

PART I

Pathology and Diagnosis

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CHAPTER 1

Disease Pathogenesis

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Introduction

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS) that primarily affects young adults [1]. The role of immune system in MS is indisputable. The primary function of the immune system is to protect the body against myriad ever-evolving pathogens and it broadly falls into two categories the “innate immune system” and “adaptive immune system.” The important difference in the innate and adaptive arms of immunity is that the adaptive immune system is highly specific toward an antigen. The immune-mediated inflammation of MS was initially recognized in 1948 by Elvin Kabat who observed the presence of oligoclonal immunoglobulins in the cerebrospinal fluid from MS patients. In following years, great strides have been made in understanding the role of both adaptive and innate immune system in Experimental Autoimmune Encephalomyelitis (EAE, an animal model of MS) MS but it is not known the degree to which the adaptive and innate immune systems interact in MS.

In most instances, MS begins as a relapsing remitting disease that in many patients becomes secondary progressive. Approximately 10% of patients begin with a primary progressive form of the disease. Although primary progressive MS differs clinically and in treatment response from relapsing MS [2], it is somehow related as there are families in which one member has relapsing MS and another the primary progressive form. Not all patients enter the secondary progressive stage and, in addition to these, there are benign and malignant forms of MS. This heterogeneity of the clinical course may relate to changes that occur in the adaptive and innate immune system over the course of the illness (Figure 1.1). The progressive forms of the disease are the most disabling and are likely similar in terms of pathogenic mechanisms. Epidemiologic studies have raised the question

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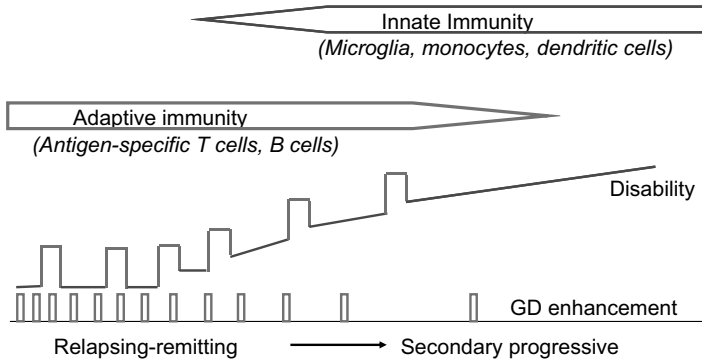


Figure 1.1 Immune status and disease course in multiple sclerosis. MS involves a relapsing-remitting phase followed by a secondary progressive phase. The relapsing-remitting phase is characterized by clinical attacks, gadolinium enhancement on MRI, minimal disability, and is driven by the adaptive immune response. The secondary progressive phase is characterized by the progressive accumulation of disability in the absence of clinical attacks and is driven by the innate immune system. (Reproduced from Weiner [147] with permission from Wiley–Blackwell.)

whether relapses are related to or are independent from the development of progressive MS [3]. This raises the central question: will current therapy that is effective in reducing relapses also delay or prevent the onset of progression? The understanding of MS pathology and immune system helped us to design various treatment strategies for MS and, given this progress, we must now ask: “What would it mean to cure MS?” and “What is needed to achieve this goal?” [4]. When one examines these questions, it becomes clear that there are three definitions of “cure” as it relates to MS: (1) halt progression of the disease; (2) reverse neurologic deficits; and (3) develop a strategy to prevent MS. We are making progress in halting or slowing the progression of MS, have approaches that may help to reverse neurologic deficits, and, for the first time, are beginning to develop strategies to prevent MS.

Clinical and pathologic heterogeneity of MS

Multiple sclerosis is a nondescript term that refers to “multiple scars” that accumulate in the brain and spinal cord. MS is more a syndrome than a single disease entity and the MS syndrome has both clinical and pathologic heterogeneity [5–6]. The clinical heterogeneity is reflected in the different types and stages of the disease. An important question in MS is the relationship of the progressive to relapsing forms. Devic disease appears

to be an MS variant associated with antibodies to the aquaporin receptor [7–8]. There are rare malignant forms including Marburg’s variant, tumefactive MS and Balo’s concentric sclerosis. An unanswered question relates to why benign forms of MS exist [9–10]. Although some cases of MS are defined as benign, and progress with prolonged follow up [11] there are clearly benign forms of the disease. By definition patients with benign MS do not enter the progressive phase. The ability to identify benign or malignant MS early in the course of the illness is very important for treatment strategies. We compared brain parenchymal fraction (BPF) over a 2-year period in benign vs early relapsing-remitting MS matched for age and the EDSS and found that patients with benign MS had a smaller loss of BPF [12]. As it impinges on the EDSS, the majority of disability in MS relates to spinal cord dysfunction. The relationship between spinal cord changes and brain MRI changes is not well known, but changes in the medulla oblongata which reflect spinal cord can be visualized on brain MRI and may correlate with entering the progressive phase [13]. In addition, an HLA-DR2 dose effect may be associated with a more severe form of the disease [14].

