The Neurobiology of Multiple Sclerosis

EDITED BY

ALIREZA MINAGAR

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PREFACE

Multiple sclerosis (MS) is an immune-mediated neurodegenerative disorder of the human central nervous system (CNS), which usually affects young adults with certain genetic background who are then exposed to certain precipitating environmental antigen(s). Despite major advances of the past two decades in understanding the pathophysiology of MS, and in spite of the introduction of new immunomodulatory and immunosuppressive agents, which may slow down disease progression and delay the onset of disability, the "cause" and the "cure" for MS remain elusive. What traditionally has been viewed and researched as a demyelinating disease is a more widespread destructive process than was initially conceived and affects several resident cells of the CNS. In addition, what has been previously termed as "MS" is not a single syndrome but a conglomeration of various syndromes with unlike pathogenesis and dissimilar responses to available treatments. Although we have learned much more about the most common form of MS (relapsing-remitting MS), the molecular pathogenesis of clinical relapses and remissions remains only partially understood.

This volume of *International Review of Neurobiology* focuses on MS and related disorders. The volume can be divided into various sections with the main emphasis on MS pathogenesis, clinical features and epidemiology, neuroimaging, and treatment. These papers are followed by three other chapters on MS-related disorders.

The first section of this volume contains 10 chapters on pathogenesis and immunopathogenesis of MS. First, Minagar *et al.* (2007) reviews the interactions of leukocytes and cerebral endothelial cells in the pathogenesis of MS. This chapter is followed by three other chapters discussing the role of B cells (Nikbin *et al.*, 2007a), CD4 T cells (Chitnis, 2007), and CD8 cells (Johnson *et al.*, 2007) in the pathogenesis of MS, with emphasis on the most recent findings on these cell groups. This section then continues with an excellent review of immunopathogenesis of MS by Agrawal and Yong (2007), which provides readers with a detailed analysis of pathogenic mechanisms. The next five chapters provide readers with detailed reviews of some of the most intensely debated aspects of MS. Libbey *et al.* (2007) discusses the concept of molecular mimicry in pathogenesis of MS and present a detailed discussion about all proposed agents with molecular similarities to self-antigens and their possible involvement in the initiation of the inflammatory cascade. Next, Musse and Harauz (2007) present an excellent discussion on the role of the myelin basic protein family in pathogenesis of MS. The last two chapters of this section review look at the mechanisms in the world of MS.

Nikbin *et al.* (2007b) describe the role of microchimerism in immune-mediated diseases in general, but MS in particular. The authors raise new questions about the possible role of this fascinating phenomenon in the development of, and also protection against, MS. This interesting chapter also probes the intensely discussed issue of stem cell therapy in MS. This remarkable chapter is followed by an interesting chapter on the involvement of insulin-like growth factors in MS, providing our avid readers with the latest findings in this field (Chesik *et al.*, 2007). The last chapter delves into another fascinating subject: microparticles, exosomes, and their role in neuropathologic syndromes (Horstman *et al.*, 2007). The last decade has witnessed remarkable advances concerning the role of these newly detected participants in the inflammatory cosmos; and many scientists around the globe are now involved in exploring their nature and function.

The second section of this issue is devoted to the clinical features and epidemiology of MS. Elliot and colleagues provide the readers with two superb chapters, one on migraine and MS (Elliott, 2007) and the other on the various pain syndromes occurring in the MS population (Kenner *et al.*, 2007). Generally, MS is not considered a "painful disease"; however, this is an erroneous view that disregards the daily pain and agony experienced by MS patients. The authors of these two chapters review the commonality of migraine and other painful syndromes in MS patients. This section then continues with two outstanding reviews. The first involves the neuropsychiatric manifestations of MS (Pinkston *et al.*, 2007), and the next focuses on the role of cerebrospinal fluid analysis in diagnosing MS and excluding other disorders which can mimic MS (Luque and Jaffe, 2007). The next chapter in this section discusses the clinical features and therapeutic options for MS in very young patients (Rotasy, 2007). MS in children is not a well-described entity, and only during the last few years, there has been a surge of interest in this significant issue. The following chapter of this second section describes the epidemiology and clinical features of MS in Isfahan, Iran (Saadatnia *et al.*, 2007). The literature on MS in Middle Eastern countries, particularly Iran, is limited. The authors provide us with a new window into the clinical behavior of MS in Iranian patients, including the significant features that set them apart from the disease process, which one observes in the Western Hemisphere. The last three chapters in this section discuss differential diagnosis, prognostic factors, and gender issues in MS. Fadil *et al.* (2007) provide readers with an extensive review of other disorders which comprise the differential diagnosis of MS, potentially assisting our younger colleagues in setting MS apart from MS imitators. This useful chapter is followed by another significant chapter concerning the prognosis of MS. MS patients often make inquiry about their prognosis, that is, "what lies ahead of them." Bergamaschi (2007) has compiled a comprehensive chapter that, in great detail, examines the prognostic factors in MS. This section ends with another thorough review, the role of gender in the development of MS. Schwendimann

