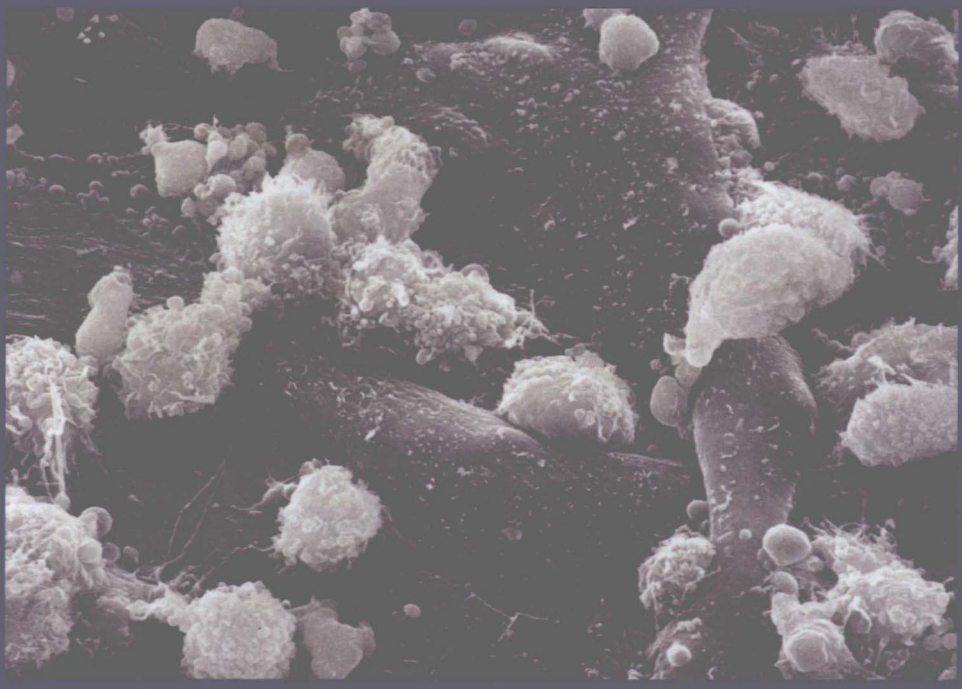
The Blood-Brain Barrier in Health and Disease

Volume 2: *Pathophysiology and Pathology*



Editor
Katerina Dorovini-Zis

CRC Press
Taylor & Francis Group
A SCIENCE PUBLISHERS BOOK

The Blood-Brain Barrier in Health and Disease

Volume 2: Pathophysiology and Pathology

Editor

Katerina Dorovini-Zis

Professor of Pathology & Laboratory Medicine
The University of British Columbia
Vancouver General Hospital
Vancouver, BC
Canada

CRC Press
Taylor & Francis Group
Boca Raton London New York

CRC Press is an imprint of the
Taylor & Francis Group, an **informa** business
A SCIENCE PUBLISHERS BOOK

Cover illustration provided by the editor of the book, Prof. Katerina Dorovini-Zis

CRC Press
Taylor & Francis Group
6000 Broken Sound Parkway NW, Suite 300
Boca Raton, FL 33487-2742

Printed on acid-free paper
Version Date: 20150825

International Standard Book Number-13: 978-1-4987-2708-2 (Hardback)

