Immunology of Multiple Sclerosis

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Multiple sclerosis (MS) is an autoimmune disease of the central nervous system (CNS) leading to demyelination, axonal damage, and progressive neurologic disability. The development of MS is influenced by environmental factors, particularly the Epstein-Barr virus (EBV), and genetic factors, which include specific HLA types, particularly DRB1*1501-DQA1*0102-DQB1*0602, and a predisposition to autoimmunity in general. MS patients have increased circulating T-cell and antibody reactivity to myelin proteins and gangliosides. It is proposed that the role of EBV is to infect autoreactive B cells that then seed the CNS and promote the survival of autoreactive T cells there. It is also proposed that the clinical attacks of relapsing-remitting MS are orchestrated by myelin-reactive T cells entering the white matter of the CNS from the blood, and that the progressive disability in primary and secondary progressive MS is caused by the action of autoantibodies produced in the CNS by meningeal lymphoid follicles with germinal centers.

Introduction

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system (CNS) and a common cause of disability in young adults. Characteristically, the disease affects the brain, spinal cord, and optic nerves in the CNS and spares the nerve roots and peripheral nerves in the peripheral nervous system. Typically the first symptoms of MS occur between the ages of 15 and 50 years, but they can commence as early as 3 years and as late as the seventh decade. Females are affected twice as often as males. Usually the disease has a relapsing-remitting course, with repeated neurologic episodes, each of which is followed by partial or complete recovery and a period free of new symptoms. Most patients with relapsing-remitting MS eventually develop secondary progressive MS, in which there is progressive deterioration independent of relapses. In about 10% of patients, MS follows a primary progressive course, with a progressive neurologic deterioration from the onset, sometimes with superimposed relapses. Most patients live for at least 40 years after the onset of MS. The time course of neurologic disability in the different forms of MS is depicted at the bottom of Figure 1.

Based on a detailed analysis of the natural history of MS, Confavreux and Vukusic [1] recently proposed a unifying concept to explain the different clinical courses of MS. They observed that the times to reach disability milestones, and the ages at which these landmarks are reached, follow a predefined schedule not obviously influenced by relapses, whenever they may occur, or by the initial course of the disease, whatever its type. They concluded that relapsing-remitting MS can be regarded as MS in which insufficient time has elapsed for the conversion to secondary progressive MS; that secondary progressive MS is relapsing-remitting MS that has "grown older"; and that primary progressive MS is MS "amputated" from the usual preceding relapsing-remitting phase.

There is now a large body of evidence indicating that MS is an autoimmune disease but, as with the other human chronic autoimmune diseases, the primary cause of this autoimmunity is unknown. An important line of evidence supporting a role for autoimmunity in the pathogenesis of MS derives from the ability to replicate the clinical and neuropathologic features of MS in experimental animals by immunization with proteins derived from CNS myelin. The induced disease initially was termed *experimental allergic encephalomyelitis* but is now labeled *experimental autoimmune encephalomyelitis* (EAE). More than 7000 published articles on EAE have contributed to a large body of knowledge on mechanisms of immune-mediated damage to the CNS in experimental animals, which guides much research in MS [2]. The key difference between EAE and MS is that the cause of the autoimmunity in EAE is known (immunization with myelin antigens or insertion of transgenes to generate encephalitogenic T lymphocytes), whereas the cause of the autoimmunity in MS is unknown. In this review, we discuss recent important advances in knowledge of the immune mechanisms contributing to the pathogenesis of MS.

Pathology in the CNS

In relapsing-remitting MS the typical lesions consist of focal inflammatory demyelinating lesions in the white

