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The Major Histocompatibility Complex Influences the Ethio-pathogenesis of MS-Like Disease in Primates at Multiple Levels

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ABSTRACT: Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease primarily affecting the central nervous system. Of the many candidate polymorphic major histocompatibility complex (MHC) and non-MHC genes contributing to disease susceptibility, including those encoding effector (cytokines and chemokines) or receptor molecules within the immune system (MHC, TCR, Ig or FcR), human leukocyte antigen (HLA) class II genes have the most significant influence. In this article we put forward the hypothesis that the influence of HLA genes on the risk to develop MS is actually the sum of multiple antigen presenting cell (APC) and T-cell inter-

actions involving HLA class I and class II molecules. This article will also discuss that, because of the genetic and immunologic similarity to humans, autoimmune models of MS in non-human primates are the experimental models "par excellence" to test this hypothesis. *Human Immunology* 62, 1371–1381 (2001). © American Society for Histocompatibility and Immunogenetics, 2001. Published by Elsevier Science Inc.

KEYWORDS: experimental autoimmune encephalomyelitis; multiple sclerosis; primates; immunology

ABBREVIATIONS

APC antigen presenting cell
BBB blood–brain barrier
CLN cervical lymph node
CNS central nervous system
EAE experimental autoimmune encephalomyelitis
HLA human leukocyte antigen
Ig immunoglobulin

MBP myelin basic protein
MHC major histocompatibility complex
MOG myelin/oligodendrocyte glycoprotein
MS multiple sclerosis
PLP proteolipid protein
TCR T-cell receptor
TMEV Theiler's murine encephalomyelitis virus
SFV Semliki Forest Virus

INTRODUCTION

Multiple sclerosis (MS) is generally regarded as an autoimmune disease that develops in genetically susceptible

individuals. MS is typically characterized by lesions in the central nervous system (CNS), which are formed by chronic inflammatory demyelination, leading to progressive loss of neurologic functions. MS affects about 1 per 1000 individuals in the moderate climate areas of Europe, the USA, and Southern Australia [1].

The cause of MS and the genetic and immunologic mechanisms that control disease progression are poorly understood. The substantial heterogeneity in clinical course and CNS pathology between MS patients suggests a multifactorial disease cause. More specifically, four main lesion patterns were found in a large number CNS samples from MS patients collected in three different

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centers from Austria, Germany, and the USA [2]. Two patterns reveal close similarity to the T-cell mediated (type I) or T-cell and antibody-induced (type II) encephalomyelitis observed in experimental animal systems. In these types a central role of (auto)immune reactions in lesion formation is likely. In patterns III and IV oligodendrocyte loss by viral infection or exposure to toxic agents seems a more likely primary cause of lesion formation. The fact that all lesions within one patient fall within one category suggests that the four lesion types may represent different forms of MS.

To date, it is not known whether MS patients have inherent neurologic abnormalities or immunologic deficiencies that can explain their susceptibility to the disease. It has been hypothesized that an autoimmune disease, such as MS, may rather be caused by "a high responsiveness to the excess release of antigens from damaged tissue by an antecedent pathological event" [3]. Two obvious core questions in this "primary lesion hypothesis" are as follows: (1) which genes make MS patients high responders; and (2) towards which antigen(s) is the high responsiveness directed?

This article will discuss that the chance to develop MS may be the sum of several risk factors operating at multiple levels of antigen presenting cell (APC)-T interaction involving myelin as well as non-myelin antigens. While reviewing literature data supporting this hypothesis, this article will also discuss the possibilities offered by the presently existing MS-like models in non-human primates in order to investigate whether this is indeed the case.

CLINICAL HETEROGENEITY IN MS

In about 80% of MS patients the disease has a chronic relapsing-remitting course. With time, and after a variable number of relapses, a secondary progressive phase starts in most cases in which full remission no longer occurs and progressive neurologic deficit develops. MS in another 15% of patients is progressive from the onset, with and without episodes of relapses, on a background of chronic progressive neurologic deficit (so-called primary progressive MS). Acute forms of MS, with a rapidly progressing course and severe inflammatory pathology, are relatively rare.

