen A. Stegeman
22 Granulomatosis with Polyangiitis (Wegener’s), 238
   Gary S. Hoffman, Carol A. Langford and Ulrich Specks
23 Eosinophilic Granulomatosis with Polyangiitis (Churg–Strauss Syndrome), 252
   Christian Pagnoux and Loïc Guillevin
vi

Contents

24 Giant Cell Arteritis, 263
Cornelia M. Weyand and Jörg J. Goronzy

25 Takayasu's Arteritis, 276
Kathleen Maksimowicz-McKinnon and Gary S. Hoffman

26 Behçet's Syndrome, 289
Yusuf Yazici, Ismail Simsek and Hasan Yazici

27 Cogan's Syndrome, 299
Rex M. McCallum and E. William St. Clair

28 Idiopathic Cryoglobulinemic Vasculitis, 312
Benjamin Terrier and Patrice Cacoub

29 Primary Central Nervous System Vasculitis, 322
Rula A. Haij-Ali and Leonard H. Calabrese

30 Single Organ Vasculitis, 332
José Hernández-Rodríguez and Gary S. Hoffman

31 Primary Cutaneous Vasculitis (Small Vessel Vasculitis), 343
Jeffrey P. Callen

32 Buerger's Disease (Thromboangiitis Obliterans), 351
Ahmet Ruchan Akar and Serkan Durdu

Part III Secondary Causes of Vasculitis

33 Virus-Associated Vasculitides, 369
Dimitrios Vassilopoulos and Leonard H. Calabrese

34 Drug-Induced Vasculitis, 380
Peter A. Merkel

35 Rheumatoid Vasculitis, 392
Kimberly P. Liang, Carl Turesson and Larry W. Moreland

36 Systemic Sclerosis with Vascular Emphasis, 403
Nezam Altorok, Omar R. Kahaly and Bashar Kahaleh

37 Vasculitis and Sjögren's Syndrome, 412
George E. Fragioulis and Haralampos M. Moutsopoulos

38 Vasculitis in Systemic Lupus Erythematosus, 419
Ricardo Garcia and Andras Perl

39 Vasculitis in the Idiopathic Inflammatory Myopathies, 433
Frederick W. Miller and Chester V. Oddis

40 Vasculitis and Relapsing Polychondritis, 441
Tanaz A. Kermani and Kenneth J. Warrington

41 Systemic Vasculitis in Sarcoidosis, 451
Alexandra Villa-Forte and Gary S. Hoffman

42 Vasculitis as a Paraneoplastic Syndrome and Direct Tumor Invasion of Vessels, 460
Claire E. Barber and Simon Carette

Part IV Recognizing Risks and Treating Damage from Vasculitis

43 Cholesterol and Modifications of Cholesterol in Rheumatic Disorders, 475
Jan Willem Cohen Tervaert

44 Prevention and Treatment of Medical Complications, 484
Atul Khasnis and Carol A. Langford

45 Ophthalmic Risks and Complications Associated with the Treatment of Systemic Vasculitis, 495
Steven Yeh and James T. Rosenbaum

46 Subglottic Stenosis of Granulomatosis with Polyangiitis (Wegener's), 505
Rahul Seth and Daniel S. Alam

47 Sinonasal Manifestations of Granulomatosis with Polyangiitis (Wegener's), 512
Daniel S. Alam, Rahul Seth and Raj Sindwani

48 Neurologic Damage of Vasculitis, 521
C. David Lin

49 End-Stage Renal Disease and Vasculitis, 534
Kirsten de Groot and Charles Pusey

50 Cardiothoracic Surgery for Takayasu's Arteritis and Giant Cell Arteritis, 544
Turki Albacker and Lars Svensson

51 Peripheral Vascular Surgery for Large Vessel Vasculitis, 558
Ravi R. Rajani and Vikram S. Kashyap

Index, 567
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
Hôpital 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, FRCP
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 MD
Senior Consultant
Vasculitis Research Unit, Department of Systemic Autoimmune Diseases
Hospital Clinic;
Associate Professor
University of Barcelona
Institut d’Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS)
Barcelona, Spain
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 Clinic  
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 García 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 Clinic  
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