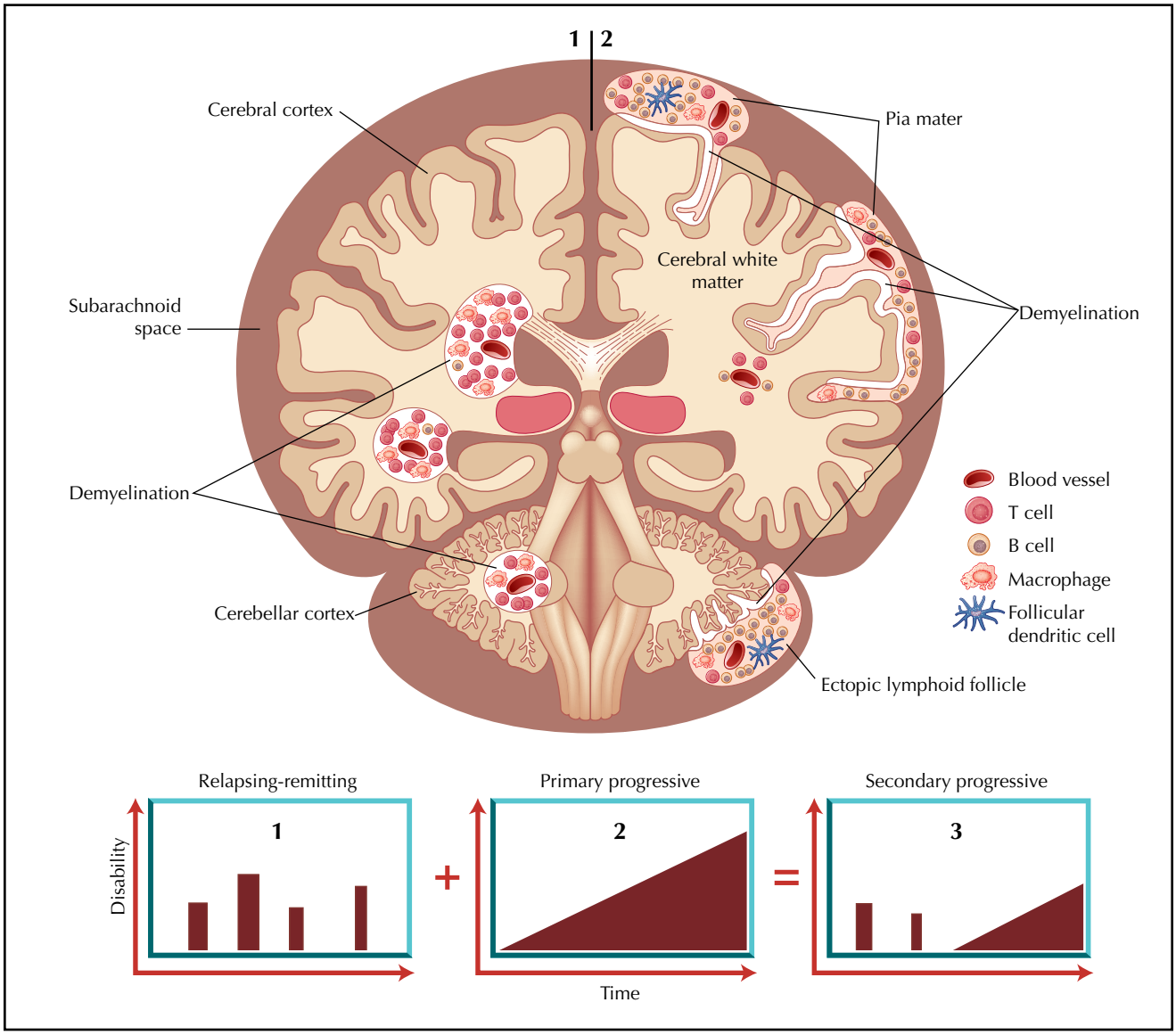

Figure 1. Proposed immunopathologic substrate of the different clinical courses of multiple sclerosis (MS). Coronal section of brain shows cerebral hemispheres, brainstem, and cerebellum, with graphs of time course of development of neurologic disability in relapsing-remitting MS *(1),* primary progressive MS *(2),* and secondary progressive MS *(3).* The immunopathology of relapsing-remitting MS is shown on the *left half* of the brain *(1),* and that of primary progressive MS is shown on the *right half (2).* Immunopathology of secondary progressive MS is initially that of relapsing-remitting MS *(1),* with later superimposition of immunopathology of primary progressive MS *(2).* It is proposed that in relapsing-remitting MS, the damage to central nervous system (CNS) white matter is mainly driven by autoreactive T cells entering the CNS from the blood, and that in primary progressive and secondary progressive MS it is driven by autoantibodies, which are produced by B cells in ectopic lymphoid follicles in the meninges and cause demyelination in adjacent underlying cerebral and cerebellar cortex. Meningeal structures resembling lymphoid follicles with germinal centers have been found in secondary progressive MS but not yet in primary progressive MS [6••]. Demyelination is represented by *white areas* in the cerebral and cerebellar white matter and in the cerebral and cerebellar cortex. (*Adapted from* Diamond et al. [51]; with permission.)