The etiology of relapsing remitting/secondary progressive MS is highly complex and likely involves a combined activity of genetic, endocrine, environmental, and immunobiologic factors. Evidence for a genetic contribution to the disease susceptibility comes from the substantially higher MS concordance between identical (25%) than non-identical (3%) twins [1]. Among the candidate genes, the influence exerted by HLA class II genes seems the most significant; the strongest genetic

association in people of Northern European descent being with the HLA-DR2/Dw2, DQ6 (DRB1*1501, DQA1*0102, DQB1*0602) haplotype [1, 4–6]. Polymorphisms in non-MHC genes, such as those encoding cytokines, cytokine receptors, Fc receptors, and chemokines, seem to have a less important contribution to disease susceptibility but have a considerable influence the clinical manifestations of MS [4, 7–10]. The facts that females are approximately 1.5 times more susceptible to MS than men and that pregnancy reduces the relapse rate indicates a hormonal influence on the disease. Migration studies and reports of epidemics of MS indicate a role for environmental influences, viral or bacteriologic infection in particular [1]. The dependence on external factors may explain why the disease concordance is lacking in a significant proportion of identical twins. In addition to the epidemiologic and demographic reports, clinical and experimental studies point to infection with microbial pathogens as a possible trigger for the disease [1, 11]. Although the etiologic agent in MS is unknown, it is intriguing that all the demyelinating diseases in which the etiologic agent is known are caused by a virus.

The general premise that MS is an autoimmune disease is mainly based on the findings that antibodies, T cells, and macrophages are abundant in MS lesions [12, 13] and that experimentally induced antimyelin reactivity in certain experimental animal models gives rise to similar neurologic deficits as in MS (see below). However, the presence of these factors in the MS brain and spinal cord does not necessarily imply that autoreactivity is the primary cause of the disease. Autoreactive T cells and antibodies may also be formed as a reaction to the (massive) myelin release by viral infections of the CNS or oligodendrocyte death.

Experimental Autoimmune Encephalomyelitis

Most current concepts of the immunologic mechanisms that regulate the initiation and progression of MS have been based on rodent and primate models of experimental autoimmune encephalomyelitis (EAE) [14, 15]. Studies in primates report a similar clinical and pathologic heterogeneity in EAE models as in MS, which depends on the immunization protocol, the myelin preparation used, and the animal species in which the disease is induced [2, 16].

In classical EAE models in inbred rodent strains neurologic disease is initiated by the CNS immigration of myelin-reactive CD4⁺ T cells with a pro-inflammatory helper 1 (Th1) phenotype across the blood–brain barrier (BBB). The interaction of these T cells with resident APC, which locally express the myelin antigen(s) to which the infiltrating T cells were originally sensitized to in the periphery, induces a sequence of events that

leads to inflammation and damage to myelin and axonal structures. In some models the disease is acute, whereas in others a chronic course is observed. Further, some animal models display an MS-like relapsing remitting disease in which, after several disease episodes, chronic unremitting neurologic deficit is observed.

Many therapeutic strategies, with the aim of treating MS have been investigated in animals, such as anti-TNF- α antibodies [17, 18], altered peptide ligands [19], and anti-CD4 antibodies [20]. Although these were found very effective in controlling EAE in rodents, they are only partially effective in MS patients and in some cases even detrimental [21–24]. Therefore, the question is raised whether the aspects of MS that are actually represented by the autoimmune models of MS are “close enough to MS” to be useful for developing therapeutic strategies.

MULTISTEP IMMUNOPATHOGENESIS OF CHRONIC MS

For this article the complex cascade of events, which leads to the lesion formation and neurologic dysfunction in chronic MS, has been separated into different phases. Phase 1 represents the initiation of autoreactivity towards myelin antigens; phase 2 demonstrates the CNS infiltration of autoreactive cells and molecules; phase 3 describes the induction of inflammatory demyelination; and phase 4 characterizes the expansion of the autoreactivity towards myelin as well as non-myelin autoantigens. These phases are not necessarily separated in time, but can coexist at the same time in the CNS of a given MS patient, for example in lesions of different age. This study postulates that in each phase one or more APC–T-cell interactions can occur, which adds a risk factor enhancing the chance to develop clinical MS.