What triggers MS?

The etiology of MS is still debatable but the current data suggests that environmental factors in genetically susceptible background can predispose an individual to MS. Family studies assessing the risk of relatives suggests that first-degree relatives are 10–25 times at greater risk of developing MS than the general population [15–17]. The strongest genetic effect is correlated with HLA haplotypes. For instance *HLA*1501*, *HLA-DRB1*0301*, *HLA-DRB1*0405*, *HLA-DRB1*1303*, *HLA-DRB1*03*, *HLA-DRB1*01*, *HLA-DRB1*10*, *HLA-DRB1*11*, *HLA-DRB1*14* and *HLA-DRB1*08* have been shown to have either positive or negative association with MS [15]. Ethnicity and sex are other contributors in susceptibility to MS. The white population is more susceptible to disease than the African American population and women are at higher risk of developing MS than men [18], which is not associated with any MS-related gene present on the X chromosome but is more correlated with female physiology and hormones [19]. Other potential environmental risk factors are infections, vaccination, climate, and diet. Infections are considered the most common risk factor for MS as many infections and antibodies generated in response to these infections are present in sera or the cerebrospinal fluid (CSF) of MS patients at higher titers than controls. Epstein–Barr virus (EBV) is of great interest as >99% of MS patients and approximately 94% of age-matched controls are infected with EBV and increased antibody titers to EBV nuclear antigen 1 (EBNA-1) antigen are reported in MS [20–21]. Other infectious agents linked to MS etiology are

herpes virus 6, retroviruses and *Chlamydia pneumonia* [22]. Evidence for association of *Chlamydia pneumonia* with MS is debatable, as contradictory presence of this virus has been reported by different groups [23–26]. Decreased sunlight exposure, vitamin D level, and vitamin intake are also associated with MS incidence or protection [27–28]. In addition, studies using different cohorts of MS patients have shown a strong association between smoking and MS [29–30]. The etiology of MS is discussed in detail in the Chapter 3.

TOP TIPS 1.1: Risk factors for MS

- HLA susceptible genes
- Ethnicity
- Infections
- Vaccinations
- Climate
- Gender
- Smoking
- Diet

Pathology of MS

The pathology of MS lesion is defined by the presence of large, multifocal, demyelinated plaques, oligodendrocyte loss, and axonal degeneration. During the early development of MS lesions, the integrity of the blood–brain barrier is compromised, permitting the invasion of monocytes and T cells to the brain parenchyma. Mononuclear cells including activated microglia and peripheral monocytes are the primary cells involved in the demyelination of MS lesions. According to Trapp’s classification, MS lesions are categorized into three groups, active (acute), chronic active, and chronic inactive. Active and chronic active lesions are characterized by the presence of evenly distributed MHC class II positive cells [31]. Chronic active plaques are characterized by the presence of MHC class II and myelin lipid positive cells that are distributed perivascularly [31], whereas, chronic inactive lesion have few MHC class II positive cells [31] (Figure 1.2). Microarray results of autopsies from acute/active vs chronic silent lesions revealed a number of differentially expressed genes present only in active lesions [32]. These differentially expressed genes are mostly related to cytokines and their associated downstream pathways [32]. According to another classification based upon a broad spectrum of immunological and neurological markers on a large set of MS pathological samples, MS lesions were characterized into four different patterns. Patterns I and II are defined by the T cell and macrophage-mediated inflammation where pattern II exclusively showed antibody and complement dependent demyelination [33]. Pattern III lesions also contained T cells and macrophages and are defined by distal oligodendroglipathy [33]. Pattern IV is characterized by the complete loss