matter of the CNS [3]. The inflammatory infiltrate consists of T cells, B cells, macrophages, and activated microglia. The most characteristic feature of these lesions is primary demyelination, where there is removal of the myelin sheath around preserved axons; however, axonal transection also occurs in these areas of focal inflammatory demyelination. In contrast to relapsing-remitting MS, the neuropathology of secondary progressive MS and primary progressive MS is characterized by the presence of demyelination in the cerebral cortex and by less active inflammation in the focal white matter lesions [4•]. In progressive MS the cortical demyelination mainly affects the subpial layers of the cerebral cortex and is associated with mononuclear infiltration of the overlying meninges. Kutzelnigg et al. [4•] also found diffuse axonal injury in the cerebral white matter in primary progressive MS and secondary progressive MS, which they attributed to diffuse mild inflammation in the white matter. An alternative

explanation for this diffuse axonal injury is axonal degeneration secondary to apoptosis of neurons and transection of axons in demyelinated cerebral cortex. Demyelination of the cortex of the cerebellum also occurs in primary progressive MS and secondary progressive MS, but not in relapsing-remitting MS [5].

An important recent observation is the finding of structures resembling B-cell lymphoid follicles with germinal centers in the meninges of patients with secondary progressive MS [6••]. These ectopic lymphoid follicle-like structures contain B cells (some proliferating), plasma cells, T cells, and a network of follicular dendritic cells producing the chemokine CXCL13, which is chemotactic for B cells. These ectopic B-cell follicles are similar to those reported in the target organs of other human chronic autoimmune diseases, such as autoimmune thyroid disease [7]. In autoimmune thyroid disease the intrathyroidal germinal center B cells have been shown to be specific for thyroid autoantigens [7]. Thus it is possible that the germinal centers in the meninges of patients with MS are the sites of production, somatic hypermutation, and class-switch recombination of B cells reactive against CNS antigens. Plasma cells differentiating from these meningeal B cells could produce antimyelin antibodies, which might induce demyelination in the adjacent underlying cerebral cortex and cerebellar cortex. They could also contribute to the synthesis of immunoglobulin (Ig) within the CNS, which is a diagnostic feature of MS [8]. Ectopic lymphoid follicles in the meninges could also be a site of activation and proliferation of CNS-reactive T cells. Serafini et al. [6••] did not find ectopic B-cell follicles in the meninges of either of two patients with primary progressive MS. However, given the occurrence of demyelination in the cerebral cortex and cerebellar cortex in primary progressive MS as well as in secondary progressive MS [4•,5], it is possible that such follicles may also occur in the meninges of patients with primary progressive MS, although they may differ in size and distribution from those in secondary progressive MS. The proposed immunopathologic substrate underlying the different clinical courses of MS is diagrammatically illustrated in Figure 1.

HLA

MS is associated with HLA class II genes, specifically the HLA-DR2 or DRB1*15 haplotype (DRB1*1501-DRB5*0101-DQA1*0102-DQB1*0602) in Caucasians, with approximately 65% of MS patients carrying this haplotype, compared to approximately 30% of healthy controls [9]. A recent analysis of DRB1 variation in 1339 MS families confirmed the strong association of MS with DRB1*15 [10]. It also demonstrated a dominant DRB1*15 dose effect: DRB1*15/15 versus DRB1*X/X: odds ratio (OR) = 7.5, and DRB1*15/X versus DRB1*X/X: OR = 3.4. This study also revealed a modest recessive dose effect for DRB1*03, and a protective effect of DRB1*14. Furthermore, a significant DRB1*15 association was observed in primary progressive MS families, similar to relapsing-remitting MS families, suggesting that DRB1-restricted mechanisms are contributing to both phenotypes. Another recent study found that primary progressive MS is associated with HLA-DR alleles encoding HLA-DR molecules containing a glutamic acid residue at positions 71 or 74 of the HLA-DRβ1 chain [11]. Because the amino acids at these positions influence the shape and charge of pocket 4 of the antigen-binding groove of the HLA-DR molecule, these residues could influence the clinical course of MS by determining antigens targeted, with resultant protection from relapsing-remitting MS or susceptibility to primary progressive MS.