The Blood-Brain Barrier in Health and Disease

Volume 2: Pathophysiology and Pathology

Preface to Volume 2

Ο βίος βραχύς, η δε τέχνη μακρή
Life is short and art long

Hippocrates (c. 460-373 BC)
Aphorisms

The blood-brain barrier is a biological barrier that separates the brain from the blood and serves to facilitate the entry of essential nutrients into the brain while protecting it from unwanted and harmful substances and cells circulating in the blood. The endothelial cells that line the cerebral blood vessels have been recognized as the anatomical substrate of the blood-brain barrier. Their structural and functional integrity is the sine qua non of central nervous system homeostasis and neuronal function. For a long time since the first demonstration of a physical barrier at the blood-brain interface, the unassuming endothelial cells, so inconspicuous when brain sections stained with conventional dyes are viewed under the light microscope, were considered a little more than an unimpressive cell layer lining the vascular lumen. The past 50 years and in particular the last three decades have witnessed a great expansion of our knowledge of the complex structure, biology and function of the blood-brain barrier. As a result of fast-paced discoveries facilitated by the development of new *in vivo* and *in vitro* experimental tools, the cerebral endothelium has been propelled to a prominent status and is presently an attractive research subject in neurosciences. As a metabolically active cell it controls the traffic of substances into and out of the brain by means of a large number of enzymes, transporters and receptors and possesses a formidable system of tight junctions which, combined with a paucity of caveolae, keeps permeability tightly controlled. It can modify its shape and function in response to cues originating from the surrounding neural microenvironment and circulating substances, cells and organisms in the blood. It has attained a prominent stature as a master switch and mediator of immune responses, being capable of producing and responding to inflammatory mediators, regulating the entry of immune cells into the brain through the expression of adhesion receptors and chemoattractant cytokines and modifying its barrier function. An important concept that has emerged in recent years is that the barrier endothelium does not operate in isolation, rather its function influences and is influenced by neighboring cells. The concept of the neurovascular unit has thus evolved that provides a meaningful conceptual framework for the blood-

brain barrier by linking the function of the endothelium to that of other cells in the surrounding neural microenvironment.

This book presents, in an integrated fashion, generally accepted facts and new and exciting concepts on the structure, function and pathobiology of the blood-brain barrier. This first volume begins with a brief historical journey, which puts into perspective seminal past and recent work. This is followed by a detailed account of the development and composition of the human cerebral microvascular system, the structure, function and heterogeneity of the cerebral microvascular endothelium, the cellular components and function of the neurovascular unit, the expression and function of a steadily increasing number of ABC transporters at the blood-brain barrier and insights into the structure and function of the blood-cerebrospinal fluid barrier. The remaining chapters of this volume focus on the immune function of the blood-brain and blood-cerebrospinal fluid barriers and on the various inflammatory mediators and signaling molecules that modify the phenotype and permeability properties of the blood-brain barrier and contribute to the initiation of inflammatory responses in the central nervous system.

Dysfunction of the blood-brain barrier is increasingly recognized as contributing to the pathogenesis of a host of diverse central nervous system diseases. Accordingly, this second volume of the book addresses the active role of the endothelium as an initiator and regulator of biological responses and as a target in a broad spectrum of disorders including infections, inflammatory diseases, hypertension, ischemia, trauma, epilepsy, neurodegenerative diseases, metabolic disturbances, tumors, as well as radiation and drug-induced damage.

This book is aimed at graduate students who work towards a degree in neuroscience, postdoctoral fellows establishing a career and wishing to formulate new ideas, medical students with special interest in neurosciences and established clinicians and scientists wishing to update and expand their knowledge in this area. In spite of great accomplishments, our understanding of the blood-brain barrier remains incomplete. The ultimate goal of this book, therefore, is to provide information and serve as a stimulus for the next generation of researchers who will carry the torch of blood-brain barrier research to the next level.

In closing, I wish to express my thanks to my publisher, CRC Press. I remain grateful to the contributing authors for their generous contribution of precious time and effort. I would like to acknowledge my family for their patience, understanding and encouragement. I would also like to express my gratitude to Odysseas Zis for his kind and generous assistance with the complexities of organizing the reference libraries. This book is dedicated to the memory of my parents, Constantinos and Fanie Dorovinis.

Katerina Dorovini-Zis

List of Contributors

Fawaz M. Alotaibi
Microvascular/Molecular Neuro-oncology Laboratory, NYU Langone Medical Center MSB 521, 550 First Avenue, New York, NY 10016.
Email: Fawaz.Alotaibi@nyumc.org

Shilpa Buch
Department of Pharmacology and Experimental Neuroscience, 985880 Nebraska Medical Center (DRC 8011), University of Nebraska Medical Center, Omaha, NE 68198-5880.
Email: sbuch@unmc.edu

Roger F. Butterworth
Neuroscience Research Unit, Hôpital St-Luc (CHUM), University of Montreal, 45143 Cabot Trail, Englishtown, NS, Canada BOC1HO.
Email: rb@enceph.com

Adam Chodobski
Neurotrauma and Brain Barriers Research Laboratory, Department of Emergency Medicine, Alpert Medical School of Brown University, Coro Center West, Room 112, 1 Hoppin Street, Providence, RI 02903, USA.
Email: Adam_Chodobski@Brown.edu

