Preface

This book critically reviews both clinical and immunological aspects of autoimmune disease with a strong emphasis on multiple sclerosis (MS). Research in MS is one of the fastest-developing areas in modern medicine. It employs some of the newest concepts in autoimmune mechanisms and an array of new treatments that would have been considered science fiction only two decades ago. It is an area in which research findings are being actively translated into treatment strategies. Advances in this area have both clinical and scientific implications for other autoimmune conditions that share many similarities with MS. The book, which comprises 24 chapters contributed by experts and thought leaders in the field, is designed to provide new insights into two arenas: our current understanding of autoimmune mechanisms and immune regulation and the latest developments in immunotherapy.

This book is intended for both researchers and clinicians. Its purpose is not only to provide a comprehensive review on the recent advances in the two arenas mentioned above but also to reflect the current opinions or concepts that influence our thinking about the disease mechanisms and our way of treating MS patients. Many of these issues have emerged from recent studies and are somewhat contradictory to traditional thinking. For example, recent studies have indicated that MS is more heterogeneous in many aspects than traditionally thought. Pathologically, in addition to demyelination and inflammation, there is axonal loss or damage detectable in the central nervous system (CNS) lesions. There is a neurodegenerative component of the disease. It is currently debated as to how significant this neurodegenerative component is and whether the neurodegenerative process found in MS is secondary to inflammation. Even with the CNS demyelination and inflammation characteristic of MS, there are distinct patterns characterized by a differential presence of heterogeneous inflammatory cells (T cells, B cells, macrophages) or antibodies in association with varying degrees of demyelination and inflammation. In addition to pathological heterogeneity, there are well known genetic, immunological, and clinical variations in MS. The heterogeneous nature of MS has important therapeutic implications. A particular drug may be more efficacious in one subset of MS than another because of the different disease processes involved. In this regard, it is important to determine suitable treatments for different subgroups

of MS patients using biomarkers characteristic of each subgroup. With this knowledge, combination therapy can be developed to capture multiple attack points involved in the various MS subgroups. Our oncology colleagues have been utilizing this strategy elegantly for years to treat cancer patients. A number of chapters in this book are devoted to these issues.

Another interesting aspect reviewed extensively here is related to how significantly the immunological research has contributed to our understanding of the disease and has translated to new treatments for MS. Much of the immunological research in MS centers on the hypothesis that myelin autoreactive T cells play an important role in CNS inflammation and demyelination of MS. These autoreactive T cells are abnormally activated—perhaps by microbial infection through molecular mimicry mechanisms—and undergo clonal expansion in conjunction with aberrant regulatory mechanisms that normally keep them in check. Based on this hypothesis, numerous specific immune therapeutic strategies have been developed through immunological research and have been proven effective in experimental autoimmune encephalomyelitis (EAE), an animal model for MS. To name a few, these approaches include altered peptide ligands, myelin-induced oral tolerance, T cell receptor (TCR) peptides, DNA vaccination and T cell vaccination (for targeting autoreactive T cells), and finally monoclonal antibodies directed at a variety of cytokines/integrins or their receptors (reducing inflammation or blocking T cell or other inflammatory cells from entering the CNS). Unfortunately, although we can cure EAE by precisely targeting a component of the TCR–peptide–major histocompatibility complex required for T cell activation, many of these approaches have failed in pilot studies or controlled human clinical trials.

There are several levels of complexity in this regard. First, the true myelin autoantigen(s) is unknown. The candidate myelin antigens used in all immunological studies are extrapolated from EAE in which the disease is commonly induced against myelin basic protein (MBP), proteolipid protein, and myelin oligodendrocyte glycoprotein. The best evidence indicative of the potential involvement of myelin antigens in MS perhaps comes from a recent clinical trial in which an altered peptide of MBP was tested to inactivate circulating T cells recognizing the immune dominant epitope (residues 83-99) of MBP. Although the approach works well in inbred rodents in which the TCR repertoire, including the contact residues involved in recognition of the MBP peptide, is highly restricted, the TCR of human MBP-reactive T cells is considerably degenerated. Thus, alanine substitution at the key TCR contact residue is able to render these T cells inactive in one MS patient but may be ineffective or may even activate the same autoreactive T cells in another. Indeed, some MS patients who received injections of the altered peptide experienced clinical exacerbation and increased lesion load, as indicated by magnetic resonance imaging. It was evident that T cells recognizing the immunodominant MBP peptide were activated by the treatment in these patients. Even if these myelin antigens are involved in the autoimmune mechanism of MS as autoantigens, there are other unresolved issues, such as "epitope spreading."

The T cell repertoire and TCR makeup are much more heterogeneous and complex in humans than in inbred rodents. This complexity is one of the key problems preventing us from extrapolating what works effectively for EAE to the treatment of MS. For example, it is known that, unlike highly restricted TCR V gene usage in myelin-autoreactive T cells seen in EAE mice, myelin-autoreactive T cells in MS display a highly diverse TCR V gene distribution pattern even in the context of the DRB1*1501 genetic background, making TCR-based immunotherapy difficult. Altered peptide ligand of MBP is another example in which a high degree of TCR degeneracy in human MBP-reactive T cells makes a critical difference, as described above. By the same token, it is debatable as to whether EAE is an adequate research model for MS. To say the least, human MS involves highly complex genetic and immunological processes, making EAE at best an incomplete match for MS.

In this regard, a "humanized mouse model" would be more suited for immunological research. Such a mouse model has been successfully generated in NOD-SCID or Rag-deficient immune compromised mice by implanting human stem cells and thymus to reconstitute an entire human immune system.

Furthermore, when a therapeutic strategy is too specific, it may carry with it significant pitfalls for the reasons described above. Many strategies are now designed to target more "downstream" processes by blocking T cell entrance into the CNS or reducing the CNS inflammation seen in MS. Interferon-β and humanized antibody to integrin-α4 are good examples. Immunological research during the last 15 to 20 years has provided important lessons, as described above, and has produced exciting results. We now have interferon-β, glatiramer acetate, perhaps natalizumab, and many other immunotherapies that are currently being tested in clinical trials at various stages. Moreover, forward-looking research, including stem cell approaches, has brought new promise that damaged myelin or neuronal tissue may be repaired or regenerated by stem cells when inflammation and demyelination are under therapeutic control.

In conclusion, we are entering an exciting time in history—witnessing rapid development of new treatments for MS and learning how to treat the disease effectively. Several chapters in this book review some of the highlights in the field and provide expert opinions on what the future holds for our patients who suffer daily from this devastating disease. I am grateful to our contributors, many of whom are long-time collaborators and friends, for bringing together this unique and timely book.

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