Association with Other Autoimmune Diseases

Patients with MS and their first-degree relatives have an increased risk of other autoimmune diseases, suggesting that there is an underlying genetic susceptibility to autoimmunity in general [12,13]. Studies on autoimmune family pedigrees have led to the proposal that autoimmunity in humans is an autosomal dominant trait with penetrance (disease expression) in about 92% of females and 49% of males carrying the abnormal gene, and with secondary genes, including HLA genes, determining the specific autoimmune disease [14]. A recent study of 176 families with two or more members with MS revealed that other autoimmune diseases occurred in 26% of the index MS cases, and in one or more first-degree relatives in 64% of families [15•]. Hashimoto's thyroiditis, psoriasis, and inflammatory bowel disease were the most common autoimmune diseases in index cases and family members.

Autoreactivity to CNS Antigens in MS

Given the characteristic primary demyelination in the CNS in patients with MS and the experimental replication of this by immunization with myelin proteins, the most likely target autoantigens in MS are myelin antigens. Table 1 lists the proteins present in CNS myelin, together with their abundance and localization within the myelin sheath. Patients with MS have been shown to have T-cell reactivity to various myelin proteins, including myelin basic protein (MBP), myelin proteolipid protein (PLP), myelin/oligodendrocyte glycoprotein (MOG), oligodendrocyte-specific protein, myelin-associated glycoprotein, 2', 3'-cyclic nucleotide 3' phosphodiesterase, and myelin-associated oligodendrocytic basic protein [16]. However, the pathologic significance of this autoreactivity has been difficult to establish because T-cell reactivity to these myelin proteins is also found in healthy subjects. In one large study, increased circulating T-cell reactivity to amino acid residues 184-209 of PLP was found in patients with relapsing-remitting or secondary progressive MS, compared with healthy subjects and patients

Table 1. Proteins of CNS myelin

Protein	Abundance	Localization
Proteolipid protein (PLP)/DM20	~50%–60% of CNS myelin protein	Integral membrane protein (tetraspanin) present throughout myelin lamellae, including on extracellular surface of myelin sheath
Myelin basic protein (MBP)	~30% of CNS myelin protein; also major component of PNS myelin	Intracellular—major dense line of myelin lamellae
Oligodendrocyte-specific protein (OSP)	~5%–10% of CNS myelin protein	Integral membrane protein
Myelin/oligodendrocyte glycoprotein (MOG)	0.05% of CNS myelin protein	Transmembrane Ig-like molecule present only on extracellular surface of myelin sheath
Myelin-associated oligodendrocytic basic protein (MOBP)	~5%–10% of CNS myelin protein	Intracellular—colocalized with MBP on major dense line
Myelin-associated glycoprotein (MAG)	~1% of CNS myelin protein; also present in PNS myelin (0.1% of PNS myelin protein)	Transmembrane adhesion molecule of Ig superfamily; glycoprotein with significant homology to N-CAM; restricted to periaxonal regions of myelin sheath
2',3'-cyclic nucleotide; 3' phosphodiesterase (CNPase)	< 1% of CNS myelin protein; also present in PNS myelin	Localized in cytoplasm of oligodendrocytes and Schwann cells; recognized by Rip antibody

CNS—central nervous system; Ig—immunoglobulin; N-CAM—neural cell adhesion molecule; PNS—peripheral nervous system.

with other neurologic diseases [17]. $PLP_{184\text{-}209}$ is a strong candidate autoantigen in MS because PLP is the most abundant CNS myelin protein (Table 1) and because $PLP_{184\text{-}209}$ is encephalitogenic in mice, is immunodominant in humans, and is expressed on the extracellular surface of the myelin sheath, thereby also being a potential target for antibody-mediated demyelination. Longitudinal studies of T-cell reactivity to $PLP_{184\text{-}209}$ in patients with MS have shown major fluctuations in the frequencies of these T cells in the blood, with surges partly correlating with MS disease activity [18].