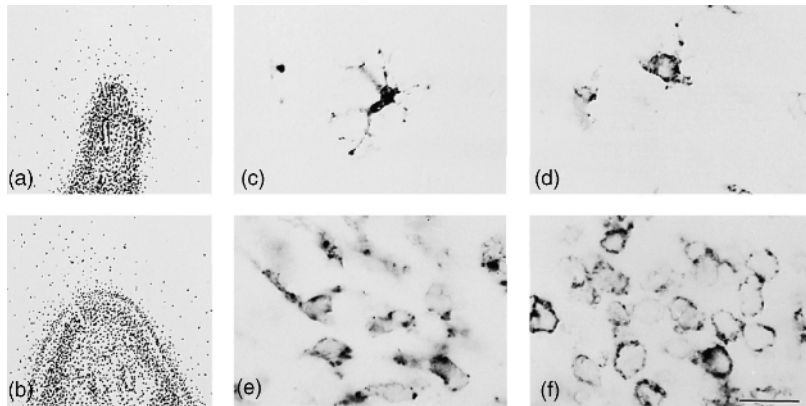


Figure 1.2 Schematic illustration (artistic rendition) of the distribution of MHC class II positive cells in active and chronic active MS lesions (A and B). Each dot represents an MHC class II positive cell. In active demyelinating lesions (A), MHC class II positive cells are evenly distributed throughout the lesion. In chronic active lesions (B), MHC class II positive cells are more concentrated at the lesion edge than within the lesion. Free-floating sections (30 μm thick) from MS brains stained with MHC class II antibody (C–F) demonstrate the morphological changes of parenchymal MHC class II positive cells that are located outside the lesion (C), near the edge of (D), at the edge of (E), and in the center of the demyelinated region (F). MHC class II positive cells closer to the lesion sites are rounder, larger than cells that are further away from the lesion site and extend fewer and shorter processes. Scale bar = 30 μm . (Reproduced from Trapp et al. [31] with permission from Elsevier.)

of oligodendrocyte in addition to the presence of inflammatory infiltrates mostly dominated by T cells and macrophages [33] (Plate 1.1).

We have identified a unique pattern of antibody reactivities to the CNS and lipid antigens in these pathological subtypes of MS patients [34]. In addition to these lesions in white matter, gray matter can be involved with evidence of brain cortical lesions or spinal cord gray matter involvement [35]. These lesions are characterized by less inflammatory infiltrates, microglial cell activation, and astrogliosis than white matter lesions and are independent of white matter lesions [36–38]. Regarding the role of B cells in MS pathology, postmortem analysis of brain tissue from secondary progressive patients, in which the initial relapsing-remitting phase was followed by a progressive phase, showed the formation of secondary B cell follicles containing germinal centers in the inflamed cerebral meninges [39] and the authors suggest that follicular positive SPMS patients have more severe disease [40], although this has yet to be confirmed. Investigation of MS pathology has provided targets for disease therapy, which are primarily directed at reduction of inflammatory cells invading the CNS.

Initiation of disease

(Th1/Th17) T cells

Cd4⁺ Pathogenic T cells: Upon antigenic stimulation, naïve CD4⁺ T cells activate, expand and differentiate into distinct subsets of T cells which are characterized by the production of different cytokines upon activation [41]. It is generally believed that acute MS lesions are initiated by a myelin reactive CD4⁺ T cell that is stimulated in the periphery and enters the brain and spinal cord (Figure 1.3). These CD4⁺ T cells have previously been felt to be IFN- γ secreting Th1 cells as IFN- γ was found to be present at the site of inflammation [42–45] and adoptive transfer of Th1 cells were able to transfer the disease [46]. However, it was found later that IFN- γ deficient mice are not resistant but highly susceptible to organ-specific autoimmune diseases [47]. It is now recognized that Th17 cells play a crucial role in autoimmunity in the experimental allergic encephalomyelitis (EAE) model [48] and increased numbers of Th17 cells have also been identified in MS [49]. Both types of pathogenic cell (Th1 and Th17) most probably play a role in MS and could account for the immunologic and clinical heterogeneity of the disease [50]. Immunohistochemical examinations of the brain demonstrate Th1/Th17 immune responses [51]. Th1 vs Th17 responses have been associated with different types of EAE [50]. TGF- β , a central cytokine in the induction of regulatory T cells, induces Th17 cells when combined with IL-6 [52]. Anti-IL-6 therapy is being investigated for the treatment of autoimmunity.