and Alekseeva (2007) attempt to provide some answers to the fundamental questions: Why MS is more frequent among female than male individuals? The authors examine the available literature on this significant topic and provide readers with interesting and thought-provoking concepts.

The third section of this volume concentrates on the various aspects of neuroimaging of MS. At first, Zivadinov and Cox (2007) present an ample review of the latest findings in the field of MS neuroimaging. This chapter sets the stage for the next two chapters. The first discusses newest MRI techniques for detection of cortical lesions (Dolezal *et al.*, 2007), and the next discusses differentiation of ischemic lesions from demyelinating lesions (Hoque *et al.*, 2007). Finally, this section contains a chapter correlating various HLA class II markers with MRI-measured disease severity (Zivadinov *et al.*, 2007).

The treatment section contains two significant chapters on the mechanisms of action of glatiramer acetate, followed by a chapter of emerging treatments for MS. Ziemssen and Schrempf (2007) present their detailed chapter delineating the immunomodulatory mechanisms of glatiramer acetate. Then, Korniychuk *et al.* (2007) provide readers with an up-to-date report on the upcoming therapies for MS. This interesting chapter presents the latest findings on the therapeutic as well as adverse effects of monoclonal antibodies, which are currently under investigation for treatment of MS. The final chapter of this section is provided by Chari (2007) who reviews the concept of remyelination in MS and presents the latest knowledge on this key issue to our readers.

The final section of this issue of the *International Review of Neurobiology* concentrates on three other disorders that often occur in MS or are in its differential diagnosis. First, Hunt and Patwardhan (2007) review the subject of trigeminal neuralgia with emphasis on its relevance to MS, since significant number of MS patients initially present with trigeminal neuralgia. Then, Kaur and Bennett (2007) review optic neuritis and other neuro-ophthalmologic presentation in MS. This excellent chapter provides clinicians with the latest findings in the field, assisting them to interpret these important visual symptoms and signs in the MS population. The issue finishes with another remarkable chapter that concerns one of the editor's favorite disorders: neuromyelitis optica (Wingerchuk, 2007). Despite major advances in our understanding of the pathogenesis of neuromyelitis optica, the cause and treatment of this unique and devastating syndrome still remain elusive. In this chapter, Wingerchuk, a world authority, presents the latest developments regarding the pathogenesis of this disorder.

In summary, the contributors to this issue of *International Review of Neurobiology* have attempted to extend the readers' knowledge of the various aspects of MS and MS-related syndromes. Each chapter addresses a critical issue in the study of MS, with the hope of stimulating further research into the pathogenesis of this elusive disease.

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THE DESTRUCTIVE ALLIANCE: INTERACTIONS OF LEUKOCYTES, CEREBRAL ENDOTHELIAL CELLS, AND THE IMMUNE CASCADE IN PATHOGENESIS OF MULTIPLE SCLEROSIS

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Multiple sclerosis (MS) is an inflammatory disease of the human central nervous system (CNS) which develops predominantly in young adults with certain predisposing genetic characteristics, often following exposure to initiating environmental insult(s) including viral infections. The causes of MS remain elusive and no entire cure is in sight. However, it is well known that interactions between the immune system and the CNS play a central role in MS pathogenesis. Patients with MS generate CD4+ autoreactive T cells that at some point differentiate to Th1 phenotype cells, which are the major players in maintaining a continuous destructive immune response against brain and spinal cord antigens. Other significant participants in MS pathogenesis involved in the destruction of the target tissue are cerebral endothelial cells, CD8+ T cells, B cells, complement, autoantibodies, cytokines, and chemokines. The presence and interactions of all these participants further complicate the pathogenesis of MS, and make finding a cure for MS challenging. This chapter looks at the roles of these factors in the development of MS.