Antibodies to myelin proteins may also have a pathogenic role in MS because some patients have been shown to have antibody and complement deposition within active lesions [19,20]. Patients with MS have increased circulating anti-PLP antibodies, which can opsonize myelin for phagocytosis [21]. Recently, Zhou et al. [22] found that patients with MS, particularly those with primary progressive MS, have increased levels of serum IgG antibodies to native MOG. Zhou et al. [22] also observed that sera from patients with high anti-MOG antibody levels enhanced demyelination and axonal damage when transferred to animals with EAE. However, they did not attempt to block this pathogenic effect by adsorption with native MOG, and it therefore remains possible that the pathogenic effect of the sera was due to antibodies against other myelin components such as PLP.

In addition to myelin proteins, gangliosides are another potential source of target autoantigens in MS. Gangliosides are complex sialic acid–containing glycosphingolipid components of the plasma membrane and are highly enriched in the CNS where they are expressed by neurons, astrocytes, and oligodendrocytes, the cells that form CNS myelin. Antibodies to gangliosides expressed in the peripheral nervous system are involved in the pathogenesis of many different forms of peripheral neuropathy. Patients with primary progressive MS have increased circulating T-cell and antibody reactivity to gangliosides, compared to healthy subjects and patients with other neurologic diseases [23,24]. Patients with secondary progressive MS also have increased circulating antiganglioside antibodies [23]. Recently Marconi et al. [25] reported that patients with MS, particularly those with secondary progressive MS, have increased serum IgM antibodies against the ganglioside GD2, which is expressed by oligodendrocytes.

Devic's disease (neuromyelitis optica) is a variant of MS in which antibodies to a nonmyelin structure may have a pathogenic role. Neuromyelitis optica is characterized clinically by severe attacks of optic neuritis and myelitis and pathologically by inflammation, demyelination, and necrosis selectively involving the optic nerves and spinal cord. The inflammatory lesions consist of macrophages, granulocytes (particularly eosinophils), B cells, and a few T cells with a pronounced perivascular deposition of Ig (mainly IgM) and complement C9neo antigen (a marker of complement-mediated tissue injury) associated with prominent vascular fibrosis and hyalinization [26]. The extent of complement activation, eosinophilic infiltration, and vascular fibrosis in neuromyelitis optica is more prominent than in typical MS and suggests a pathogenic role for antibody directed at structures associated with

CNS blood vessels. Patients with neuromyelitis optica, but not patients with typical MS, have circulating IgG antibodies that bind to the aquaporin-4 water channel, which is located in astrocytic foot processes on the abluminal face of microvessels in the CNS [27•].

Abnormalities in Cerebrospinal Fluid

A characteristic and diagnostic feature of the cerebrospinal fluid (CSF) in MS is the presence of oligoclonal bands of IgG, which are not present in the serum. This indicates IgG production in the CNS and is best detected by isoelectric focusing on agarose gels followed by immunoblotting [8]. Oligoclonal bands of IgM restricted to the CSF can also be detected in some MS patients, and this correlates with more rapid clinical progression of neurologic disability [28]. A mononuclear CSF pleocytosis may also be present in patients with MS, particularly when the CSF is collected at the time of a clinical attack. The vast majority of the mononuclear cells in the CSF are T cells, with small proportions of B cells and monocytes [29]. Interestingly, a high ratio of CSF B cells to CSF monocytes correlates with an increased rate of progression of disability [29]. Analysis of the Ig heavy-chain variable region genes of B cells recovered from the CSF of MS patients has revealed a dominant monoclonal or dual-clonal B-cell expansion with evidence of somatic hypermutation, indicating that the B cells have passed through a germinal-center reaction [30]. This finding accords well with the recent demonstration of structures resembling lymphoid follicles containing germinal centers in the meninges of some patients with MS [6••], as discussed above.