Mahalia S. Desruisseaux
Albert Einstein College of Medicine, Jack and Pearl Resnick Campus, 1300 Morris Park Avenue, Bronx, New York, 10461, USA.
Email: m.desruis@einstein.yu.edu

Ruben van Doorn
Department of Molecular Cell Biology and Immunology (MCBI), VU University Medical Center, Neuroscience Campus Amsterdam, De Boelelaan 1117, 1081 HV Amsterdam, The Netherlands.
Email: r.vandoorn@vumc.nl

Katerina Dorovini-Zis
Department of Pathology and Laboratory Medicine, The University of British Columbia, Vancouver General Hospital, 855 West 12th Avenue, Vancouver, Canada, V5Z-1M9.
Email: dorovini@mail.ubc.ca

Scott G. Filler
Division of Infectious Diseases, Department of Medicine, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, CA 90502, David Geffen School of Medicine at UCLA, Los Angeles, CA, 90095.
Email: sfiller@ucla.edu

Yun Gao
Department of Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, Omaha, Nebraska, USA.
Email: terminator_Yun@hotmail.com

Kathy Guo
Department of Cellular and Molecular Medicine, Cleveland Clinic Lerner College of Medicine, NB-20 LRI, 9600 Euclid Ave Cleveland, OH 44195, USA.
Email: kguo2010@gmail.com

Henri van der Heyde
La Jolla Infectious Disease Institute, 3525 Del Mar Heights Road, San Diego, CA, 92130, USA.
Email: hvande@ljidi.org

Sheng T. Hou
Human Health Therapeutics, National Research Council Canada, 1200 Montreal Road, Ottawa, ON, Canada K1A 0R6.
Email: Sheng.Hou@nrc.ca

Rajan Jain
Department of Radiology, Clinical Co-Director, Center for Advanced Imaging and Research, NYU Langone Medical Center, 550 First Avenue, New York, NY 10016.
Email: Rajan.Jain@nyumc.org

Damir Janigro
Department of Cellular and Molecular Medicine, Cerebrovascular Research, Cleveland Clinic Lerner College of Medicine, NB-20 LRI, 9600 Euclid Ave Cleveland, OH 44195, USA.
Email: janigrd@ccf.org

Kwang Sik Kim
Division of Pediatric Infectious Diseases, Johns Hopkins University School of Medicine, 200 North Wolfe St., Room 3157, Baltimore, MD 21287.
Email: kwangkim@jhmi.edu

Lih-Fen Lue
Banner Sun Health Research Institute, 10515 West Santa Fe Drive, Sun City, Arizona, USA.
Email: lihfen.lue@bannerhealth.com

Yuri Chaves Martins
Albert Einstein College of Medicine, Department of Pathology, 1300 Morris Park Ave, Bronx, NY 10461, USA.
Email: yuri.chaves@einstein.yu.edu

Dorian B. McGavern
NINDS/NIH, 10 Center Drive, Bethesda, MD 20892.
Email: mcgavernd@mail.nih.gov

Steven F. Merkel
Department of Pathology and Laboratory Medicine, Temple University School of Medicine, 3500 North Broad Street, Medical Education and Research Building, 8th Floor, Room 880A, Philadelphia, Pennsylvania 19140 (USA).
Email: Tue39636@temple.edu

Mark Mizee
Department of Molecular Cell Biology and Immunology (MCBI), VU University Medical Center, Neuroscience Campus Amsterdam, De Boelelaan 1117, 1081 HV Amsterdam, The Netherlands.
Email: m.mizee@vumc.nl

Sukriti Nag
Department of Pathology, Rush University Medical Center, AAC, Suite1020 F, 600 South Paulina Street, Chicago, IL 60616 USA.
Email: Sukriti_Nag@ rush.edu

Souhel Najjar
Department of Neurology (Epilepsy Center Division), 223 E 34th St., New York, NY 10016.
Email: Souhel.Najjar@nyumc.org

Yuri Persidsky
Department of Pathology and Laboratory Medicine, Temple University School of Medicine, 3500 North Broad Street, Medical Education and Research Building, 8th Floor, Room 841, Philadelphia, Pennsylvania 19140 (USA).
Email: Yuri.Persidsky@tuhs.temple.edu

Nemani V. Prasadarao
Division of Infectious Diseases, Departments of Pediatrics and Surgery, Children's Hospital Los Angeles and University of Southern California School of Medicine, Los Angeles, CA 90027.
Email: pnemani@chla.usc.edu