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I. Introduction

Multiple sclerosis (MS) is an immune-mediated neurodegenerative disorder which affects the human central nervous system (CNS) (Frohman *et al.*, 2006; Noseworthy *et al.*, 2000). In the United States alone, more than 350,000 individuals suffer from MS, and it is the most common neurological cause of disability in young adults. Generally, MS is not lethal, but imposes devastating neurological and psychiatric limits on patients. It is important to realize that MS is not a single disease but a conglomerate of different neurological syndromes with different pathological bases and hence dissimilar responses to therapeutic intervention. Relapsing-remitting MS (RRMS), the most common form of MS, affects females twice as often as males (Keegan and Noseworthy, 2002). Many patients with RRMS, with or without treatment, will later develop secondary progressive MS (SPMS). SPMS is characterized as a neurodegenerative syndrome with less clinical relapses, less response to immunomodulatory treatments, and persistent progression of the disease with accumulation of disability. Primary progressive MS (PPMS) is manifested by an insidious onset and steady disease progression. Patients with PPMS show the least responsiveness to therapy. Neuropathological studies have shown that each of these different forms of MS show different patterns of morphological and histological alterations in the CNS (Lucchinetti *et al.*, 2000). For example, RRMS is pathologically characterized by the predominant presence of inflammatory cells, while the neuropathology of PPMS mainly consists of less severe inflammation, more prolonged T-cell infiltration, more pronounced oligodendrocyte loss, and an ongoing low level of axonal damage in PPMS (Bruck *et al.*, 2002). The factors responsible for this diverse underlying neuropathology remain largely unknown but most likely reflect compound interactions between individual genetics and environmental antigenic "triggers," all of which provoke immune responses and/or increased levels of susceptibility to the inflammatory cascade. In addition to these initiating factors, chronic inflammation also alters and impairs mechanisms related to repair and restitution in the CNS (Frohman *et al.*, 2006).

Currently, there are two main views about disease onset in MS: central versus peripheral. Some neuropathologists and neuroscientists believe that MS begins within the CNS and then propagates to the peripheral immune system (Barnett and Prineas, 2004). A neuropathology study by Barnett and Prineas (2004) of patients with RRMS strongly supports this concept. The investigators reported clinical and pathological findings in 12 patients with relapsing and remitting MS, who died during or shortly after the onset of a relapse. On the basis of their observations, neuropathological changes not previously associated with the formation of new symptomatic lesions were observed in seven cases, and included extensive oligodendrocyte apoptosis. Microglia were activated in the myelinated tissue which

contained few or no lymphocytes or myelin-associated phagocytes. The findings of this study raise the possibility that MS may be initiated within the CNS and then move to the periphery.

On the other hand, the majority of neuroscientists believe that MS is triggered only after an individual's exposure to certain environmental factors like viral agents (Steinman and Zamvil, 2006). This initial viral exposure/infection activates CD4+ T cells against CNS tissue antigens. These imprinted cells eventually gain access to the CNS microenvironment, which in turn perpetuates ongoing cycles of neuroinflammation and neurodegeneration (Lovett-Racke and Racke, 2006). Most neuroimmunologists favor the peripheral onset model of MS based on composition of cellular infiltrates of the CSF and MS lesions, and data obtained from experimental allergic (autoimmune) encephalomyelitis (EAE). In EAE and perhaps in MS, CD4+ T cells somehow become sensitized against myelin basic proteins (MBPs), and eventually cross the endothelial barrier of the blood–brain barrier (BBB). This concept of MS pathogenesis is further supported by the fact that certain class II HLA molecules act as the antigen-presenting molecules to the activated pathogenic CD4+ T cells (Kort *et al.*, 2006).

The dramatic increase in research into MS pathogenesis during the last two decades has expanded our knowledge of the involvement of other cellular/molecular elements in pathogenesis of this elusive and complicated neurological disease. In recent years, we have learned more about the various roles of B cells, CD8+ T cells, cerebral endothelial cells, and various pro- and anti-inflammatory cytokines in the development and maintenance of the continuous pathology of MS. The roles of B cells, CD4+ T cells, and CD8+ T cells have been described in detail in separate chapters in this volume. Therefore, we will only focus on the role of cerebral endothelial cells and their interactions with activated leukocytes in pathogenesis of MS.