Attempts to identify the antigen specificity of the oligoclonal Ig in the CSF have, until recently, been largely unsuccessful. To address this question, Cepok et al. [31•] screened CSF IgG with a protein expression array containing 37,000 tagged proteins generated from a human brain cDNA expression library. Interestingly, they found that the two most frequent MS-specific reactivities were directed at peptide sequences derived from two proteins of the Epstein-Barr virus (EBV), namely Epstein-Barr nuclear antigen-1 (EBNA-1) and BRRF2. Cepok et al. [31•] found higher levels of IgG reactivity to EBNA-1 and BRRF2 in the serum and CSF of MS patients compared to patients with other neurologic diseases and showed that CSF oligoclonal IgG from MS patients specifically bound both EBV proteins. DNA has also been identified as a target of IgG produced in the CNS in MS [32]. Williamson et al. [32] found that antibodies binding specifically and with high affinity to double-stranded DNA were a significant component of IgG1 produced by B cells isolated from an active brain lesion of one MS patient and from the CSF of another MS patient. This finding is intriguing because of the occurrence of MS and systemic lupus erythematosus (SLE) in different members of the same family [12,15•] and because MS patients have an increased frequency of circulating antinuclear antibodies [33]. Recently, myelin lipids, particularly phosphatidylcholine, have been identified as antigens recognized by CSF oligoclonal IgM in MS patients [34]. In MS patients with oligoclonal IgM bands restricted to the CSF, the predominant B-cell population in the CSF comprises $CD5^+$ B-1 B cells, a subset of B cells responsible for the secretion of so-called natural antibodies, which are usually of IgM isotype and directed against nonprotein antigens such as lipids [34].

Triggering of Attacks of MS by Systemic Infection

Attacks of MS are three times more likely to occur at the time of systemic infection (between 2 weeks before and 5 weeks after the onset of the first symptom of infection) than at other times [35]. In a recent study, Correale et al. [35] found that most of the attacks associated with systemic infection occurred during the first 2 weeks after the clinical onset of infection. They also found that viral and bacterial infections were equally associated with relapses of MS and that exacerbations associated with systemic infection were likely to be more severe and of longer duration than those not associated with infection. Possible mechanisms for the triggering of attacks by infections include a general upregulation of the immune system and cross-reactivity between microbial antigens and CNS antigens.

Role of EBV in Pathogenesis of MS

A large body of evidence indicates that infection with EBV has a role in the pathogenesis of many human chronic autoimmune diseases, including MS [36,37]. A review of eight published case-control studies comparing EBV serology in MS patients and controls revealed that 99% of MS patients were EBV-seropositive compared to 90% of controls (OR = 13.5) [38]. This universally high seropositivity rate does not apply to other herpes viruses [39]. A recent study has shown that children with MS also have an EBV-seropositivity rate of 99%, compared to 72% in age-matched controls [40•]. This suggests that EBV infection is a *causa sine qua non* for the development of MS. Furthermore, a recent meta-analysis of 14 studies found that a clinical history of infectious mononucleosis, which indicates a late primary infection with EBV with a high frequency of infected B cells, increases the risk of MS, with a relative risk of 2.3 [41]. A study of blood samples collected from US military personnel before the onset of MS showed that the presence of high titers of IgG antibodies to the EBNA complex increases the risk 36-fold for developing MS [42•]. This risk was associated with IgG antibodies to EBNA-1 but not EBNA-2.

These studies suggest that, among infectious agents, EBV has a unique role in the pathogenesis of MS. The role of EBV is usually attributed to immunologic cross-reactivity between EBV antigens and CNS antigens. Because EBV has the unique ability to infect, activate, and latently persist in B lymphocytes, it has been suggested that the role of EBV in MS relates to EBV infection of autoreactive B cells [36]. EBV-infected CNS-reactive B cells might not only produce pathogenic autoantibodies but also lodge in the CNS, where they could act as professional antigen-presenting cells (APC) and present CNS antigens to activated CNS-reactive T cells trafficking through the CNS [36]. Healthy subjects experience surges of circulating CNS-reactive T cells, presumably activated by cross-reacting infectious agents [18]. It has been proposed that these T cells would normally be eliminated in the CNS by activation-induced apoptosis [43], as in animals with EAE [44–46], but could survive if they received costimulatory survival signals from professional APC in the CNS [43]. B cells infected by EBV might provide this costimulatory signal [36]. Infection of autoreactive B cells by EBV might also contribute to the pathogenesis of other autoimmune diseases [36,37], for example, SLE where 99% of patients are also EBV-seropositive [47].