Cd8⁺ Pathogenic T cells: These cells are another subset of T cells that mostly provide defense against viral infections using cytotoxic weapons. Although CD8⁺ T cells have not been at the forefront of thinking in MS, CD8⁺ T cells are found in MS lesions at a higher frequency and CD8⁺ T cells reactive to myelin antigens have been reported in MS. It is likely that CD8⁺ T cells play a role in MS and also contribute to disease heterogeneity [53–54]. CD8⁺ T cells are also well poised to contribute directly to demyelination and axonal loss during inflammation by expression of various cytotoxic molecules (e.g. perforin and granzyme B) as well as death receptor ligands (e.g. FasL, TNF- α , TNF-related molecules). CD8⁺ T cells isolated from brain lesions show evidence of antigen-driven clonal expansion [55]. T cell lines generated from CD8⁺ T cell clones isolated from MS patients and healthy controls could mediate MHC class I restricted lysis of oligodendrocytes [56]. CD8⁺ T cells could also target other CNS resident cells including microglia, astrocytes, and neurons [57] suggesting a pathogenic potential of these cells in MS biology. The same group also observed the close proximity of granzyme B expressing CD8⁺ T cells to injured axons in MS lesions, which

furthermore emphasizes their role in the direct cytotoxicity of axons [57]. The importance of CD4⁺ and CD8⁺ T cells in EAE was compared in CD4 and CD8 knockout mice in a MOG-DBA/1 model. CD8^{-/-} mice had reduced demyelination and CNS inflammation compared to wild type animals. CD4^{-/-} animals, however, were refractory to EAE induction, suggesting a pathogenic role for CD8⁺ T cells [58]. Furthermore, CD8⁺ T cells are also able to contribute toward the secretion of IL-17 [59] and IFN- γ [57], which, as discussed above, are the important cytokines involved in disease pathology. These observations suggest that both CD4⁺ and CD8⁺ T cells are capable of playing pathogenic roles and their relative contribution might be responsible for disease heterogeneity.

B cells and antibodies

B cells are another essential component of an adaptive immune system, which mediates immunity against pathogens by the secretion of antigen-specific antibodies and by acting as an antigen presenting the cells required for T cell differentiation. Like T cells, B cells are also efficient in the production of various cytokines including IL-1, IL-4, IL-6, IL-10, IL-12, IL-23 and IL-16 [60–61]. Antibodies secreted by B cells or immune complexes can also activate other antigen-presenting cells like dendritic cells (DCs) and macrophages through the Fc receptor (Figure 1.3). Although autoantibodies (antibodies against self-antigens) have been reported in MS, there is no evidence that there are high affinity pathogenic antibodies in MS as in other antibody mediated autoimmune diseases such as myasthenia gravis [62]. Antibodies to myelin components, however, may participate in myelin loss [63]. A classic finding in MS is increased locally produced IgG and oligoclonal bands in the CSF, the pathogenic significance of which remains unknown. Treatment with rituximab, a monoclonal antibody that deletes B cells, dramatically reduces inflammatory disease activity as measured by MRI without affecting immunoglobulin levels, demonstrating a clear role for B cells in relapsing forms of MS [64]. The almost immediate response to rituximab suggests that B cells are either affecting T cell regulation via their antigen presentation function or by directly participating in lesion formation. B cells may have both anti-inflammatory and pro-inflammatory functions [60–65].

Regulation/remission of disease

Regulatory cells

Cd4⁺ and CD8⁺ regulatory T cells: It is now clear that the adaptive immune system consists of a network of regulatory T cells (Tregs) [66]. Regulatory