Alexandre Prat
Neuroimmunology Research Laboratory, Hospital Complex of the Université de Montréal, Notre Dame Hospital, Faculty of Medicine, University of Montréal, 1560 Sherbrooke Street East, Montreal, Quebec, Canada H2L 4M1.
Email: a.prat@umontreal.ca

Vikram V. Puvenna
Department of Cellular and Molecular Medicine, Cleveland Clinic Lerner College of Medicine, NB-20 LRI, 9600 Euclid Ave Cleveland, OH 44195, USA.
Email: puvennv@ccf.org

Servio H. Ramirez
Department of Pathology and Laboratory Medicine, Temple University School of Medicine, 3500 North Broad Street, Medical Education and Research Building, 8th Floor, Room 844, Philadelphia, Pennsylvania 19140 (USA).
Email: Servio@temple.edu

Seema Shroff
Department of Pathology, NYU Langone Medical Center TH-444, 550 First Avenue, New York, NY 10016.
Email: Seema.Shroff@nyumc.org

Hany Soliman
Department of Radiation Oncology, Sunnybrook Health Sciences Centre, University of Toronto, 2075 Bayview Avenue, Toronto, ON Canada, M4N 3M5.
Email: hany.soliman@sunnybrook.ca

Danica Stanimirovic
Human Health Therapeutics, National Research Council Canada, 1200 Montreal Road, Ottawa, ON, Canada K1A 0R6.
Email: Danica.Stanimirovic@nrc.ca

Monique Stins
Johns Hopkins School of Medicine, Department of Neurology and Bloomberg School of Public Health, Malaria Research Institute, 600 N Wolfe Street, Mayer 6-113, Baltimore, MD 21287, USA.
Email: mstins@jhmi.edu

Phillip A. Swanson II
National Institute of Neurological Disorders & Stroke, National Institutes of Health, 10 Center Drive, Bethesda, MD 20892.
Email: swansonpa@mail.nih.gov

Joanna Szmydynger-Chodobska
Neurotrauma and Brain Barriers Research Laboratory, Department of Emergency Medicine, Alpert Medical School of Brown University, Coro Center West, Room 112, 1 Hoppin Street, Providence, RI 02903, USA.
Email: Joanna_Szmydynger-Chodobska@Brown.edu

Spencer Tung
Department of Pathology & Laboratory Medicine (Neuropathology), David Geffen School of Medicine at UCLA, Los Angeles, CALIFORNIA, USA.
Email: stung@mednet.ucla.edu

Harry V. Vinters
Departments of Pathology & Laboratory Medicine (Neuropathology) and Neurology, Brain Research Institute and Mental Retardation Research Center, David Geffen School of Medicine at UCLA, Los Angeles, CALIFORNIA, USA.
Email: hvinters@mednet.ucla.edu

Helga E. de Vries
Department of Molecular Cell Biology and Immunology (MCBI), VU University Medical Center, Neuroscience Campus Amsterdam, De Boelelaan 1117, 1081 HV Amsterdam, The Netherlands.
Email: he.devries@vumc.nl

C. Shun Wong
Department of Radiation Oncology, Sunnybrook Health Sciences Centre, University of Toronto, 2075 Bayview Avenue, Toronto, ON Canada, M4N 3M5.
Email: shun.wong@sunnybrook.ca

Douglas G. Walker
Banner Sun Health Research Institute, 10515 West Santa Fe Drive, Sun City, Arizona, USA.
Email: douglas.walker@bannerhealth.com

Honghong Yao
Department of Pharmacology, School of Medicine, Southeast University, Nanjing, Jiangsu, China.
Email: 101011704@seu.edu.cn

David Zagzag
Division of Neuropathology, Microvascular and Molecular Neuro-Oncology Laboratory, Department of Pathology, NYU Langone Medical Center, 550 First Avenue, TH-444, New York, NY 10016.
Email: David.Zagzag@nyumc.org

Brian J. Zink
Department of Emergency Medicine, Alpert Medical School of Brown University, Claverick 2, 593 Eddy Street, Providence, RI 02903, USA.
Email: BZink@Lifespan.org

Wandong Zhang
Human Health Therapeutics, National Research Council Canada, 1200 Montreal Road, Ottawa, ON, Canada K1A 0R6.
Email: Wandong.Zhang@nrc.ca

