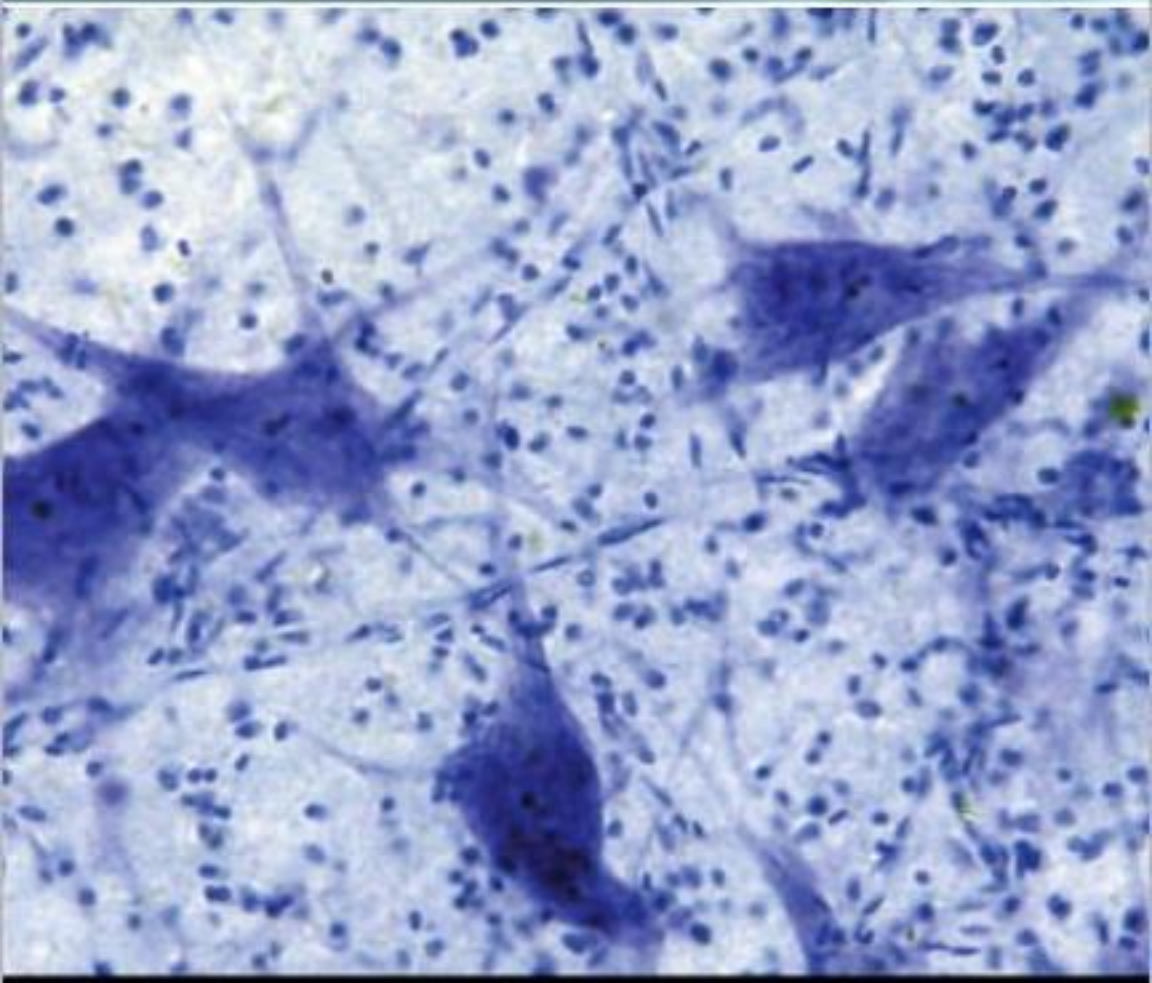
ELSEVIER INSIGHTS



NEUROINFLAMMATION

Edited by ALIREZA MINAGAR

Neuroinflammation

Neuroinflammation

Edited by

Alireza Minagar

ELSEVIER

AMSTERDAM • BOSTON • HEIDELBERG • LONDON • NEW YORK • OXFORD
PARIS • SAN DIEGO • SAN FRANCISCO • SINGAPORE • SYDNEY • TOKYO