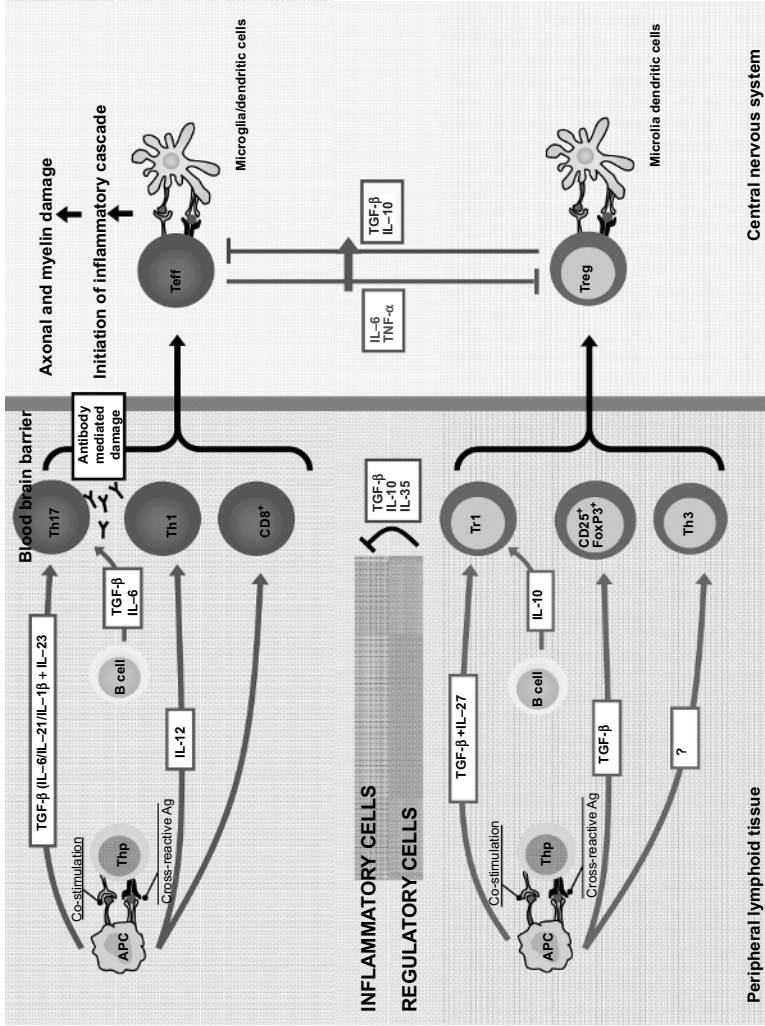


Figure 1.3 Immune pathways and adaptive immunity in the initiation of MS. MS is initiated by myelin reactive inflammatory T cells that cross the blood brain barrier and initiate an inflammatory cascade in the CNS. These inflammatory T cells are modulated by regulatory T cells both inside and outside the CNS. B cells may influence both inflammatory and regulatory T cells. (Reproduced from Weiner [147] with permission from Wiley–Blackwell.)

T cells mediate active suppression of self-antigen specific T cell responses and in the maintenance of peripheral tolerance [67–68]. Regulatory T cells can broadly be classified as natural Tregs and induced Tregs. Foxp3 is the major transcription factor for Tregs. CD25 marks natural Tregs and TGF- β induces Treg differentiation. Th3 cells are induced Tregs that secrete TGF- β [69] and Tr1 cells are induced Treg cells that secrete IL-10 [70]. Defects in regulatory T cell percentages [71–72] and function have been described in MS [73–75] and a major goal of MS immunotherapy is to induce regulatory cells in a physiologic and nontoxic fashion [76–77]. Th2 cells which are recognized by secretion of IL-4, IL-5, and IL-13, may also have regulatory T cell function as patients with parasitic infections that induce Th2 type responses have a milder form of MS [78]. Experimental data suggests that regulatory cells may not be effective if there is ongoing CNS inflammation [79]. We have taken the approach of using the mucosal immune system to induce regulatory cells and have found that oral anti-CD3 monoclonal antibody [80], and ligands that bind the aryl hydrocarbon receptor induce TGF- β dependent regulatory T cells that suppress EAE and provide a novel avenue for treating MS [81–82]. The regulatory function of CD8⁺ T cells is mostly ascribed to a population of T cells lacking expression of CD28 on their cell surface. These cells induce regulatory effect in a MOG-induced EAE model via induction of tolerogenic dendritic cells which in turn induces CD4⁺ and CD8⁺ regulatory T cell subpopulations [83–85]. Another interesting regulatory population in CD8⁺ T cell subset is CD8⁺CD122⁺ T cells which mediate suppressive effects via IL-10 [85–86]. The human counterpart of this population is recognized as CD8⁺CXCR3⁺ [87]. Depletion of CD8⁺CD122⁺ T cells increased the duration of disease symptoms. Conversely, transfer of this population ameliorated the disease in the MOG EAE model on a C57BL/6 background, suggesting a protective role of this population [88]. In addition, we have described the existence of a novel LAP⁺CD8⁺ T cell population that exhibited regulatory properties in EAE mice in a TGF- β and IFN- γ dependent manner [89].