Effect of Immunomodulatory Therapy

The importance of inflammation of the CNS in the pathogenesis of MS has recently been clearly demonstrated by the beneficial clinical effect of natalizumab therapy in relapsing MS. Natalizumab blocks the entry of circulating lymphocytes and monocytes into the CNS by inhibiting the binding of leukocyte α4 integrins to their receptors on vascular endothelial cells. In a large 2-year phase 3 trial, monthly intravenous infusions of natalizumab in patients with relapsing MS led to an 83% reduction in the accumulation of new or enlarging hyperintense lesions on T2-weighted magnetic resonance imaging of the brain, a 68% reduction in the rate of clinical relapse, and a 42% reduction in the risk of sustained progression of disability [48•]. However, because this therapy also blocks the normal immunosurveillance of the CNS by lymphocytes, it can be complicated by opportunistic infection of the CNS by the JC polyomavirus, which causes progressive multifocal leukoencephalopathy, a usually fatal disease [49]. The importance of immune-mediated CNS damage in the pathogenesis of MS is also supported by the beneficial, albeit less dramatic, effects of therapy with other immunomodulatory agents such as high-dose intravenous methylprednisolone, interferon-β, glatiramer acetate, and mitoxantrone [50].

Proposed Scenario for Development of MS

We propose that the following scenario may lead to the development of MS. EBV infection in individuals genetically susceptible to autoimmunity results in a high frequency of EBV-infected memory B cells, possibly because of defective elimination of EBV-infected B cells by $CD8^+$ T cells. The EBV-infected B cells include autoreactive memory B cells, which may seed the CNS. In those individuals with class II HLA types (such as DRB1*1501) which predispose to MS, common systemic infections lead to the activation of $CD4^+$ T cells, which cross-react with CNS antigens and traffic into the CNS, where they are reactivated by EBV-infected B cells presenting CNS antigens. These EBV-infected B cells provide costimulatory survival signals to the T cells and thereby inhibit the activation-induced T-cell apoptosis, which normally occurs when autoreactive T cells enter the CNS. The autoreactive T cells orchestrate an immune attack on the CNS through the recruitment of macrophages and B cells. CNS antigens released by this attack lead to spreading of the immune response to other CNS antigens. In most individuals the initial targets of the T cells are in the white matter of the CNS. This leads to a relapsing-remitting course where clinical attacks are due to demyelination induced by autoreactive T cells entering the CNS from the blood and where remission is due to down-regulation of the immune attack on the CNS followed by CNS remyelination by oligodendrocytes. Repeated T-cell attacks on the CNS supported by local EBV-infected B cells lead to the development, in the meninges, of structures resembling lymphoid follicles with germinal centers. These lymphoid follicles generate CNS-reactive B cells, which produce antibodies that diffuse into the adjacent underlying cerebral and cerebellar cortex and damage myelin and neurons there, leading to a secondary progressive clinical course that is not dependent on the influx of autoreactive T cells from the blood. In a small proportion of individuals, the initial targets of the autoreactive T cells are in the gray matter of the CNS, resulting in clinically silent inflammation until the development of meningeal lymphoid follicles, which generate B cells producing antibodies that diffuse into the adjacent cerebral and cerebellar cortex and damage myelin and axons there, leading to a primary progressive clinical course (Fig. 1).

Conclusions

The development of MS is dependent on genetic factors, which include specific class II HLA types and a predisposition to autoimmunity in general, and environmental factors, which include common infectious agents, particularly EBV. In relapsing-remitting MS, clinical attacks appear to be dependent on the entry of autoreactive T cells into the white matter of the CNS from the blood, whereas in primary and secondary progressive MS, the progressive disability might be caused by the action of autoantibodies produced in the CNS by B cells in meningeal structures resembling lymphoid follicles with germinal centers.

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