# PREFACE

Multiple sclerosis (MS) is a chronic neurological disorder with potentially devastating, long-term complications. Although not considered a life-threatening, terminal illness, MS is incurable and most therapies may treat only the symptoms, leaving the patient with a reduced quality of life for extended periods of time. Given that the onset of MS can occur as early as the second or third decade of life, patients can be compromised in their lifestyles for many decades. This book focuses on different biological pathways associated with MS and contains current information on the prevalence of MS, novel treatments that target pathophysiology, and new approaches for management of the disorder, as well as general knowledge about the disease process. Basic science research and clinical research continues to make advances into understanding MS. The book focuses on specific deficits related to this autoimmune disorder. Over the last few years, a number of different therapies have gained momentum, and new perspectives on the pathogenesis of MS have been established.

The book is divided into two sections that are related to the etiology and treatment of MS, and the pathophysiology and mechanistic pathways underlying the disease. Section I of the book provides a comprehensive overview on clinical studies, providing details on the prevalence of the disease and current therapies, both defined and postulated, for both pediatric and adult patients with MS. Section II of the book provides current information on fundamental pathways involved in etiology, development, and progression of disease. The contributing authors represent an international group of scientists and clinicians with expertise in a broad range of disciplines, including molecular and cellular biology, immunology, bioinformatics, genetics, neurology, psychiatry, pharmacology, and internal medicine.

The first chapter in Section I by Didonna and Oksenberg provides a comprehensive review on the genetics of MS, highlighting the use of genome-wide association studies to identify nonmajor histocompatibility complex genes that appear to be prevalent in families with MS. This information will be useful in predicting risk and worldwide incidence. The genetic approach extends into Chapter 2 which provides a detailed summary of the prevalence of MS in Europe, with selected information on individual countries. The chapter by Gitto brings to the forefront the need for improved communication among clinicians and patients related to approved and/or novel therapies and research into autoimmune disorders. In Chapter 3, Jancic and coauthors provide a thorough discourse on challenges that are specifically related to the treatment of pediatric patients with MS. This population of patients is symptomatic very early in life and thus has ample time to experience numerous relapses. The authors review the strengths and weaknesses of immunomodulatory therapies including steroid treatment and even plasmapheresis. The message from this chapter is the need for treatment modalities that approach MS longitudinally to reduce both the severity and frequency of relapses. A major symptom of MS that is often overlooked in lieu of the mobilization issues is that of pain. As discussed in Chapter 4, alleviation of pain is not always the primary target of MS treatment, yet many MS patients will self-report that they suffer from chronic pain. Murphy and colleagues discuss

treatment strategies of pain when it becomes sufficiently severe to reduce the quality of life. Unfortunately, research efforts are limited in this area and current strategies may use ineffective drugs such as antidepressants, narcotics, or cannabinoids. The take-home message from this chapter is the need for understanding the mechanisms of MS-related pain and applicable treatment modalities. Chapters 5 and 6 provide information on two novel therapeutic strategies for the treatment of autoimmune disorders including dietary supplementation and stem-cell therapy. In Chapter 5, Zahoor and Haq present compelling information to approach the etiology of MS by targeting vitamin D deficiency. These authors provide mechanistic pathways that support the relationship of sunlight, vitamin D circulatory levels, and prevalence of MS. In summary, vitamin D supplementation may be a valuable, but often overlooked, adjunctive therapy. The final chapter in this section provides a comprehensive evaluation of stem cell biology and the role of stem-cell therapy in autoimmune disorders. This field is still in its infancy, but is gaining research momentum worldwide. Bojnordi and colleagues provide two extensive treatises on stem-cell therapy as a promising approach for reversing MS progression. These authors divide their work into comprehensive discussions on exogenous stem-cell therapy and endogenous stem-cell niches that when stimulated may serve to reduce neurodegeneration by inducing oligodendrocyte proliferation and activation of resident oligodendroglial precursors and adult neural stem cells. Each chapter in this section is provocative and provides insights into the diagnosis, management, and treatment of MS.