Disease relapses

Disease relapses/exacerbation are the defining feature of the relapsing-remitting form of MS and reflect focal inflammatory events in the CNS. Relapse events occur on average 1.1 times per year during the early course of disease and decrease as the disease advances with increasing neurologic symptoms and age [90]. Disease relapse could last for a week to months or even more. Thus it's important to identify the conditions that could trigger relapse to determine if preventative measures could be taken to avoid

relapse. A strong correlation was found between upper respiratory tract infections and MS relapses [91–92]. This study confirmed that two-thirds of the attacks occur during a period of risk (the interval 1 week before and 5 weeks after the initiation of URI symptoms) and attack rates were 2.92 per year at risk compared to 1.16 per year when not at risk [92]. Another longitudinal study with 73 patients also confirmed these results, showing an increased attacks rate (rate ratio 2.1) during the period of risk that was associated with an increase in the number of gadolinium-enhancing regions suggesting that systemic infections result in more sustained damage than other disease exacerbations [93]. No specific virus was identified among these studies. Viral infection is associated with activation of autoreactive T cells through molecular mimicry (T cell reactive to viral antigen cross-react with self-antigen) [94], epitope spreading (release of sequestered antigen secondary to tissue destruction

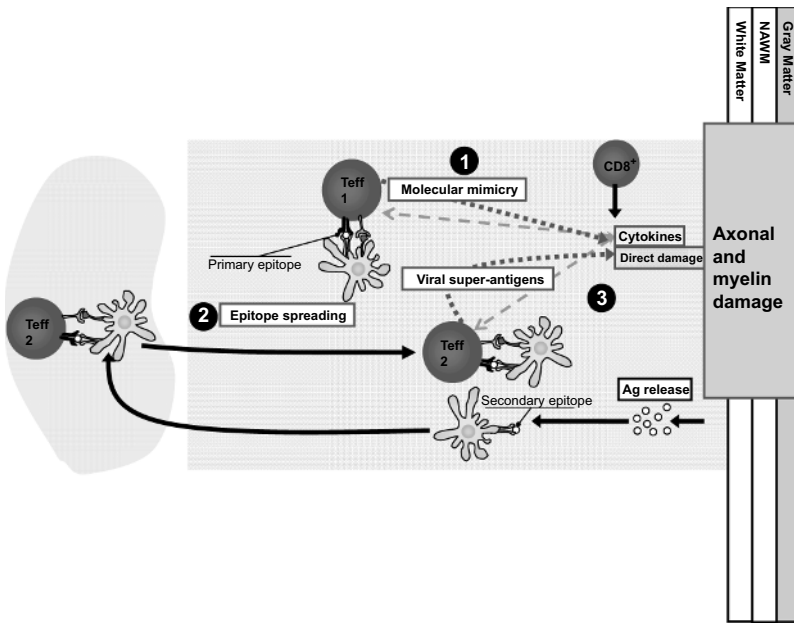


Figure 1.4 Disease relapse. (1) Cells reactive to a viral antigen can cross react to myelin self-antigen (molecular mimicry) and initiate a self-reactive immune response. (2) Inflammatory T cells that enter the CNS initiate a complex immunologic cascade consisting of epitope spreading which triggers new attacks through activation of more self-reactive T cells (epitope spreading). (3) Nonspecific activation of autoreactive T cells through cytokines released during an immune response against viral infection (viral super antigens). Dashed arrows indicate activation of T cells and dotted arrows suggest inflammation mediated by T cells through cytokine secretion and by direct damage of myelin sheath. (Reproduced from Weiner [147] with permission from Wiley–Blackwell.)

mediated by viral antigen) [95–96], and viral superantigens (nonspecific stimulation of autoreactive T cells) (Figure 1.4) [97]. Similarly, inflammatory cytokines like TNF- α and IFN- γ also increase during disease relapses [98]. Thus treatments targeting or controlling these cytokine responses should help to reduce relapse rates. Blocking TNF- α using antibodies or soluble receptors could decrease disease severity in murine EAE but has a worsening effect in MS patients [99–101]. Other factors that contribute toward disease relapse include a stressful life event [102–103], pregnancy [104], and high-dose cranial radiation [105–106]. Based upon studies describing important factors in the initiation, relapse, and progression of the disease it appears that lifestyle changes (including stress management, diet, exercise, smoking, alcohol consumption) in combination with anti-inflammatory therapy can modify the disease activity and should be suggested to MS patients.