Phase 1: The Initiation of Antimyelin Reactivity

The autoimmune reactions in MS are initiated by the activation of a pre-existing repertoire of T and B cells specific for components of the CNS white matter. It has been well established that myelin specific and potentially encephalitogenic T cells are part of the normal immunologic repertoire of rodents [25] and non-human primate species, such as the common marmoset [26] and the rhesus macaque [27]. Myelin-reactive T cells are also present in the immune system of healthy humans at frequencies that are comparable with those found in MS patients [28]. However, the potential of human T cells to incite encephalomyelitis cannot be tested in transfer experiments, as suitable recipients are lacking for obvious ethical reasons.

The potentially autoreactive T cells are normally kept in a resting state but become activated in MS by envi-

ronmental triggers, such as viral infection or stress for example. The activation from the resting state requires interaction with “professional” APC, which should not only present the relevant antigen in the context of self MHC-DR molecules, but also provide essential costimulatory signals without which naïve T cells are not activated but anergized instead [29]. Several resident cells in the CNS have the capacity to present antigens, such as microglia cells, astrocytes, and endothelial cells. Resident CNS microglia cells in MS have an activated appearance, expressing the three major MHC class II molecules (HLA-DR, -DQ, and -DP [30]) and several costimulatory molecules [31, 32]. Likewise, in early stages of acute EAE in animals, the resident APC have acquired an activated appearance [32, 33].

A variety of viruses have been associated with MS, including measles virus, rubella virus, influenza virus, respiratory corona virus, and a variety of herpes viruses, such as herpes simplex virus 1, cytomegalovirus, human herpesvirus type 6, Epstein-Barr virus, and Marek’s disease virus. However, none of these have been identified as exclusive trigger of MS. Viruses may induce myelin damage through a number of mechanisms either directly or indirectly [34, 35]. An example of a neuroinvasive virus that directly infects and damages oligodendrocytes and myelin is JC virus [36]. Other viruses may incorporate host cell antigens, such as myelin proteins, into the viral envelope thereby allowing the peripheral immune recognition of CNS restricted antigens [37]. A third possible mechanism is that the autoreactive T cells respond to mimicry motifs of myelin antigens in viral proteins [38]. As a general reaction to tissue damage, including cytolytic viral infection, myelin is phagocytosed and processed either locally [38] or carried to the cervical lymph nodes (CLN), which drain the cerebrospinal and interstitial fluids of the brain, where myelin-reactive T cells and B cells are activated *de novo* [39–41].

Many viral infections of animals have been used as models of MS but it is often difficult to dissect the exact mechanisms that lead to myelin damage. The most useful mouse models to investigate the activation of myelin-reactive T cells during a virus infection are Theiler’s encephalomyelitis virus (TMEV) and Semliki Forest virus (SFV) [42, 43]. In both models demyelination is immune mediated, although myelin-reactive T cells play a major but not exclusive role in the pathogenesis of disease. The pathogenic mechanisms in these models include the persistence of virus within the CNS and the induction of myelin-reactive T cells and antibodies via molecular mimicry. The specificities and functions (pro- or anti-inflammatory) of the repertoire of activated CD4+ and CD8+ T cells is determined by the interaction of multiple genes. These include genes encoding the MHC class I and II molecules that select and present

viral antigens and genes encoding cytokines and cytokine receptors.

Phase 2: The CNS Infiltration of Cells and Molecules

Primed T cells that have encountered their antigen in peripheral lymph nodes are thought to be less dependent on costimulatory molecules than naïve cells and, therefore, can be activated by antigen without the need of costimulation [44]. It is thought that the relative independence of autoreactive T cells of costimulation rescues them from apoptotic cell death [44, 45].