José Hernández-Rodríguez MD
Senior Specialist
Vasculitis Research Unit, Department of Autoimmune and Systemic Diseases
Hospital Clinic, University of Barcelona
Institut d’Investigacions Biomèdiques August Pi i Sunyer (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
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
Staff
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 MD
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
List of Contributors

Kathleen Maksimowicz-McKinnon DO
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, FACP
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

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 Clinic
Institut d’Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS)
Barcelona, Spain

Charles Pusey DSc, FRCP
Professor
Renal Section
Imperial College London
London, UK

Ravi R. Rajani MD
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, Germany

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
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 Institute  
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, Los Angeles, CA, USA

**Ismail Simsek MD**
Associate Professor  
Department of Medicine  
Division of Rheumatology  
Gülgüne 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

**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, FRCP**
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 clinician-scientists 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
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 embryonic 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 pre-cardiac 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 β1 (TGF-β1) 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)
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 μm.

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.
It has been established that vasculogenesis occurs also in postnatal life, as “postnatal vasculogenesis,” which is de novo vessel formation by *in situ* incorporation, differentiation, migration and/or proliferation of bone marrow-derived endothelial precursor cells (EPC).

The term angiogenesis, applied to the formation of capillaries from pre-existing vessels, is based on endothelial sprouting or intussusceptive microvascular growth (IMG) (Figure 1.2). With IGM, the capillary network increases its complexity and vascular surface by inserting a

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**Figure 1.2** Electron micrographs of angiogenic areas in the chick embryo CAM. In A and B, sprouting processes penetrate into the perivascular mesenchyme at day 10 of incubation and show slit-like lumina (solid asterisks). Empty asterisks indicate the vascular lumen. The growing front of the vessel (sprouting endothelial tip) is devoid of pericytes. C and D depict the angiogenic process of intussusceptive growth. In C, an intravascular endothelial pillar (solid asterisk) is observable. In D, taken from an erythropoietin-stimulated CAM, the process of longitudinal segmentation of the original capillary into two newly formed blood vessels (empty asterisks) is completed. The perivascular stroma is penetrated deeply into the original lumen, pushing the endothelial lining inward and causing the formation of two distinct new vessels. Part D reproduced from Crivellato et al. [21] with permission from Nature. Bars, A–C = 1 μm; D = 3 μm.
multitude of transcapillary pillars, through four consecutive steps:
1. Creation of a zone of contact between opposite capillary walls;
2. Reorganization of the intercellular junctions of the endothelium, with central perforation of the endothelial bilayer;
3. Formation of an interstitial pillar core; and
4. Subsequent invasion of the pillar by cytoplasmic extensions of myofibroblasts and pericytes, and by collagen fibrils.

It is thought that the pillars then increase in diameter and become a capillary mesh. The majority of vessels of the developing embryo are formed through angiogenesis. Sprouting capillaries are guided by specialized EC called tip cells, which express vascular VEGFR-2, and are located at the leading front of growing vessels and continually extend and retract numerous filopodia, thus defining the direction in which the new vascular sprout grows.

The gross anatomy of the vascular system is characterized by highly reproducible branching patterns, with major and secondary branches forming at precisely designed sites and with organ-specific vascular architectures. For example, in lung development, there is a close structural expansion of lung parenchyma and lung vascularization. Developing lung vessels come into increasing proximity to the epithelial cells, which leads to the formation of functional exchange regions of the alveolus. Otherwise, in brain development vascular endothelial cells penetrate in the brain anlagen recruited by endothelial cell mitogens released by neuroblasts. EC, in turn, release factors that support neuron development. Flow is critical to maintain vessel branches and a process termed intussusceptive branching remodeling has been described and shown to operate in changing branching angles.

Pruning involves the removal of supernumerary blood vessels from redundant channels. It results in reduction of the number of vascular branches and vascular density. This is one of the mechanisms allowing the vascular system to adapt to the changing hemodynamic and metabolic influences and to create a more efficient angioarchitecture.

Blood flow generally ceases in these excess capillaries, the lumens are obliterated and the EC retract toward adjacent capillaries. Remodeling is known to involve the growth of new vessels and the regression of others as well as changes in the diameter of vessel lumen and vascular wall thickness. Some vessels may fuse to form a larger one, such as fusion of the paired dorsal aortae, or they may establish new connections like the coronary vessels which connect to the aorta. It is likely that only a smaller number of embryonic blood vessels persist into adulthood, with most capillaries of the embryonic plexus regressing at some time in development (Figure 1.3).