Disease progression

Activation of the innate immune system

The innate immune system consists of dendritic cells, monocytes, microglia, natural killer (NK), and mast cells. It is increasingly recognized that the innate immune system plays an important role in the immunopathogenesis of MS. Although the secondary progressive phase of MS may be related to neurodegenerative changes in the CNS, it is now clear that the peripheral innate immune system changes when patients transition from the relapsing-remitting to the progressive stage. We found increased expression of osteopontin and costimulatory (CD40) [107] molecules and decreased expression of IL-27 (unpublished) in dendritic cells isolated from relapsing MS. Conversely, we observed abnormalities in the expression of CD80 and secretion of IL-12 and IL-18 in the dendritic cells from progressive patients [108–110]. Chronic microglial activation also occurs in MS [111] and this activation contributes to MS and EAE pathology via secretion of various pro-inflammatory cytokines and through antigen presentation [112]. Persistent activation of microglial cells has also been observed in the chronic phase of relapsing-remitting EAE and a correlation has been found between activated microglia and the loss of neuronal synapses [113]. Natural killer (NK) cells, another component of innate immune cells, are present in demyelinating lesions of patients with MS [114] and are thought to play a protective role through the production of various neurotrophic factors [115] and cytokines. An increase in IL-5 and IL-13 secreting “NK2” subpopulation was observed in MS patients in remission compared to patients in relapse, suggesting that the NK2 subpopulation

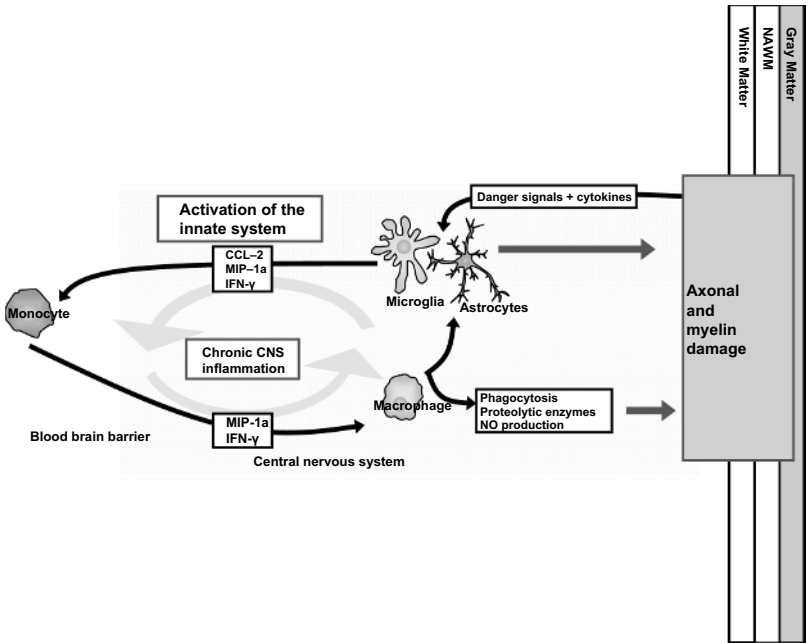


Figure 1.5 Inflammatory T cells that enter the CNS initiate a complex immunologic cascade consisting of cytokine secretion and exposure of new self-antigens that could triggers new attacks through activation of the innate immune system (microglia, dendritic cells, astrocytes, B cells), which leads to chronic CNS inflammation. (Reproduced from Weiner [147] with permission from Wiley–Blackwell.)

may have a beneficial role in maintaining the remission phase [116]. The same subset of NK cells seemed to negatively regulate the activation of antigen-specific autoreactive T cells [117]. In addition, a decreased cytotoxic activity of circulating NK cells has been described in patients with MS in their clinical relapses [118–119]. We have recently described a reduction of another subpopulation of NK cells, characterized as $CD8^{dim}CD56^{+}CD3^{-}CD4^{-}$, in untreated subjects with MS as well as clinical isolated syndrome (CIS) [120]. Treatment with immunomodulatory and immunosuppressant therapies, like daclizumab [121], interferon- β [122], and cyclophosphamide [123] show a beneficial effect through their action on a $CD56^{bright}$ NK cell subset in MS. Mast cells contain cytoplasmic granules rich in histamine and are known for their role in allergic and anaphylactic response. These cells can interact with the innate and acquired immune systems, including dendritic cells, neutrophils, and T and B lymphocytes [124–126]. In MS, histopathological analysis showed an accumulation of mast cells in MS plaques and normal appearing white matter [127–128]. In addition, the mast cell

specific enzyme tryptase is elevated in the CSF of MS patients [129] along with other mast-cell-specific genes in MS plaques.

In summary, the immunopathogenesis of MS integrates both limbs of the immune system and links them to different disease stages and processes. Thus, the adaptive immune system drives acute inflammatory events (attacks, gadolinium enhancement on MRI) whereas innate immunity drives progressive aspects of MS. A major question is whether aggressive and early anti-inflammatory treatment will prevent the secondary progressive form of the disease. There is some evidence that this is occurring: studies are beginning to show that treatment with interferons delays the onset of the progressive stage [130]. Of note, there is a form of EAE driven by the innate, rather than the adaptive, immune system [131]. There are no specific therapies designed to affect the innate immune system in MS, and efforts to investigate the innate immune system in MS and characterize it are now being explored to determine how the innate immune system relates to the disease stage and response to therapy. Furthermore, like the adaptive immune system, there are different classes of innate immune responses, e.g. protective and tolerogenic vs pathogenic and pro-inflammatory.