Elsevier
32 Jamestown Road London NW1 7BY
30 Corporate Drive, Suite 400, Burlington, MA 01803, USA

First edition 2011

Notices
Knowledge and best practice in this field are constantly changing. As new research and experience broaden our understanding, changes in research methods, professional practices, or medical treatment may become necessary.

Practitioners and researchers must always rely on their own experience and knowledge in evaluating and using any information, methods, compounds, or experiments described herein. In using such information or methods they should be mindful of their own safety and the safety of others, including parties for whom they have a professional responsibility.

To the fullest extent of the law, neither the Publisher nor the authors, contributors, or editors, assume any liability for any injury and/or damage to persons or property as a matter of products liability, negligence or otherwise, or from any use or operation of any methods, products, instructions, or ideas contained in the material herein.

British Library Cataloguing-in-Publication Data
A catalogue record for this book is available from the British Library

Library of Congress Cataloging-in-Publication Data
A catalog record for this book is available from the Library of Congress

ISBN: 978-0-12-384913-7

Preface

During the past two decades the scientific community has witnessed many major achievements and technical advances in our knowledge and understanding of the fundamental molecular mechanisms underlying various neuroinflammatory disorders affecting the human nervous system. The major players in the pathogenesis of these complex and intriguing neuroinflammatory and neurodegenerative disorders include activated immune cells, endothelial cells, immune cells resident within the central nervous system (CNS), and effects of several recently identified immunomodulators, cytokines and chemokines, which initiate and sustain the underlying pathologic processes of these often enigmatic disorders. Scientists around the world, through innumerable collaborative studies, have partially determined the diverse roles of these players in the course of neuroinflammation and are now applying this wealth of information toward the development of more potent and specific and less dangerous therapies for these difficult-to-treat diseases.

The main objective of this book, entitled *Neuroinflammation*, is to provide interested readers with the most up-to-date and detailed reviews of current scientific concepts of neuroinflammation, with extensive updates on the most recent concepts on the pathogenesis of these CNS diseases. The core emphasis of this series of reviews on basic and clinical features of neuroinflammation will be of interest to a broad continuum of both basic scientific researchers and clinical scientists. Neuroinflammation is a rapidly expanding field, and our collection on this topic represents an educational tool that can assist students, scientists, and clinicians around the planet to better understand, diagnose, and treat these complex diseases.

I very much appreciate the scholastic efforts of several wonderful contributors to this book, who made *Neuroinflammation* a reality and provided us with their excellent chapters on various topics. I also appreciate the efforts of Mr. Paul Prasad Chandramohan and the hardworking staff at Elsevier's publishing production team, who provided us with their support and expertise during the production of this book. I hope that my colleagues will find this book to be a useful resource in their continuous research into the fundamental concepts of neuroinflammation.

Alireza Minagar, MD, FAAN

Contributors

J. Steven Alexander Department of Molecular and Cellular Physiology, Louisiana State University Health Sciences Center, Shreveport, LA, USA

Peter O. Behan Division of Clinical Neuroscience, Faculty of Medicine, University of Glasgow, Glasgow, Scotland, UK; School of Life Sciences, Glasgow Caledonian University, Glasgow, Scotland, UK

Aimee Borazanci Department of Neurology, Louisiana State University Health Sciences Center, Shreveport, LA, USA

Isabel Bosca Neuroimmunology Unit, Centre for Neuroscience and Trauma, Blizard Institute of Cell and Molecular Science, Barts and the London School of Medicine and Dentistry, London, UK; Neurology Department, La Fe University Hospital, Valencia, Spain