![Figure 1.3](image-url)
CHAPTER 1 Vascular Development

Endothelial cell heterogeneity and organ specificity

EC form a continuous monolayer between the blood and the interstitial fluid. The EC surface in an adult human is composed of approximately $6 \times 10^{13}$ cells and covers a surface area of approximately 7 m$^2$ [2].

The endothelial lining synthesizes, metabolizes, and releases a number of humoral and hormonal substances which act on adjacent cell systems or on some further distant structures. Quiescent EC generate an active antithrombotic surface through the expression of tissue factor pathway inhibitors: heparan sulfate proteoglycans that can interfere with thrombin-controlled coagulation, and thrombomodulin that facilitates transit of plasma and cellular constituents throughout the vasculature. Perturbations induce EC to create a prothrombotic and antifibrinolytic microenvironment.

Cessation of blood flow into a capillary segment causes vessel regression, whereas an increase in pressure may induce local recruitment of smooth muscle cells and lead to a differentiation of a capillary into an artery or vein.

There are differences between the endothelium of different species, between large and small vessels, and between EC derived from various microvascular beds and/or organs. Such differences have been ascribed to genetic predisposition and microenvironmental influences [3]. These latter include extracellular matrix components and locally produced growth factors, interactions with neighboring cells and mechanical forces. Interactions between the different microvascular cells and surrounding stromal cells have a major role in determining vascular structure and function. These interactions may occur through the release of cytokines and the synthesis and organization of matrix proteins on which the endothelium adheres and grows. The organ microenvironment can directly contribute to induction and maintenance of the angiogenic factors. The different angiogenic stages of the vasculature are precisely regulated by microenvironmental balance of proangiogenic and antiangiogenic molecules. Moreover, EC release in a paracrine fashion and express on the cell surface many signaling molecules that can affect the density of developing tissue cells intimately associated to them. This might be of crucial significance during organ formation. It has been speculated that EC–tissue interactions may “offer the opportunity to control organ development and growth systematically, rather than individually for each organ” [4].

EC and organ-specific cells interact with each other continuously, and this interaction is mutual in that EC and organ-specific cells exchange signals, allowing the generation of a functional organ provided with an endothelium adjusted to the needs of the adjacent tissue cells.

The introduction of electron microscope in the 1950s revealed that EC lining the capillaries of different organs are morphologically distinct. For instance, the vasculature of liver, spleen and bone marrow sinusoids is highly permeable because vessels are lined by discontinuous EC that allow cellular trafficking between intercellular gaps. Conversely, EC capillaries in the brain and retinal capillaries, dermis, bone tissue, skeletal muscle, myocardium, testes and ovaries are continuous. In the brain capillaries, the endothelium participates in the formation of the blood–brain barrier (BBB). EC in endocrine glands and kidney are fenestrated. Fenestration in the capillary endothelium seems to depend on VEGF-A secretion [5]. EC heterogeneity is also evident in individual organs. For example, the kidney contains fenestrated EC in its peritubular capillaries, discontinuous EC in its glomerular capillaries and continuous EC in other regions.

A novel angiogenic factor selective for endocrine gland endothelium known as EG-VEGF has been shown to induce fenestrations in capillary vessels [6]. EG-VEGF is unrelated to the VEGF family and acts via G-protein-coupled receptors.

The phenotype of EC is unstable and likely to change when they are removed from their microenvironment. The principal problem in defining organ-specific endothelial markers is the impurity of the EC used for in vitro analysis and the lack of organ-specific markers of EC in culture.

The presence of a unique organelle discovered by Weibel and Palade in 1964 was found to be an important marker to identify bona fide EC. Antigens are differentially expressed on EC of certain organs and tissues [7]. The von Willebrand factor (vWF) marker is widely but not uniformly expressed on EC. It is expressed at higher levels on the venous rather than on the arterial side of the capillary circulation, and in human tissues in the endothelium of larger vessels and in the adult endocardium. It is largely absent from sinusoidal EC.