II. Role of Activated Cerebral Endothelial Cells in Pathogenesis of MS

Cerebral endothelial cells create the anatomic and physiological barrier of the BBB and play an essential role in forming the demyelinating lesions of MS. Under normal circumstances, CNS endothelial cells prevent transendothelial escape of various blood-borne molecules and the migration of leukocytes into the CNS. Indeed, the combined endothelial barrier and the supporting astrocytes keep the CNS out of reach of the peripheral immune system, homeostatically maintaining a stable environment for neurons to function. Cerebral endothelial cells possess several unique characteristics which enable them to protect the CNS. Cerebral endothelial cells are metabolically highly active, lack fenestrations, create a complex network of tight junctions that adheres between

adjacent cells, and block paracellular movement of cells and molecules into the CNS compartment (Abbott *et al.*, 2006; Minagar and Alexander, 2003). Cerebral endothelial cells contain selective transport mechanisms which mediate transport of nutrients into and toxic metabolites out of the CNS (Abbott *et al.*, 2006). Under normal circumstances, cerebral endothelial cells do not express class II HLA molecules and cannot act as antigen-presenting cells. In addition, CNS does not have a lymphatic system, a feature which makes CNS more immunoprivileged (Hatterer *et al.*, 2006).

However, during neuroinflammatory disorders, such as MS, the inflammatory cells (especially MBP reactive CD4+ T cells), macrophages, and B cells readily gain access to and initiate a continuous cascade of destruction within the CNS.

III. Potential Role of Endothelial Microparticles in Pathogenesis of MS

It is known that under normal circumstances, endothelial cells continuously shed small membranous vesicles called "endothelial microparticles" (EMP) $<1\ \mu$m, consisting mainly of membrane phospholipids and proteins. Released EMP also carry the same adhesion molecules as their parent cells and have been extensively studied in the context of various pathological conditions including MS (Jimenez *et al.*, 2005). During pathogenesis of active MS *in vivo* and on exposure of cerebral endothelial cells to elevated serum levels of proinflammatory cytokines, such as TNF-α and IFN-γ, high numbers of EMP are released into peripheral circulation (Jy *et al.*, 2004). We reported elevated plasma of EMP carrying CD31/PECAM-1 (CD31 + EMP) during MS relapses (Minagar *et al.*, 2001). We observed the elevation of CD51/endoglin + EMP during both relapse and remission. Elevated plasma levels of CD31 + EMP was associated with presence of contrast-enhancing lesions on brain MRI scans. In another set of experiments, Jy *et al.* (2004) showed that EMP formed bonds with monocytes and created EMP-monocyte conjugates. The plasma levels of these CD54/ICAM-1 + EMP-monocyte conjugates were elevated in MS patients with active disease. The investigators also assessed the role of EMP-monocyte conjugates in transendothelial migration of monocytes and observed that the formation of such complexes facilitated transendothelial migration of monocytes. The investigators concluded that EMP could enhance inflammation and increase transendothelial migration of monocytes in MS by binding to and activating monocytes through CD54/ICAM-1. Further research into role of EMP in MS pathogenesis revealed that beta-interferons (IFN-β1a and IFN-β1b) were able to reduce the amount of EMP released by MS patients, both *in vitro* (Jimenez *et al.*, 2005) and *in vivo* (Sheremata *et al.*, 2006).

IV. Interactions Among Endothelial Cells and Activated Leukocytes in Pathogenesis of MS

Transendothelial migration of activated leukocytes in pathogenesis of MS is a dynamic and complicated process which remains marginally understood. Passage of the activated leukocytes through the junctions between adjacent endothelial cells involves interactions among passing cells and junctional components.

The classic model of leukocyte migration through endothelium consists of a number of key steps: rolling and tethering, interactions of activated leukocytes with adhesion molecules expressed by stimulated endothelium, which leads to adhesion, and migration. Tethering and rolling captures the activated leukocytes and is a crucial step in MS pathogenesis. Initially, leukocytes come in contact with the underlying endothelium, a process which is mediated by adhesion molecules of the selectin family and their corresponding carbohydrate ligands. The rolling process slows leukocytes, letting them contact the endothelial surface sampling for the presence of platelet-activating factors and chemokines. Suppressing rolling behavior inhibits leukocyte adhesion, but inhibiting firm adhesion does not block rolling.