During transmigration across the BBB, T cells encounter brain endothelial cells, astrocytes, and pericytes, all of which have the potential to act as APC [46, 47]. The function of the BBB is mainly affected by the endothelial cells, which are joined by tight junctions of high electrical resistance and lack of fluid-phase endocytosis. In healthy individuals this barrier limits the passage of proteins and cells from the blood. However, during inflammation many changes take place on the surfaces of activated lymphocytes, monocytes, and the endothelial cells themselves [48, 49]. These all act to allow transmigration of leukocytes through the vascular endothelium and into the CNS parenchyma. Activated T cells also express proteases and glycosidases, which augment migration and open the endothelial barrier, allowing the passage of not only additional cell types, such as macrophages, but also various effector molecules (cytokines, complement factors, and antibodies). The transmigrated cells collect in the perivascular Virchow-Rubin space as a characteristic cuff of mononuclear cells. Only T cells recognizing the epitopes to which they were sensitized in the periphery or a mimicry motif thereof, presented by local APC, migrate further into the brain parenchyma [46, 49, 50].

This phase of the disease has been extensively modeled in inbred strains of rodents where EAE is induced by adoptive transfer of myelin-specific T helper 1 cells from immunized animals into naïve syngeneic recipients. In the present model, the selection and presentation by the local APC of mimicry motifs shared by myelin and viral antigens for recognition by infiltrating CD4⁺ T cells is an important factor in the EAE pathogenesis. The success rate of EAE induction by adoptive transfer of MBP-specific T helper 1 cells in nonhuman primates is high in common marmosets [26], but it is much lower in rhesus monkeys [27]. One explanation may be that, due to the much higher degree of polymorphism of MHC class II genes in the latter species (see below), only in some animals does local presentation of a mimicry epitope take place.

Phase 3: Induction of Inflammatory Demyelination

Thus far, no abnormalities in the CNS of MS patients have been demonstrated prior to initiation of the first lesion. We assume, therefore, that the first infiltrating T cells encounter intact myelin sheaths and inactive local APC, which likely present low levels of myelin antigens released during normal myelin turnover. This is not an optimal environment for T-cell activation as T cells are usually inactivated under such conditions. It is not clear by which mechanisms resident APC become activated. Infiltration of cells that were activated in peripheral lymphoid organs can stimulate APC via the release of cytokines, such as IL-12, IFN γ , and TNF α [49]. Moreover, various products from cell destruction (cell debris, DNA) or viruses and bacteria (double-stranded RNA or cell wall constituents) can directly activate APC via Toll-like receptors [51].

T-cell derived, pro-inflammatory cytokines and chemokines will induce locally enhanced permeability of the BBB, thus facilitating infiltration of B cells, antibodies, and macrophages. Whereas the actual mechanisms involved in the initial myelin damage are unknown, soluble factors such as TNF α are known to induce abnormalities during myelin formation *in vitro* [52] and myelin damage *in vivo* [53]. The initial local destruction of white matter may subsequently lead to increased release of free myelin antigens and further triggering of new T- and B-cell specificities.

The initial damage to the myelin sheaths in chronic MS likely involves a complement-dependent attack of antibodies binding to antigens exposed on the myelin surface [54]. Molecules of the size of antibodies and complement factors can gain access to the CNS via the vasogenic edema at sites where the BBB leaks [55]. Among the various myelin and non-myelin antigens that have been implicated in the MS immuno-pathogenesis, the minor myelin protein myelin/oligodendrocyte glycoprotein (MOG) has now emerged as a likely primary target of the autoimmune reaction. MOG is exclusively located in the CNS where, by its exposure on the outer surface of myelin sheaths and oligodendrocytes, the protein is directly accessible to infiltrating T cells and antibodies. Several groups have reported an increased incidence and more persistent activity of anti-MOG T cells or antibodies in MS than in patients with other inflammatory neurologic diseases or healthy controls. In a variety of animal species (mice, rats, and primates) experimentally-induced autoimmune reactions to MOG give rise to similar clinical and neuropathologic features as found in MS [56, 57]. In both MS and the marmoset model of EAE, anti-MOG antibodies were found localized in areas where pathologic changes of white matter occur [58]. Moreover, a pathogenic role for anti-MOG

antibodies has been demonstrated in rats [59], mice [60], and marmosets [61]. In all three studies it was found that, whereas transfer of antimyelin T cells induces CNS inflammation, the induction of demyelination likely requires the presence of anti-MOG antibodies binding to conformational epitopes on the MOG molecule ([62] and own unpublished observations). It can be envisaged that once an initial lesion has been formed normally sequestered myelin antigens, such as MBP and PLP, become exposed and accessible for antibody binding.