Hermine Brunner Division of Rheumatology, Department of Pediatrics, College of Medicine, University of Cincinnati, Cincinnati, Ohio (HB)

Abhijit Chaudhuri Department of Neurology, Queen's Hospital, Romford, Essex, England, UK

Tiffany Chang Department of Neurology, Tulane University School of Medicine, New Orleans, LA, USA

Andrew L. Chesson Jr. Sleep Medicine Program, Department of Neurology, Louisiana State University Health Sciences Center, Shreveport, LA, USA

Xi Chen Department of Physiology, Emory University School of Medicine, Atlanta, GA, USA

Paweł Cieślik Department of Internal, Autoimmune and Metabolic Diseases, Medical University of Silesia, Katowice, Poland

Randall J. Cohrs Department of Neurology, University of Colorado School of Medicine, Aurora, CO, USA

Natalie Cornay Louisiana State University School of Medicine, Shreveport, LA, USA

Robin Davis Louisiana State University School of Medicine, Shreveport, LA, USA

Francesco Deleo Division of Epilepsy, Clinic and Experimental Neurophysiology, IRCCS Foundation Neurological Institute C. Besta, Milano, Italy

Gabriele Di Comite Department of Immunology, National Institute of Neuroscience, Tokyo, Japan

Ludovico D'Incerti Department of Neuroradiology, IRCCS Foundation Neurological Institute C. Besta, Milano, Italy

Donard S. Dwyer Department of Psychiatry, Louisiana State University Health Sciences Center, Shreveport, LA, USA; Department of Pharmacology, Toxicology and Neuroscience, Louisiana State University Health Sciences Center, Shreveport, LA, USA

Masoud Etemadifar Isfahan Research Committee of Multiple Sclerosis (IRCOMS), Isfahan, Iran; Department of Neurology, Isfahan University of Medical Sciences, Isfahan, Iran

Clare Fraser The National Hospital for Neurology and Neurosurgery, London, UK; Moorfields Eye Hospital, London, UK; St Thomas' Hospital, London, UK

Don Gilden Department of Neurology, University of Colorado School of Medicine, Aurora, CO, USA; Department of Microbiology, University of Colorado School of Medicine, Aurora, CO, USA

Gavin Giovannoni Neuroimmunology Unit, Centre for Neuroscience and Trauma, Blizard Institute of Cell and Molecular Science, Barts and the London School of Medicine and Dentistry, London, UK

Eduardo Gonzalez-Toledo Department of Radiology, Louisiana State University Health Sciences Center, Shreveport, LA, USA; Department of Neurology, Louisiana State University Health Sciences Center, Shreveport, LA, USA

D. Neil Granger Department of Molecular and Cellular Physiology, Louisiana State University Health Sciences Center, Shreveport, LA, USA

Viktoria Gudi Department of Neurology, Hannover Medical School, Hannover, Germany

Meghan Harris Department of Neurology, Louisiana State University School of Medicine, Shreveport, LA, USA

Antoni Hrycek Department of Internal, Autoimmune and Metabolic Diseases, Medical University of Silesia, Katowice, Poland

Stephen Jaffe Department of Neurology, Louisiana State University Health Sciences Center, Shreveport, LA, USA

Edward Johnson Louisiana State University School of Medicine, Shreveport, LA, USA

Roger E. Kelley Department of Neurology, Tulane University School of Medicine, New Orleans, LA, USA

Marisa Klein-Gitelman Division of Rheumatology, Department of Pediatrics, Northwestern University Feinberg School of Medicine, Chicago, IL (MKG)

Cesar Liendo Department of Physiology, Emory University School of Medicine, Atlanta, GA, USA

Alexandra Lopez-Soriano Department of Neurology, Buffalo Neuroimaging Analysis Center, State University of New York, Buffalo, NY, USA

Amy E. Lovett-Racke Department of Neurology, Ohio State University Medical Center, Columbus, OH, USA; Department of Molecular Virology, Immunology and Medical Genetics, Ohio State University Medical Center, Columbus, OH, USA