The selectins are type 1 transmembrane glycoproteins which attach to sialylated carbohydrate motifs in a Ca^{2+}-dependent manner. Three different types of selectins are identified: L-, P-, and E-selectins and all three groups of selectin genes are located on chromosome 1. These selectins share a lectin-like domain at the N-terminus followed by an epidermal growth factor (EGF)-like domain. L-selectins (CD62L) is expressed by neutrophils, myeloid, naive T cells, memory, and activated T cells. P-selectins (CD62P) are expressed constitutively by platelets (in their α-granules), and later on the activated platelet surface. Similarly, endothelial Weibel–Palade bodies store P-selectin which is rapidly mobilized to the cell surface following activation. E-selectin (CD62E) is expressed exclusively by endothelial cells. However, E- and P-selectins and PGSL-1 are not involved in pathogenesis of EAE and the entry of immune cells to the CNS and thus may play a relatively minor role in human MS (Engelhardt *et al.*, 2005; Osmers *et al.*, 2005).

Firm adhesion of the activated leukocyte precedes transendothelial migration. Under normal circumstances, the complexion of the resting cerebral endothelium differs significantly from activated cells and has low selectin levels, but constitutively expresses ICAM-1 and ICAM-2. Studies on animals with EAE demonstrated that the expression of intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) are dramatically upregulated by inflamed cerebral endothelium (Baron *et al.*, 1993; Cross *et al.*, 1990; Steffen *et al.*, 1994). The activated leukocytes within the perivenular cuffs of MS lesions express ligands for ICAM-1 and VCAM-1 (e.g., LFA-1 and $\alpha 4\beta 1$ integrins), suggesting these are involved in the efflux of these cells (Engelhardt *et al.*, 1998). Upregulated VCAM-1 and ICAM-1 expression play a significant role in the

pathogenesis of EAE and MS since studies have demonstrated adhesion of encephalitogenic CD4+ T cells and monocytes to mouse or human cerebral endothelial cells via $\alpha 4\beta 1$ integrin-VCAM-1- and LFA-1-ICAM-1-mediated interactions (Floris *et al.*, 2002; Greenwood *et al.*, 1995; Laschinger and Engelhardt, 2000; Seguin *et al.*, 2003).

Mucosal addressin cell adhesion molecule-1 (MAdCAM-1) is another adhesion molecule which may be intimately involved in the pathogenesis of EAE (Engelhardt *et al.*, 2001) and human MS. The ligand for MAdCAM-1 is $\alpha 4\beta 7$ (Briskin *et al.*, 1993) and under inflamed conditions, epithelial cells of the choroid plexus express ICAM-1, VCAM-1, and MAdCAM-1 (Engelhardt *et al.*, 2001). The precise role of MAdCAM-1 in MS remains unknown, but MAdCAM-1 expression is known to be induced by cytokines, TNF-α, in particular (Sasaki *et al.*, 2004, 2005; Sikorski *et al.*, 1993) in an oxidant-dependent, NO-inhibitable manner (Oshima *et al.*, 2001). MAdCAM-1 is implicated in MS since it is abundantly expressed within the chronically inflamed cerebrum in human MS and in MS models (Kanwar *et al.*, 2000; Kumpfel *et al.*, 2002), and importantly antibodies against MAdCAM-1 block disease progression in EAE when given early in its course (Kanwar *et al.*, 2000). The humanized anti-$\alpha 4$ and anti-$\alpha 7$ integrin monoclonal antibody, "*Tysabri*," the most recent treatment for MS (Miller *et al.*, 2003) and Crohn's disease (Ghosh *et al.*, 2003), targets both VCAM-1- and MAdCAM-1-dependent adhesion mechanisms (Kumpfel *et al.*, 2002).