Microvascular endothelium is more prone than large vascular endothelium to form capillary-like structures when seeded on extracellular matrix preparations and to respond to certain cytokines.
EC alter their morphology in response to angiogenic factors. There is an increase in the expression of endoplasmic reticulum and Golgi apparatus, together with changes in mitochondrial size and number. The EC surface forms finger-like protrusions on the abluminal side adjacent to the basement membrane, intercellular gaps appear and the complex of EC and pericytes retracts.

### Key Concepts: Microvascular beds

- Endothelium derived from various microvascular beds and organs displays tissue-specific differences.
- Such differences depend on genetic and microenvironmental factors, including extracellular matrix components, locally produced cytokines and growth factors, interactions with neighboring cells and mechanical forces.
- EC express histogenetic and organogenetic properties. They release in a paracrine fashion and express on the cell surface many signaling molecules that can affect the destiny of developing tissue cells intimately associated with them.

Arterial and venous endothelial cell distinctions

Arteries and veins are structurally and functionally distinct. Classically, it was believed that EC of the primary capillary plexus constitute a rather homogeneous group of cells and that differentiation into arteries and veins occurred because of the influence of hemodynamic forces.

Labeling experiments in zebrafish indicate that the arterial and venous fate of endothelial precursors may be determined before the formation of the blood vessels. The discovery that members of the ephrin Efn family are differentially expressed in arteries and veins from very early stages of development was one of the first indications that artery–vein identity is intrinsically programmed. Efn-B2 expression cannot be seen in the arterial part of the extraembryonic vascular plexus even though the expression of NRP is already segregated. These observations suggested that Efn-B2 is a relatively late marker of arteries.

Notch signaling is required for remodeling the primary plexus into the hierarchy of mature vascular beds and maintaining arterial fate, and is essential for the homeostatic functions of fully differentiated arteries. Genetic studies have suggested a key role for Notch signaling, downstream of VEGF-A, in specifying arterial versus venous fate. During vascular development, defects in signaling through the Notch pathway, which comprises ligands such as Jagged-1, Jagged-2 and Delta-like-4, and receptors, such as Notch-1, Notch-2 and Notch-4, disrupt normal differentiation into arteries or veins, resulting in loss of artery specific markers [9].

Shear stress is considered to be the driving force behind arteriogenesis, which operates to increase the diameter of those vessels forced to handle more flow and hence subjected to an elevated shear stress. Le Noble et al. [10] used a time-lapse video microscopy system and examined arterial–venous differentiation in the developing yolk sac of the chick embryo. They observed that prior to the onset of flow, EC expressing arterial and venous specific markers are localized in a posterior–arterial and anterior–venous pole. Ligation of one artery by means of a metal clip, lifting the artery, and arresting arterial flow distal to the ligation site could morphologically transform the artery into a vein. When the arterial flow was restored by removal of the metal clip, arterial makers were reexpressed, suggesting that the genetic fate of arterial EC is plastic and
CHAPTER 1 Vascular Development

Key Concepts: Arteries and veins
- In zebra fish, arterial and venous fate of endothelial precursors may be determined before the formation of the blood vessels.
- Efn-B2, a member of the ephrin family, is expressed in arterial endothelial cells and the principal receptor for Efn-B2, Eph-B4, displays a reciprocal expression pattern in embryonic veins.
- In the chick and mouse, specific markers for the arterial system include neuropilin-1 (NRP-1) and members of the Notch family, Notch-3, DDL4 and GRIDLOCK (Grl).
- Notch-1, Notch-2 and Notch-4 receptors bind to ligands such as Jagged-1, Jagged-2 and Delta-like-4.
- Shear stress is considered to be the driving force behind arteriogenesis.

Lymphatic capillaries
Structural features of lymphatic capillaries include:
- Their endothelium has an extremely attenuated cytoplasm, except in the perinuclear region;
- 5′-nucleotidase activity of the endothelium;
- Tight and adherent junctions are not frequently seen;
• A discontinuous basement membrane, expressing collagen type IV and laminin;
• The absence of pericytes;
• Lymphatic endothelial cells (LEC) are closely linked to surrounding connective tissue by fine (10–12 nm) anchoring filaments. These filaments are attached to the cell's abluminal surface and extended deeply into the connective tissue, firmly attaching endothelium to extracellular matrix fibres.