Amir-Hadi Maghzi Neuroimmunology Unit, Centre for Neuroscience and Trauma, Blizard Institute of Cell and Molecular Science, Barts and the London School of Medicine and Dentistry, London, UK; Isfahan Research Committee of Multiple Sclerosis (IRCOMS), Isfahan, Iran; Isfahan Neuroscience Research Center, Isfahan University of Medical Sciences, Isfahan, Iran

Monica Marta Neuroimmunology Unit, Centre for Neuroscience and Trauma, Blizard Institute of Cell and Molecular Science, Barts and the London School of Medicine and Dentistry, London, UK

Ravi Mahalingam Department of Neurology, University of Colorado School of Medicine, Aurora, CO, USA

Nicholas E. Martinez Department of Microbiology and Immunology, Louisiana State University Health Sciences Center, School of Medicine in Shreveport, Shreveport, LA 71130, USA

Rae Ann Maxwell Medical Science Liaison, Biogen Idec Neurology, US Medical Affairs

Jeanie McGee Department of Neurology, Louisiana State University Health Sciences Center, Shreveport, LA, USA

David E. McCarty Sleep Medicine Program, Department of Neurology, Louisiana State University Helath Sciences Center, Shreveport, LA, USA

Ute-Christiane Meier Neuroimmunology Unit, Centre for Neuroscience and Trauma, Blizard Institute of Cell and Molecular Science, Barts and the London School of Medicine and Dentistry, London, UK

Mandana Mohyeddin Bonab Department of Immunology and the Molecular Immunology Research Center, Tehran University of Medical Sciences, Tehran, Iran

Alireza Minagar Department of Neurology, Louisiana State University Health Sciences Center, Shreveport, LA, USA

Mutsumi Nagai Department of Molecular and Cellular Physiology, Louisiana State University Health Sciences Center, Shreveport, LA, USA

Maria A. Nagel Department of Neurology, University of Colorado School of Medicine, Aurora, CO, USA

Behrouz Nikbin Department of Immunology and the Molecular Immunology Research Center, Tehran University of Medical Sciences, Tehran, Iran

Eileen M. O'Connor Medical Science Liaison, Biogen Idec Neurology, US Medical Affairs

Seiichi Omura Department of Microbiology and Immunology, Louisiana State University Health Sciences Center, School of Medicine in Shreveport, Shreveport, LA 71130, USA

Magdalena Olszanecka-Glinianowicz Department of Pathophysiology, Medical University of Silesia, Katowice, Poland

Parrin Patterson Department of Psychiatry, Louisiana State University Health Sciences Center, Shreveport, LA, USA

Gordon T. Plant The National Hospital for Neurology and Neurosurgery, London, UK; Moorfields Eye Hospital, London, UK; St Thomas' Hospital, London, UK

Refik Pul Department of Neurology, Hannover Medical School, Hannover, Germany

Brain Rubin Department of Neurology, Louisiana State University School of Medicine, Shreveport, LA, USA

Amy C. Rauchway Department of Neurology and Psychiatry, Saint Louis University School of Medicine, St. Louis, MO, USA

Michael K. Racke Department of Neurology, Ohio State University Medical Center, Columbus, OH, USA; Department of Molecular Virology, Immunology and Medical Genetics, Ohio State University Medical Center, Columbus, OH, USA; Department of Neuroscience, Ohio State University Medical Center, Columbus, OH, USA

Mohammad-Reza Savoj Isfahan Research Committee of Multiple Sclerosis (IRCOMS), Isfahan, Iran

Fumitaka Sato Department of Microbiology and Immunology, Louisiana State University Health Sciences Center, School of Medicine in Shreveport, Shreveport, LA 71130, USA

Robert N. Schwendimann Department of Neurology, Louisiana State University Health Sciences Center, Shreveport, LA, USA