It is unclear by what mechanism(s) anti-MOG antibodies are induced prior to the induction of the first demyelinated lesion. MOG is exclusively localized in the CNS, where it constitutes only a quantitatively minor component of myelin. It is difficult to envisage that sufficient quantities of MOG reach the secondary lymphoid organs. One mechanism that may induce anti-MOG antibodies is a similar molecular mimicry mechanism, as discussed above for T cells, namely that protein conformations in a virus induce antibodies to similar conformations in MOG [63]. However, we regard this unlikely because, in that case, the MS-inducing virus should contain a linear T-cell mimicry epitope as well as a conformational B-cell mimicry epitope.

Recent experiments in rhesus monkeys indicate that a Trojan horse type of mechanism may take place in the initiation of MS, as was described in AIDS-associated dementia [64]. In brief, CD4⁺ T cells activated in the periphery by infection with a herpesvirus, may transfer that virus across the BBB into the CNS by virtue of cross-reactivity with myelin antigens. We have recently found a candidate mimicry motif shared by dominant epitopes of MOG and cytomegalovirus (manuscript in preparation). Preliminary data indicate that the virus is locally released from the infiltrated cells and infects CNS cells. We hypothesize that the infected CNS cells are destroyed by infiltrating anti-viral cytotoxic T cells and antibodies. Such a mechanism would explain the thus far unexplained dominance of CD8⁺ over CD4⁺ T lymphocytes in MS lesions [65, 66].

The described mechanism of lesion initiation implies MHC class I restricted cytotoxic reaction of infiltrated antiviral CD8⁺ T cells towards virus-infected CNS white matter cells as an additional risk factor to develop MS. It can be concluded from the TMEV model of MS that chronic inflammatory demyelination within the CNS can be the result of a persistent infection of the brain [42]. Therefore, the question can be asked to what extent the MHC-associated incapacity to effectively clear virus from the CNS may contribute to MS susceptibility [67].

Phase 4: The Expansion of Antimyelin Autoimmune Reactions

Progression of MS seems associated with the appearance in the circulation of T- and B-cell neoreactivities to a variety of myelin and nonmyelin antigens, including stress proteins [68, 69]. The phenomenon that T cells involved in the initiation of disease are specific to a narrow range of myelin epitopes/antigens, but during the later stages of disease T cells respond to a broad variety of myelin epitopes and antigens, is known as epitope spreading. The TMEV model demonstrates that such diversification of the repertoire may also occur after a neurotropic virus infection that leads to subsequent episodes of myelin damage and myelin-specific autoreactivity [42].

In several mouse models of EAE the potentially pathogenic role of T-cell neoreactivity to spreading epitopes has been well established [70–72]. In these models the neoreactivities even overgrow the T-cell autoreactivities that initiated the disease [73]. The activation of a naïve repertoire of T cells responding to spreading epitopes/antigens likely takes place outside the brain, as T cells activated within the CNS do not likely escape to the circulation [74, 75]. It has been well established in rats that myelin antigens released from an experimentally induced cryolesion in the brain white matter are drained to the T- and B-cell areas of the CLN, which drain the cerebrospinal and interstitial fluids from the brain [39, 40]. In the cryolesion model, myelin-reactive T cells activated within CLN were found to preferentially home to the brain and to enhance MBP-induced EAE in syngeneic rats [76]. This suggests that during their priming within CLN (antimyelin) T cells may receive instructions to traffic to the CNS white matter and enhance inflammatory demyelination. In this context the finding that the CLN of EAE-affected marmosets and rhesus monkeys contain significant numbers of APC loaded with immunoreactive myelin antigens (MBP and PLP) is of particular interest [41]. Such activated myelin-loaded APC were lacking in the CLN of monkeys with a nonrelated autoimmune disease, such as collagen-induced arthritis.