During EAE pathogenesis, two members of $\beta 2$ integrin family LFA-1 and Mac-1 and their ligands ICAM-1 and ICAM-2 have also been implicated in transendothelial migration of T cells (Laschinger *et al.*, 2002). The role of $\beta 2$ integrins in the extravasation of encephalitogenic T cells into the CNS is also supported by the fact that ICAM-1 and ICAM-2 endothelial knockouts exhibit significantly decreased T-cell migration (Lyck *et al.*, 2003), but it is not clear which of the different structural motifs in ICAM-1 are involved in the adhesion and migration of autoreactive CD4+ T cells in MS (Greenwood *et al.*, 2003; Lyck *et al.*, 2003).

Platelet-endothelial cell adhesion molecule (PECAM-1/CD31) is a 130-kDa glycoprotein member of the immunoglobulin family supporting extravasation of activated leukocytes into the CNS in MS. In MS pathogenesis, both the soluble (Losy *et al.*, 1999) and insoluble (microparticulate) forms of PECAM-1 (Minagar *et al.*, 2001) have been implicated. PECAM-1's role in extravasation is complex, and may both inhibit and facilitate leukocyte emigration. While Qing *et al.* (2001), using T-cell receptor transgenic mice, showed that intravenous injection of anti-PECAM-1 antibody or PECAM-Ig chimera diminished migration of α/β TCR^+ $V\beta 3^+$ $Mac1^-$ cells into the CNS, Graesser *et al.* (2002) demonstrated that PECAM-1 KO mice in the EAE model of MS showed an increased extravasation of leukocytes across the BBB.

Other molecules implicated in leukocyte migration in MS pathophysiology may include CD99. CD99 is a 32-kD dense type I transmembrane protein expressed

by hematopoietic cells, leukocytes, and endothelial cells. CD99 is densely *O*-glycosylated and its concentration at cell junctions may suggest that it supports transjunctional movement. For example, Schenkel *et al.* (2002) demonstrated that anti-CD99 lowered monocytes migration across the endothelial cell layers by more than 90%. The junctional adhesion molecules or JAMs are also expressed at endothelial tight junctions, and may support monocytes and neutrophils extravasation in MS as well (Del Maschio *et al.*, 1999; Martin-Padura *et al.*, 1998).

V. MS and Endothelial Tight Junctions

The molecular basis of the final step in trafficking of antigen-specific CD4+ T cells into the CNS—migration beyond the endothelium—remains largely unknown. The two mechanisms for transendothelial leukocyte migration include paracellular and transcellular migration. A major unanswered question is whether activated leukocytes, particularly activated CD4+ T cells, migrate paracellulary through circulating endothelial cell (CEC) junctions, or whether they penetrate the BBB, membrane/cytoplasm with no junction involvement (Greenwood *et al.*, 1994; Lossinsky *et al.*, 1989; McMenamin *et al.*, 1992; Raine *et al.*, 1990; Wekerle *et al.*, 1991; Wolburg, 2005). To explore endothelial tight junctions in pathogenesis of MS, Plumb *et al.* (2002) investigated the expression of tight junction (TJ) proteins (occludin and ZO-1) in blood vessels in active MS lesions from eight cases of MS, and in six cases of normal-appearing white matter (NAWM). Blood vessels were imaged by confocal microscopy, which revealed abnormal TJs in vessels with premortem serum protein leakage. The investigators concluded that the existence of abnormal or opened TJs, associated with inflammation, might contribute to BBB leakage in enhancing MRI lesions and may also be involved in subtle leakage in nonenhancing focal and diffuse lesions in NAWM.

Our own observations show that serum from MS patients disturbs tight and adherens junctions [through downregulation of the expression of occludin and vascular endothelium (VE) cadherin] (Minagar *et al.*, 2003) and cytokine-altered BBB junctions may represent an MS-specific mechanism creating a pathway for both protein and cell leakage in MS.

VI. Conclusions

Interactions among many components of the inflammatory cascade: inflamed endothelial cells, activated leukocytes, inflammatory cytokines, and chemokines play central roles in initiating and sustaining the cerebrovascular consequences of

the unchecked immune system in MS. Each step of this complex immune cascade, however, represents a potential therapeutic opportunity. The currently generalized and nonspecific immunosuppressive therapy for MS is gradually giving way to more selective approaches, as we improve our understanding of the major mechanisms in MS. Consequently, continued research into the basis of these interactions is needed, which will develop more specific effective therapies with less adverse effects for relieving MS symptomatology and disease progression.

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