More than 10 years ago, highly specialized and specific antibodies against LEC have been identified. Prospero-related homeobox-1 (Prox-1) is a homeobox gene, expressed only by LEC. Studies of mice deficient in Prox-1 revealed that these mice were unable to develop a lymphatic vascular system and that Prox-1 was required for a subset of venous EC in the embryonic cardinal veins to migrate out and to form the initial lymphatic vessels during early embryogenesis. Sox-1 has been identified as a novel protein that trans-activates Prox-1 expression in LEC of mice. Lymphatic vessel endothelial hyaluronan receptor-1 (LYVE-1) is a homolog of the CD44 glycoprotein expressed by LEC. In normal tissues, LYVE-1 is highly expressed in lymphatic vessels of the intestinal villi, dermis, lymph nodes, vermiform appendix and stomach. Podoplanin is an integral plasma membrane protein primarily found on the surface of rat podocytes expressed by LEC, but not by blood vessels. Podoplanin was first used to identify lymphatic vessels, but it was later shown that it is a useful marker for some malignant tumors. D2-40, which recognizes the formalin-resistant epitope of podoplanin, is the most specific and sensitive marker of LEC. Desmoplakin, a protein of the junctional system, connecting very flat LEC, is a marker for small lymphatic vessels and is not expressed by larger lymphatic collecting ducts, including the thoracic duct.

Comparative microarray analyses of specific transcriptomes of LEC versus vascular EC have revealed a number of novel differentially expressed genes, although approximately 98% of genes are expressed at comparable levels in those genetically closely related cell types. Transcriptional profiling studies revealed increased expression of several extracellular matrix and adhesion molecules in vascular EC, including versican, collagens, laminin and N-cadherin, and of the growth factor receptors endoglin and VEGFR-1. Among several genes with specific expression in LEC, VEGFR-3, Prox-1, LYVE-1 and podoplanin should be mentioned.

VEGF-C and VEGF-D have a crucial role in lymphangiogenesis through the activation of VEGFR-3. Selective activation of VEGFR-3 in transgenic mice expressing VEGF-C or VEGF-D is sufficient to induce lymphangiogenesis without major effects on angiogenesis. Ang-2 is expressed by LEC and is involved in the normal development of the vascular system. Ang-2 null mice show disorganization and hyperplasia of the lymphatic capillaries associated with changes in the media of collecting ducts and lymphedema.

There was accumulated evidence that supports the proliferative activity of LEC in prenatal and/or postnatal life, both in physiologic and pathologic conditions. Based on these observations, it was hypothesized that lymphatic vessel growth and/or growth factors that induce lymphangiogenesis, such as VEGF-C and VEGF-D, platelet-derived growth factor-BB (PDGF-BB) and hepatocyte growth factor may be inhibited by specific antibodies.

Tumor lymphangiogenesis is stimulated by VEGF-C and VEGF-D, and both lymphangiogenesis and lymph node metastases are inhibited by VEGF-C and VEGF-D antagonists. Numerous studies have demonstrated a direct correlation between VEGF-C and VEGF-D expression in human cancer and tumor metastasis, suggesting that lymphangiogenesis has an important role in promoting tumor metastasis.

LEC-specific markers have multiple functions in physiologic and pathologic conditions, are helpful to identify tumor tissue changes related to lymphangiogenesis and to search for a rational therapeutic approach. Some questions regarding tumor lymphangiogenesis remain unanswered, including the mechanisms of migration and invasion of tumor cells into the lymphatic vessels, which is the key factor for tumor metastasis, and the differences between pre-existing and newly formed lymphatic vessels. The immunohistochemical application of podoplanin has been used to investigate the relationship between lymphatic vessel density and lymph node metastasis, for tumor cell detection in lymphatic vessels and for the diagnosis of some vascular tumors.

Key Concepts: Lymphatic capillaries
• Lymphatic capillaries have an extremely attenuated, 5′-nucleotidase-positive endothelium which exhibits few tight and adherent junctions and lines a discontinuous basement membrane, expressing collagen type IV and laminin.
CHAPTER 1 Vascular Development

- Pericytes are absent and anchoring of lymphatic endothelial cells (LEC) to the surrounding connective tissue is effected by fine (10–12 nm) filaments.
- Specific gene and molecular marker profile is expressed by LEC. The homeobox gene prospero-related homeobox-1 (Prox-1) is expressed only by LEC.
- Molecular markers for LEC include the lymphatic vessel endothelial hyaluronan receptor-1 (LYVE-1), podoplanin, D2-40 and desmoplakin.