The processing of phagocytosed myelin by macrophages within lesions implies that a broad spectrum of previously sequestered antigens and cryptic epitopes becomes available for recognition by the immune system. Also, neoantigens that are induced under pathologic conditions will become available, such as α B-crystallin. This stress protein was found to be expressed in MS lesions and to represent a potential autoantigen in MS [70]. In our model, myelin damage caused by different pathogenic mechanisms, including an anti-viral immune response or an autoimmune attack, may all give rise to the CLN immigration of activated APC. The APC are

not only localized in the CLN areas where T- and B-cell priming can take place but also express high levels of MHC and costimulatory molecules. Therefore, we assume that the APC can potentially induce T- and B-cell neoreactivities directed to the core of myelin and non-myelin antigens in the white matter material that they have phagocytosed during CNS demyelination.

The *in vivo* diversification of the autoimmune T-cell repertoire has been assumed to contribute mainly to tolerance induction. However, certain MHC class II specificities may instead propagate autoreactivity and disease progression by presentation of spreading/cryptic epitopes to the immune system [77].

MODELING THE MS PATHOGENESIS IN NONHUMAN PRIMATES

To be able to model the complex sequence of events contributing to the MS pathogenesis, lab animals, comprised of a comparable genetic complexity as humans, are needed. Outbred colonies of rhesus monkeys and common marmosets qualify in this respect and valid EAE models have been developed in both species [15, 16]. It has been well established that humans and rhesus monkeys share not only MHC-DP, -DR, and -DQ loci, but also allelic lineages [78, 79]. The sharing of allelic lineages of the MHC-DRB locus has clear functional implications, as was demonstrated by antigen presentation across the species barrier [80, 81].

The susceptibility to myelin-induced EAE in the rhesus monkey colony at the BPRC maps, at least partially, to the Mamu-DP locus; overlapping MHC-DP lineages in rhesus monkeys and humans have not been found [82, 83]. An important additional argument for the use of rhesus monkeys is that this species not only contains natural infections with the equivalent versions of human herpesviruses but also that infections follow a similar course as in humans, for example in the case of herpes simplex virus 1 [84] and cytomegalovirus [85]. Thus, the rhesus monkey provides a potentially interesting model to unravel how viruses (similar to those found in humans) are involved in the induction of inflammatory demyelination of the CNS and how they may influence the course of EAE.

The CNS white matter lesions in the rhesus monkey model of EAE mainly resemble those in the MS type 1, which is characterized by strong inflammation and limited demyelination [2]. This is a remarkable species-related difference with the EAE model in common marmosets. Rhesus monkeys immunized with recombinant human MOG (rhMOG) in complete adjuvant develop acute clinical EAE with predominantly hemorrhagic/necrotic brain lesions [86]. However, the identical immunization procedure in common marmosets induces

chronic EAE with lesions formed by selective demyelination of brain and spinal cord [57]. The pathologic pattern resembles the type 2 lesions of chronic MS [2]. We are currently investigating whether this strikingly different disease pattern has a genetic and/or immunologic explanation.

A much more MS-like type of EAE can be induced in rhesus monkeys by immunization with pMOG34-56, a synthetic peptide representing amino acids 34-56 of the extracellular domain of rhMOG (manuscript in preparation). An intriguing finding in that study was that in a randomly collected group of 13 rhesus monkeys sensitized to this MOG peptide a variable disease pattern develops, which ranges from an acute to a chronic relapsing/remitting course.

EAE in the common marmoset is an excellent model of chronic MS because strong similarities between the clinical and pathologic aspects of the model and the human disease exist [14, 87, 88]. However, immunologically, the marmoset stands somewhat more distinct from the humans than rhesus monkeys [79]. The model is unique in a number of respects. Although we deal here with an outbred species, 100% of randomly selected animals from two independent colonies housed at the primate centers in Rijswijk (The Netherlands) and Göttingen (Germany), were found to develop EAE after immunization with human myelin in complete adjuvant, but the disease course varies between individual animals ($n > 50$). The most likely explanation for the high disease susceptibility is that EAE initiation in all animals depends on the same event, namely the Caja-DRB*W1201-restricted activation of CD4⁺ T cells specific for the encephalitogenic MOG peptide pMOG14-36 [57]. This monomorphic MHC class II molecule is expressed in all marmosets tested thus far [89]. The time of disease onset and the pattern of clinical signs, however, differ between individual animals. We are now investigating whether the clinical heterogeneity is related to a different regulatory role of Caja-DR molecules encoded by the two polymorphic MHC class II loci Caja-DRB1*03 and -DRB1*W16. An indication that this may indeed be the case comes from monkeys immunized with the rhMOG protein. In the few monkeys that did develop acute EAE the T-cell reactivity remained limited to pMOG14-36, whereas T cells from monkeys with chronic EAE responded to a much broader range of MOG peptides. We hypothesize that the activation of T cells specific for different "spreading epitopes," presented in the context of different Caja-DR molecules, gives rise to the variable disease pattern. Marmosets provide a unique system to directly test this hypothesis as T-cell transfer between (nonidentical) fraternal siblings can be performed. The natural bone marrow chimerism between twin animals ascertains that