Section II of this book includes chapters on the disease pathobiology, highlighting advancements in immunomodulation, endogenous regulatory pathways, and oxidative stress mechanisms underlying the etiology and pathogenesis of MS and other autoimmune disorders. These chapters are no less important than those on treatment and include preclinical, animal research to demonstrate the basis of new and exciting theories on the pathogenesis of MS. Moreover, each chapter adds basic science or clinical data to an underlying theme of identifying or defining new biomarkers that can effectively be used for the diagnosis and treatment of MS. Data are presented on three novel thematic areas including primary neuroinflammation, oxidative stress pathways, and the role of endogenous opioids and their receptors in MS. Each chapter discusses the possibility of the pathway becoming dysregulated during development of the disease. The final chapter provides some insight into the strengths and weaknesses of animal models when studying a multi-modality disorder such as MS. As detailed in Chapter 7, neuroinflammation is a primary response to antigen presentation as well as a secondary immunological response. Dr. Palumbo presents evidence on arachidonic acid metabolism as an active pathway, leading to further demyelination, glial loss, and axonal pathology in animal models with experimental autoimmune encephalomyelitis and humans with MS. The author presents arguments for the treatment of MS with nonsteroidal anti-inflammatory drugs to control COX-2 mediated inflammation following arachidonic acid stimulation. In Chapter 8, Zagon and McLaughlin introduce an endogenous opioid pathway as a homeostatic regulatory axis that can modulate progression of experimental autoimmune encephalomyelitis (EAE) or MS using a number of different paradigms. These authors summarize preclinical work on chronic progressive and relapse-remitting EAE, as well as clinical data from patients with MS. Treatment with endogenous opioids such as opioid growth factor (OGF), chemically termed [Met$^5$]-enkephalin, or low doses of naltrexone

(LDN) that upregulate secretion of OGF are effective at stalling the onset of disease, reversing the progression of EAE, and inhibiting neurodegeneration. MS patients on LDN report significantly better quality of life, improved ambulation, and have little or no side effects. Moreover, levels of OGF declined in animal models of EAE following immunization, suggesting that this noninvasive measurement of an endogenous peptide might serve as a specific biomarker for the onset of MS. Chapters 9 and 10 continue the thematic concept of identification of biomarkers. Teniente-Serra and collaborators present evidence to validate biomarkers by monitoring peripheral blood mononuclear cells with a characterization of lymphocytes. Adamczyk-Sowa and coauthors provide a comprehensive report on the role of oxidative stress mechanisms and their role in both pathophysiology and therapy of MS. Oxidative stress may enhance processes of demyelination—the ultimate neurological pathology associated with MS. These authors argue that the balance between reactive nitrogen species and reactive oxygen species, and the production of free radicals, supports the environment for demyelination in MS. Furthermore, these compounds could also serve as biomarkers specific for MS. The last chapter by Palumbo and Pellegrini sheds light on the use of animal models to investigate MS. Currently, three *in vivo* paradigms are predominately used to study autoimmune disorders—antigen-producing autoimmune encephalomyelitis, cuprizone intoxication, and Theiler's murine virus. Each model is discussed with the strengths and weaknesses highlighted.

The book is intended to provide an authoritative source of current knowledge on the field. Given that MS is only one of the many autoimmune disorders that have limited definitive etiology and treatment, we hope that the comprehensive studies detailed in the book may stimulate other researchers to explore their specific diseases of interest, thereby adding to the knowledge on autoimmunity.

When organizing and editing this book, it was our intention to combine broad-based reviews of human and animal studies on MS so that the information would appeal to researchers as well as patients with an interest in knowing more about MS. We thank the authors for their time and concerted efforts in organizing the current literature. The intended audience of this book are students, basic scientists, and clinicians who are interested in the basic and/or clinical aspects of MS. The goal of this book is to provide a cohesive, but comprehensive, view of the state of the art on MS and encourage new investigations that could lead to novel insights into the etiology, pathogenesis, management, and treatment of MS.

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