Blood–brain barrier

The existence of a specialized barrier at the level of cerebral vessels was first postulated in 1900 by Lewandowsky, based on the observation that the intravenous injection of cholic acids or sodium ferrocyanide had no pharmacologic effects on the central nervous system, whereas neurologic symptoms occurred after intraventricular application of the same substances. Lewandowsky introduced the term blood–brain barrier (BBB) to describe this phenomenon.

The BBB is a complex cellular system of EC, astroglia, pericytes and neurons, to establish a functional “neurovascular unit.” Brain EC have particularly complex tight junctions (comprising several classes of transmembrane molecules, including occludins and claudins, which interact with transmembrane proteins of adjacent EC), and few pinocytotic vesicles that together act as a physical barrier. Moreover, they are endowed with a variety of transport proteins, such as transferrin receptors, gamma-glutamyl transpeptidase, Glut-1 and P-glycoprotein. Establishing the barrier is accompanied by further changes in the phenotype of the brain EC, such as upregulation of the HT7-antigen/basigin, or downregulation of the MECA-22 antigen.

Astrocytes project their endfeet tightly to cerebral EC, and both influence and conserve the barrier function. Early tissue culture studies have demonstrated that conditioned medium by astrocytes can induce tight junction formation in capillary EC. Subsequent characterization of astrocyte–endothelial interactions have identified a number of factors that can modulate the expression of tight junctions and/or transendothelial permeability, such as TGF-β1, fibroblast growth factor-2 (FGF-2), glial-derived neurotrophic factor (GDNF) and Ang-1, which induce BBB properties such as high electrical resistance and reduced permeability in EC. The effects between EC and astrocytes are reciprocal, with alterations between the two cell types leading to alterations in astrocyte shape and growth.

Pericytes limit the transport across the endothelial barrier and release Ang-1 and TGF-β1 which induce and maintain critical BBB functions. More recently, it has been demonstrated in the human fetal telencephalon that growing microvessels are formed by a pericyte-driven angiogenic process in which EC are preceded and guided by migrating pericytes. The basement membrane lies beneath EC, envelops pericytes and comes in contact with the subjacent and tightly adherent glial processes.

The features of barrier vessels are acquired during the embryonic development by progressive decrease in their permeability, by structural modifications involving both endothelial tight junctions and glial perivascular endfeet differentiation, and by expression of specific endothelial transporters and antigens. It is well accepted that the vessel morphofunctional maturation is coupled with the expression of tight junction proteins, such as zonula occludens-1 (ZO-1), and of the glial end-feet proteins, such as aquaporin 4 (AQP4) and glial fibrillary acidic protein (GFAP).

The loss of the BBB is commonly observed when tumors invade and grow into the brain. It has been attributed to the generation of neovasculature with fenestrated endothelium, opened intercellular junctions and incomplete basement membrane.

Key Concepts: The blood–brain barrier

- The blood–brain barrier (BBB) is a neurovascular unit shaped by neurons, endothelial cells, astrocyte end-feet and pericytes.
- Brain EC express distinct transmembrane molecules, such as occludins and claudins, as well as transport proteins, such as transferrin receptors, gamma-glutamyl transpeptidase, Glut-1 and P-glycoprotein.
- BBB properties are molded by astrocyte–endothelial interactions which modulate the expression of tight junctions and/or transendothelial permeability, through TGF-β1, FGF-2, GDNF and Ang-1 signaling.
- Ang-1 and TGF-β1 are also released by pericytes that function as endothelial tube guides.
- Maturation of the BBB is coupled with the expression of tight junction proteins, such as zonula occludens-1 (ZO-1), and of the glial end-feet proteins, such as aquaporin 4 (AQP4) and glial fibrillary acidic protein (GFAP).
Implications of vascular diversity for disease expression and therapy