Yadollah Shakiba Department of Immunology and the Molecular Immunology Research Center, Tehran University of Medical Sciences, Tehran, Iran

Thomas Skripuletz Department of Neurology, Hannover Medical School, Hannover, Germany

Karen Small Louisiana State University School of Medicine, Shreveport, LA, USA

Martin Stangel Department of Neurology, Hannover Medical School, Hannover, Germany

Malú G. Tansey Department of Physiology, Emory University School of Medicine, Atlanta, GA, USA

Corinna Trebst Department of Neurology, Hannover Medical School, Hannover, Germany

Ikuo Tsunoda Department of Microbiology and Immunology, Louisiana State University Health Sciences Center, School of Medicine in Shreveport, Shreveport, LA 71130, USA

Elke Voss Department of Neurology, Hannover Medical School, Hannover, Germany

Yuhong Yang Department of Neurology, Ohio State University Medical Center, Columbus, OH, USA; Department of Molecular Virology, Immunology and Medical Genetics, Ohio State University Medical Center, Columbus, OH, USA

Robert Zivadinov Department of Neurology, Buffalo Neuroimaging Analysis Center, State University of New York, Buffalo, NY, USA; Department of Neurology, The Jacobs Neurological Institute, State University of New York, Buffalo, NY, USA

1 Multiple Sclerosis: Pathophysiology, Clinical Features, Diagnosis, and Management

Amir-Hadi Maghzi[1,2,3], Aimee Borazanci[4], Jeanie McGee[4], J. Steven Alexander[5], Eduardo Gonzalez-Toledo[4,6], Alireza Minagar[4]

[1]Isfahan Research Committee of Multiple Sclerosis (IRCOMS), Isfahan, Iran
[2]Isfahan Neuroscience Research Center, Isfahan University of Medical Sciences, Isfahan, Iran
[3]Neuroimmunology Unit, Centre for Neuroscience and Trauma, Blizard Institute of Cell and Molecular Science, Barts and the London School of Medicine and Dentistry, London, UK
[4]Department of Neurology, Louisiana State University Health Sciences Center, Shreveport, LA, USA
[5]Department of Molecular and Cellular Physiology, Louisiana State University Health Sciences Center, Shreveport, LA, USA
[6]Department of Radiology, Louisiana State University Health Sciences Center, Shreveport, LA, USA

Introduction

Multiple sclerosis (MS) is an immune-mediated neurodegenerative disease of the central nervous system (CNS), which largely affects young adults with certain genetic backgrounds, often following exposure to several as yet unidentified environmental antigen(s) [1,2]. It is believed that the interactions between environmental and genetic influences are required to trigger the massive immune response against putative CNS antigens (e.g., myelin proteins that surround axons). This progressive inflammatory process affects both gray and white matters of the brain and spinal cord and ultimately causes neurodegeneration and axonal loss, with resultant permanent disability. Inflammatory demyelination in MS slows impulse conduction or leads to complete cessation of nerve impulse transmission. Axonal loss and neurodegeneration are the fundamental mechanisms underlying brain atrophy and permanent loss of motor function. The lesions of MS can affect any region of the neuroaxis; therefore, the anatomic location of MS lesions plays a significant role in determining clinical symptoms.

Based on the clinical disease pattern, four types of MS are recognized: relapsing–remitting MS (RRMS), secondary progressive MS (SPMS), primary progressive