TOP TIPS 1.2: Immune cell involvement in MS pathogenesis

- Decreased percentages of CD4+ regulatory T cells
- Increased frequency of Th1 and Th17 CD4+ T cells
- CD8+ T cells
- B cells
- Activated dendritic cells
- Natural killer cells
- Microglial cells and monocytes

Neurodegeneration in MS

Axonal and myelin loss are prominent pathologic features of MS [132] and can be directly caused by immune cells (e.g. cytotoxic CD8 cells damaging neurons or macrophages stripping myelin from the axon [133]); or can result from release of toxic intermediates (e.g. glutamate, nitric oxide). These intermediates can trigger immune cascades that further enhance inflammatory-mediated CNS damage. Thus, glutamate and nitric oxide can lead to enhanced expression of CCL2 on astrocytes which, in turn, leads to infiltration of CD11b cells and additional tissue damage [134]. AMPA antagonists have been shown to have an ameliorating affect in acute EAE models [135–136] and we have found that a carbon-based fullerene linked to an NMDA receptor with anti-excitotoxic properties slows

progression and prevents axonal damage in the spinal cord in a model of chronic progressive EAE [134]. Although the compound is not an immune compound, it reduces the infiltration of CD11b cells into the CNS. Another important component of neurodegeneration relates to changes in sodium channels, suggesting that these could be potential therapeutic targets [137].

TOP TIPS 1.3: Potential therapeutic pathways for the treatment of MS

- Deplete Th1/Th17 cells
- Induce regulatory T cells
- Prevent lymphocyte trafficking
- Deplete B cells
- Affect innate immunity
- Provide neuroprotection
- Promote remyelination

Conclusion

In summary, MS represents an immune cell mediated neurologic syndrome rather than a single disease entity that has both clinical and pathologic heterogeneity [5–6]. A major tool to address the pathological heterogeneity of MS and devise appropriate treatment strategies is to develop reliable biomarkers. MRI has served as the primary biomarker for MS [138] and although conventional imaging does not link strongly to clinical outcomes, every FDA-approved MS drug has shown efficacy on MRI outcomes. Advances in magnetic resonance imaging are beginning to better define MS and its heterogeneity. We have also developed a Magnetic Resonance Disease Severity Scale (MRDSS) which combines multiple measures to provide an index of disease severity and progression as measured by MRI [139]. The addition of spinal cord imaging and gray matter involvement to the MRDSS should enhance its value as a biomarker. In addition, we and others have shown immune measures that are associated with disease activity and MRI activity [140–142]. RNA profiling is beginning to identify gene expression patterns associated with different forms of MS and disease progression [143–144]. In addition, we have demonstrated unique serum immune signatures linked to different stages and pathologic processes in MS that could provide a new avenue to understand disease heterogeneity, to monitor MS, and to characterize immunopathogenic mechanisms and therapeutic targets in the disease.

A complex disease such as MS will require treatment(s) that can affect multiple pathways, including (1) suppression of Th1/Th17 responses, (2) induction of Tregs, (3) altering the traffic of cells into the CNS, (4) protecting axons and myelin from degeneration initiated by inflammation that affects the innate immune system. If multiple drugs are required to achieve this effect, we must be certain that one treatment does not interfere with another. For example, it has been reported that statins

may interfere with the action of interferons [145]. Because of disease heterogeneity, there will be responders and nonresponders to each “effective” therapy and the earlier that treatment is initiated, the more likely it is to be effective. Inherent in the concept of curing MS by halting progression is the ability to demonstrate that progression has been halted in a group of patients and to identify those factors associated with preventing the onset of progressive disease. We have thus initiated the CLIMB natural history study in which more than 2000 patients with MS will be followed over a period of time with clinical evaluation, MRI studies, and immune and genetic markers, to identify the factors that are associated with the various stages of the disease and disease progression [146]. We believe that the identification of such factors may lead to the stratification of MS patients into smaller subclinical groups with defined common mechanisms of initiation of disease, inflammation, and demyelination during the disease progression that could help in designing/selecting subtype-specific treatment.

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