**Demonstrated or accepted**

The characteristics of the endothelium – in addition to environmental factors, which also include the type of local blood flow – are of critical relevance in determining disease susceptibility. For instance, it has long been recognized that systemic vasculitides impact distinct segments and branches of the vascular tree. New findings indicate the importance of smooth muscle cells and dendritic cells in the pathogenesis of systemic vasculitides. Dendritic cells are localized at the adventitia-media border of the normal medium-sized arteries and expressed a series of Toll-like receptors in a vessel-specific pattern. Whereas necrotizing sarcoid granulomatosis, Takayasu's arteritis, and giant cell arteritis cause macrovascular compromise, cryoglobulinemic vasculitis affects microcirculation. The pulmonary vascular bed has intensely been investigated in relation to its structural and functional differentiation into segmental compartments. Remarkably, selective location of Weibel–Palade bodies within EC of arteries and arterioles but not capillaries has been recognized. Thus, the different EC subpopulations and their surrounding microenvironment may represent important factors in pulmonary vasculitides. Selective involvement of the skin vascular bed has been recognized in mouse models of diffuse sepsis [11]. In these studies, polymerase chain reaction (PCR) analysis evidenced increased mRNA levels of EC activation markers, such as P-selectin, endothelial intercellular adhesion molecule-1 (ICAM-1) and plasminogen activator inhibitor-1 (PAI-1), which were restricted to the skin vasculature whereas brain, heart and lung vessels appeared unaffected. Even thrombotic or hemorrhagic states recognize specific vascular beds as the sites of disease occurrence. It is the endothelium, indeed, that synthesizes a large number of anticoagulants and procoagulants, which are unevenly expressed in the vasculature. The prothrombotic factors include tissue factor; vWF; protease-activated receptors (PAR-1 and PAR-4), serving as thrombin receptors; thromboxane A2 and platelet-activating factor; PAI-1, which inhibits fibrinolysis; and adhesive molecules, which attract leukocytes to the endothelial surface. In contrast, there are antithrombotic factors consisting of tissue factor pathway inhibitor; protein C and protein S; thrombomodulin; heparan; nitric oxide synthetase; prostacyclin; and members of the plasminogen–plasmin system. Data indicate that hemostasis is differentially regulated between different vessel types and organs, and most hyper- and hypocoagulable states – including those associated with a systemic imbalance in anticoagulants and procoagulants – lead to local thrombotic lesions or hemorrhagic complications.

The tumor growth-stage-specific efficacy of drugs suggests that qualitative differences exist in the tumor vasculature at different stages [12]. Distinct tumor vessels may need specific vascular growth factors and cytokines at defined tumor stages. Remarkably, only the mother vessel and the glomeruloid microvascular proliferation types of tumor vessels require VEGF-A for their maintenance, whereas the other types of tumor vessels have acquired VEGF-A independence. This fact may explain the limited success of anti-VEGF-A/VEGFR therapy in human cancer.

Finally, there are vascular tumors that derive from EC and express unique autonomous properties. In infantile hemangioma, a benign vascular lesion of EC origin, molecular profiling has provided evidence for a placental derivation of EC [13]. Kaposi's sarcoma, an AIDS-defining vascular tumor, involves a phenotypically unique spindle cell that appears to derive from lymphatic EC [14].

**Hypothetical**

In speculative terms, the phenotypic heterogeneity of EC in the different vascular beds may have profound implications in disease natural history. As previously mentioned, vWF, P-selectin and factor VIII are located within Weibel–Palade bodies in pulmonary arteries and arterioles, but these prothrombotic and proinflammatory organelles are absent in capillaries. Despite the absence of Weibel–Palade bodies, pulmonary capillaries express vWF, P-selectin and factor VIII. This distinct segmental organization may have important implications in the mechanisms of pulmonary thrombosis and neutrophil trafficking during pneumonia.