Neuroinflammation. DOI: 10.1016/B978-0-12-384913-7.00001-0

MS (PPMS), and progressive relapsing MS (PRMS) [3]. Interestingly, it appears that these four different forms of MS have dissimilar underlying neuropathologies, which in turn indicates that MS may represent a heterogeneous group of related diseases. The clinical course of RRMS is characterized by clear disease relapses with development of new neurologic deficits or worsening of older symptoms that last more than 24 h; each relapse is typically separated from the last attack by at least 1 month of stability. Patients with relapse of MS, either with treatment with corticosteroids or spontaneously, may return to their baseline neurologic status or may recover partially, with residual neurologic deficits. Usually, during the interval between relapses there is no clinical disease progression. Clinically, RRMS is the most common form of MS; more than 85% of patients initially present with this form. SPMS is recognized by an initial RRMS that progresses to SPMS within 10–15 years. During this phase of MS, the underlying inflammatory cascade and clinical relapses decrease in severity, while the neurodegenerative process builds to become the dominant pathology. In certain ways, SPMS may be regarded as a long-term product of RRMS. Up to 15% of MS patients initially present with PPMS, which is characterized by a relentless progression with no obvious relapses; patients occasionally exhibit transient minor improvement. PRMS is characterized by progressive and devastating attacks of the disease from the beginning with acute relapses, with or without recovery. Importantly, the intervals between relapses are marked by continuous disease progression. This form of MS is the least common clinical form.

The most common form of MS, RRMS, begins with a single unifocal or multifocal demyelinating attack (known as clinically isolated syndrome [CIS]), with a complete or partial resolution of the attack. This form of MS with its dominant neuroinflammatory sequelae is clinically recognized by relapses and development of new lesions on magnetic resonance imaging (MRI) studied by CNS neuroimaging. Of course, during this process, the neurodegenerative arm of MS continuously proceeds with progressive axonal and neuronal loss to the point that the patient's capacity to sustain any new attacks without suffering additional disability decreases. Within a few years of the onset of RRMS, the underlying neuropathology of MS involves more neurodegeneration with fewer clinical relapses, more clinical deterioration, and accumulating disability. Patients with PPMS have a progressive course from the beginning without significant evidence of inflammatory lesions on CNS neuroimaging and with no proven therapeutic response to immunomodulatory medications as compared to RRMS.

Epidemiology

The diverse worldwide epidemiology of MS provides clues to the genetic and environmental risk factors for MS. The observations from migrant studies showing that migration from high- to low-risk areas before puberty provides some protection against developing MS, and vice versa, highlight the importance of environmental factors in MS [4]. The highest incidence and prevalence of MS are more likely to be observed at the highest latitudes in both the northern and southern hemispheres.

In addition, the prevalence and incidence of MS are shown to be associated with the distance from the equator [5]. This has been mostly linked to the effects of sunlight exposure and vitamin D, leading to the formulation of a hypothesis that vitamin D deficiency may enhance the risk of MS; this hypothesis was later strengthened by further immunologic studies [6]. In addition, similarities between the epidemiology of MS and primary Epstein–Barr virus (EBV) infection (infectious mononucleosis [IM]) have been well documented, and several studies have shown that the risk of MS is elevated after IM, which has led to a growing body of evidence linking EBV to MS [7]. MS is also observed more commonly among smokers, those of higher socioeconomic class, and those with low dietary vitamin D intake [8–10].

The epidemiology of MS has been changing during recent decades. Generally, there has been an increase in the prevalence and incidence of MS worldwide, especially in previously low-risk regions such as the Middle East [5,11]. This has been partly attributed to the better diagnosis of MS secondary to enhanced diagnostic criteria, an increase in the number of neurologists, more availability of disease-modifying drugs, enhanced awareness, and more widespread use of MRI. However, these factors cannot fully explain the increase in the prevalence of MS. It is plausible that changes in lifestyle and environmental exposures have also contributed to the increase in the prevalence and incidence of MS. More evidence comes from studies that have documented an increase in the sex ratio of MS during recent decades in different parts of the world [5,12,13]. Since all these changes have occurred during a short period, they are more likely due to environmental changes rather than genetic ones. For instance, in Western countries, where smoking has been recognized as a risk factor for MS, the increase in the sex ratio of MS has been attributed to the growing number of female smokers, while in an Iranian study this was linked to an increase in the vitamin D deficiency among the young female population [12,14].