Contents

1

Blood-Brain Barrier Disruption in Multiple Sclerosis

Mark Mizee,[1,a] *Ruben van Doorn,*[1,b] *Alexandre Prat*[2] and *Helga E. de Vries*[1,*]

Introduction

The blood-brain barrier is specialized to function as a barrier to protect the central nervous system by restricting entry of unwanted molecules and immune cells into the brain and inversely, to prevent central nervous system-born agents from reaching the systemic circulation. The blood-brain barrier endothelium, together with cells involved in its regulation forms the neurovascular unit. Blood-brain barrier dysfunction is an important hallmark of early multiple sclerosis pathophysiology, leading to a consequent loss of the imperative brain homeostasis and subsequent neuronal dysfunction and damage. The neuroinflammatory changes at the blood-brain barrier are numerous and include the loss of barrier function, altered communication with surrounding cells, and activation of both inflammation promoting and dampening mechanisms. A better understanding of blood-brain barrier alterations in neuroinflammation might lead to new ways to promote blood-brain barrier function in neurological diseases like multiple sclerosis.

[1] Department of Molecular Cell Biology and Immunology (MCBI), VU University Medical Center, Neuroscience Campus Amsterdam, De Boelelaan 1117, 1081 HV Amsterdam, The Netherlands.
[a] Email: m.mizee@vumc.nl
[b] Email: r.vandoorn@vumc.nl
[2] Neuroimmunology Research Laboratory, Hospital Complex of the Université de Montréal, Notre Dame Hospital, Faculty of Medicine, University of Montréal, 1560 Sherbrooke Street East, Montreal, Quebec, Canada H2L 4M1.
Email: a.prat@umontreal.ca
* Corresponding author: he.devries@vumc.nl

Multiple Sclerosis

Clinical Features and Diagnosis

Multiple sclerosis (MS) is a chronic inflammatory disorder of the central nervous system (CNS). MS is characterized by the presence of focal inflammatory lesions scattered throughout the brain. Depending on their stage, lesions are hallmarked by inflammation, demyelination, gliosis, axonal injury and diffuse axonal degeneration (Frohman et al. 2006, Noseworthy et al. 2000). According to the World Health Organization, globally its median estimated prevalence is 30 per 100.000 resulting in over two million people affected with MS worldwide with a global women versus men ratio of 3:1. As the average age of onset is between 25 and 32 years, MS is one of the most common neurological disorders and causes of disability in young adults (World Health Organization 2008).

Presentation and symptoms of MS are characterized by great variability and diversity. In general, the initial symptoms and signs are sensory impairment, optic neuritis, motor deficits, limb ataxia and difficulty with balance (Weinshenker et al. 1989). The majority of MS patients are subject to a relapse with onset of MS, referred to as clinically isolated syndrome (CIS), which may eventually convert to MS (Miller et al. 2012). Over time, the clinical manifestation of MS varies and consensus was reached to describe three clinical course definitions. Relapsing–remitting (RR) MS, onset of disease in about 85% of MS patients, is described by clearly defined disease relapses with full recovery or with residual deficit upon recovery. Secondary-progressive (SP) MS is described by initial RR disease course followed by progression with or without occasional relapses, minor remissions, and plateaus (Lublin and Reingold 1996). Primary–progressive (PP) MS, onset of disease in about 10% of MS patients, is described by disease progression from onset with occasional plateaus and temporary minor improvements allowed.

The international Panel on the Diagnosis of Multiple Sclerosis announced new diagnostic criteria for MS in 2001. These criteria, the McDonald Criteria, were widely adopted by neurologists, providing them a diagnostic scheme for reliable diagnosis of MS (McDonald 2001). Diagnosis of MS is primarily based on clinical grounds comprising neurological examination and clinical history. If a diagnosis can not be made based on clinical presentation, radiological and laboratory assessments such as magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) analysis may be essential for diagnosing MS. MRI analysis detects MS lesions in brain and in spinal cord and can therefore provide evidence of dissemination of MS lesions in both time and space, two potential criteria for the diagnosis of MS. CSF analysis may provide supportive evidence in the form of the presence of oligoclonal bands.

Aetiology

So far, the precise aetiology of MS remains unknown which is partly due to the complexity and heterogeneity of the disease. Epidemiological studies indicate that both environmental and genetic factors may contribute to development of MS (Dyment et al. 2004). It is suggested that development of MS must commence in genetically