TABLE 1 A *hypothetical* multistep model of the MS pathogenesis

<i>Step 1:</i>	MS is initiated by a viral infection. The specific viral epitopes presented to CD4 and CD8 cells in peripheral lymph nodes are selected at the level of Mhc-class I and II polymorphisms,
<i>Step 2:</i>	All activated T-cells transmigrate the blood brain barrier, but only those recognising the epitope to which they were primed in peripheral lymph nodes, or a mimicry epitope thereof in myelin antigens, penetrate into the CNS. The specific myelin epitopes presented by resident APC to infiltrated T-cells are selected at the level of Mhc class I and II polymorphisms.
<i>Step 3:</i>	CNS infiltrating CD4+ T-cells or co-infiltrating macrophages, carry (herpes)viruses across the blood brain barrier into the CNS white matter. Shedded virus locally infects white matter cells, including endothelium, oligodendrocytes, astrocytes etc.
<i>Step 4:</i>	The initial attack to the myelin sheaths (Wilkin's "primary lesion") involves the Mhc class I restricted cytotoxic killing of virally infected white matter by infiltrating CD8 cells. Insufficient clearance of the virus may lead to persistent infection of the CNS.
<i>Step 5:</i>	The intra-CNS activation of infiltrated CD4 cells involves Mhc class II-restricted interaction with resident APC inducing release of factors cytokines that enhance BBB permeability, such as cytokines (IL-1, TNF- α) and matrix metalloproteinases. Several of these factors are encoded by polymorphic genes.
<i>Step 6:</i>	The APC-mediated transport or passive drainage of myelin from the "primary lesions" to the cervical lymph nodes triggers a broad repertoire of autoreactive T- and B-cells in susceptible individuals.
<i>Step 7:</i>	Pathogenic T-cells and antibodies specific for cryptic and/or spreading myelin epitopes are released in the circulation and penetrate the CNS to enhance the encephalitis. Disease remission is determined by the patient's capacity to control the activation of autoreactive T- and B-cells.

transferred cells are not rejected despite the genetic disparity [90].

Concluding Remarks

In conclusion, we postulate that during the pathogenesis of MS multiple APC and T-cell interactions take place (summarized in Table 1). MHC polymorphisms operating at each interaction may either enhance or reduce the chance to develop clinical MS. On top of this, polymorphisms in regulatory genes, such as those encoding for cytokines/chemokines and their receptors, may enhance pathogenic and reduce protective activities of the immune system [7–10]. We hypothesize, therefore, that the susceptibility of an individual to MS is determined by the sum of these risk factors.

In our model each renewed exposure to the virus that has initiated MS can induce initial myelin destruction and subsequent autoimmune reactions, giving rise to the exacerbation of clinical signs. We think that remissions are induced by the patient's capacity to control the autoimmune reactions. Several of the viruses that have been implicated in MS cause a latent infection in humans, which can be reactivated without a clear external cause. For example, activation of latent herpes simplex virus 1 or cytomegalovirus infection can occur associated with apparently unrelated events, such as immunosuppression, fever, and stress. Conceptually, activation of a latent infection in individuals with a genetic risk phenotype may exacerbate MS via T cells that respond, for example, to a mimicry motif shared by herpes simplex virus 1 and MBP [91] or one shared by cytomegalovirus and MOG ('t Hart *et al.*, manuscript in preparation).

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