Epidemiologic investigations have shown that individuals of Western European ancestry have a higher susceptibility to MS. On the contrary, there are ethnic populations such as Hutterites and the Natives of western Canada who appear to be resistant to the disease despite living in relatively high-risk regions for MS. First-degree relatives of MS patients have a 20 times higher incidence of MS than the general population. Studies on monozygotic twins show that the concordance rate is 30% compared with rates of less than 5% in dizygotic twins [15]. Genetically unrelated family members living in the same environment have a risk of MS that is no higher than the background population. All these observations point toward a genetic component for MS. To date the most significant genetic component discovered remains the HLA-DRB1*15 [15].

Pathophysiology

The exact cause of MS remains unknown, but evidence indicates that its pathophysiology includes two key and interconnected components: neuroinflammation and neurodegeneration [1,16]. The inflammatory component of the pathophysiology of MS includes abnormally excessive activation of the immune system against

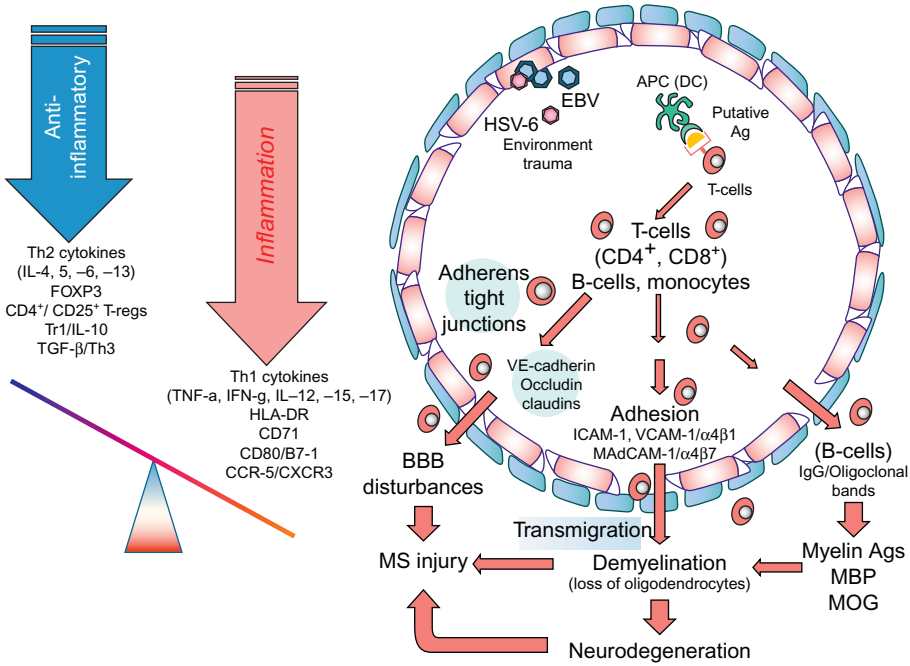


Figure 1.1 Proposed MS pathogenesis. After exposure to environmental antigen(s) (e.g., EBV or HSV-6), myelin-sensitized autoreactive leukocytes are activated via binding of the T-cell receptor to the putative antigen(s), which is conveyed to them by antigen-presenting cells (such as dendritic cells) (trimolecular complexes). The activated leukocytes (T cells, B cells, and macrophages) cross the BBB (transmigration) through the disrupted cerebral endothelial tight and adherens junctions (by disintegrating junctional complexes containing VE-cadherin, occludin, claudin, and junctional adhesion molecules). The activated leukocytes also secrete a number of pro- and anti-inflammatory cytokines that play regulatory roles in polarization of the peripheral environment toward inflammatory or anti-inflammatory mechanisms. Once these cells gain access to the CNS environment, they identify more autoantigens and generate and release more cytokines and autoantibodies, causing loss of myelin/oligodendrocyte complex as well as neurodegeneration.

CNS antigen(s), which leads to interactions between autoreactive leukocytes and the inflamed cerebral endothelium, disintegration of the blood–brain barrier (BBB), and penetration of these activated leukocytes into the CNS parenchyma [1,17–19] (Figure 1.1).