Coronary artery disease is an example of a disease that targets the arterial EC. In response to hypercholesterolemia, myocardial EC increase the expression of adhesion molecules, which leads to intimal thickening and plaque formation. Indeed, atherogenic oxidized low density lipoprotein (LDL) preferentially induces cellular proliferation and adhesion pathway genes in human coronary artery EC, whereas in human saphenous vein EC, focal adhesion, inflammatory response, apoptosis and NFκB pathway genes are downregulated [15]. Furthermore, molecular signals, such as tumor necrosis factor...
α (TNFα) and interleukin 1β (IL-1β) activation, induce apoptosis and downregulate anti-inflammatory genes in human coronary artery EC, whereas both antiapoptotic and antiatherogenic genes are induced in human saphenous vein EC. Long-term exposure to systemic disease conditions can also alter the basal gene expression pattern and functional behavior of EC in an EC subset-specific manner. This may have important implications in metabolic diseases such as diabetes. Using the type 2 diabetic Goto-Kakizaki rat model, it has been demonstrated that myocardial microvascular EC express decreased protein levels of VEGF, VEGFR-1 and VEGFR-2, and exhibit decreased phosphorylation of the receptors compared with their healthy controls, whereas aortic EC from the diabetic rats do not exhibit such an altered phenotype [16]. Selective EC activation may be responsible for the development of some brain pathologies. For instance, BBB dysfunction may be linked with Alzheimer’s disease. Brain microvessels appear thin and tortuous and their basement membrane is thickened and vacuous.

Local blood flow is an important factor for EC stability in a given vascular segment. EC lack preferential cell alignment and often show a polygonal morphology in zones of disturbed vascular flow in regions susceptible to atherogenesis such as the aortic arch or heart valves. Analysis of EC gene expression at such locations exhibits an upregulation of genes associated with endoplasmic reticulum processing of proteins, endoplasmic reticulum stress and unfolded protein response. This genetic profile may, in turn, contribute to enhanced endothelial permeability via focally increased EC proliferation in these regions [17,18]. Studies performed in the swine aortic valve have shown that the endothelium of the normal aortic side was phenotypically distinct from that of the ventricular side, expressing a balance of pro- and anti-inflammatory transcripts and a procalcified profile [19]. Transcript profiling of valve endothelial populations demonstrated that the susceptible aortic side was much more sensitive to 2 weeks of hypercholesterolemic diet than the ventricular side [20].

Clinical implications
- EC diversity has crucial implications for the susceptibility to vascular disease.
- Smooth muscle cells and vascular dendritic cells contribute to vascular diversity.

- Systemic vasculitides and diffuse septic reactions target distinct segments and branches of the vascular tree as well as selective vascular beds.
- Thrombotic or hemorrhagic conditions recognize specific vascular beds.
- Vascular diversity has potential implications for the pathogenesis of metabolic diseases like atherogenesis and diabetes.
- EC heterogeneity is recognizable in the tumor vasculature at different stages, a situation that may profoundly affect the efficacy of tumor treatment.

Conclusions

Blood vessels develop early during embryo life by vasculogenesis and represent an essential component of all organs. Both genetic and epigenetic factors are involved in blood vessel formation. They arrange into a sophisticated, highly branched sequence of vascular channels lined by EC that express a precise spatial and temporal hierarchy. This segmental heterogeneity implies a local multiplicity of structural and functional diversifications. Recent data are consistent with the assumption that EC phenotypes differ in space and time providing a foundation for the identification of specific molecular signatures to a given microvascular bed. As clearly expressed by Barnes et al. [13], “at any given point in time, no two ECs in the body are phenotypically identical.” In addition, a unique EC type, expressing the basic structural and molecular profile of vascular EC but also exhibiting distinct morphologic and functional characters, lines lymphatic vessels.

EC diversity has crucial implications for the development of vascular diseases. Systemic vasculitides and diffuse septic reactions target distinct segments and branches of the vascular tree as well as selective vascular beds. Even thrombotic or hemorrhagic conditions recognize specific vascular beds as the sites of disease occurrence. Potential implications for the pathogenesis of vascular metabolic diseases like atherogenesis and diabetes are also strong. EC differences exist in the tumor vasculature at different stages, a situation that may profoundly affect the efficacy of tumor treatment.

In conclusion, understanding how early, basic EC can differentiate into a specialized assortment of organ- and tissue-associated EC is essential for appreciating the complexity of vascular disorders and for establishing critically designed strategies of treatment for vascular diseases.
Indeed, identification of vascular-bed-specific molecular profiles should facilitate the development of molecular imaging for diagnosis and surveillance as well as the improvement of “intelligent” molecules targeting selected vascular districts.

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