The early events that trigger these exuberant immune responses and activation of leukocytes against self-antigens remain hard to pin down, but viral and bacterial antigens are relevant and probable stimuli triggering the original MS pathophysiology [7,20]. Exposure to or infection with a number of viruses, such as hepatitis B and EBV, has been proposed as the activating factor for the T lymphocytes that are sensitized against viral proteins that share similar structural motifs with CNS proteins such as myelin basic protein (MBP); this is the so-called “molecular mimicry hypothesis.”

Pathophysiology of MS involves both the innate and acquired immune systems. One hypothesis about the pathophysiology of MS is that the initial event begins in the peripheral circulation with activation of immune cells outside the CNS such as dendritic cells [18,19]. Numerous scientific studies on experimental MS in mice (experimental autoimmune encephalomyelitis [EAE], the closest animal model of MS) have revealed that autoreactive CNS-antigen(s)-directed T lymphocytes (CD4+, CD8+) play significant roles in the development of CNS demyelinating lesions. At some point in the early stages of the MS development, T lymphocytes become sensitized against several suspected CNS antigens, including MBP, proteolipid protein, and myelin oligodendrocyte glycoprotein [21], and activate a massive immune response that leads to their migration across the BBB, leading to its dysregulation. Autoreactive T lymphocytes and monocytes interact with inflamed cerebral endothelial cells through rolling and firm binding in the cerebrovascular space. This binding process is the most significant component of the leukocyte–endothelial interaction and commits the leukocytes to migrate across postcapillary venules into the CNS environment [17]. Loss of the BBB endothelial integrity layer is associated with disassembly and destruction of endothelial tight junctions and junctional proteins such as occludin and VE-cadherin [22] as well as claudins, which facilitate movement of the leukocytes. Once autoreactive T lymphocytes and monocytes breach the CNS at the perivenular areas, the immune cascade escalates and more varied CNS antigens become identified as potential immune targets for T cells, a diversification of antigenic specificity over the course of the disease (the episode spreading concept) [23]. The pro-inflammatory Th1 lymphocytes express high levels of activation markers (HLA-DR and CD71), co-stimulatory molecules (CD80/B7-1), and Th1-cell chemokine receptors (CCR5 and CXCR3). These cells produce high levels of pro-inflammatory cytokines such as TNF-α, IFN-γ, IL-12, IL-15, and IL-17. The Th2 lymphocytes, which switch the environment toward anti-inflammatory or protective mode, secrete cytokines such as IL-4, IL5, IL-6, and IL-13 [24]. Other cells involved in reducing the inflammatory response include various kinds of CD4+ regulatory cells such as FOXP3+ CD4CD25+ Tregs, the IL-10–generating Tr1 cells, and the transforming growth factor β–generating Th3 cells. However, regardless of their Th polarization, the movement of immune cells into the CNS parenchyma can disturb BBB integrity.

During the past decade, neuroimmunologists have focused on the role of emerging cytokines such as IL-12, IL-27, and IL-23 in the pathogenesis of MS. Members of the IL-12 family proteins are involved in regulation of T-lymphocyte responses and may be important in the pathophysiology of MS [25]. IL-17, a potent inflammatory cytokine, promotes CNS inflammation by disrupting the BBB, allowing greater permeation of autoreactive peripheral CD4+ T cells into the CNS [26]. Recently, Alexander et al. [27] published the results of a 1-year prospective study of serum levels of IL-12p40, IL-17, and IL-23 prior to and at 3-month intervals after treatment with IFN-β1b. The investigators reported that continuous treatment with IFN-β1b reduced serum levels of IL-12p40 and IL-23 and showed a trend for decreasing IL-17. The investigators concluded that early treatment of MS with IFN-β1b may stabilize the clinical course of MS by decreasing levels of these inflammatory cytokines.