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The Role of Autoimmunity in Multiple Sclerosis

Monika Bradl and Hans Lassmann

1. Introduction

Multiple sclerosis (MS), a chronic inflammatory disease of the central nervous system (CNS), is one of the most common neurological diseases of young adults in developed countries. Hallmarks of this disease are focal plaques of demyelination in the white matter of the CNS. Evidence for autoimmune processes in this disease is mostly circumstantial. First, autoreactive T cells are found in the blood of most patients. This by itself does not yet point to a role of these cells in the disease process, since CNS antigen–specific T cells are also normal components in the immune system of healthy individuals. However, experiments in animal models of autoimmune encephalomyelitis clearly demonstrated that such cells can initiate CNS inflammation once they are activated. Second, autoreactive T cells and antibodies have been found in MS lesions, and immunotherapies targeting CNS antigen–specific T cells may delay or ameliorate the disease progression in MS patients. However, the situation is much more complex. To date, no MS specific autoimmune response has been described. The triggers, which might set off or maintain autoimmunity in a chronic disease course lasting years or decades, remain unknown. Autoimmune responses in the CNS of MS patients are not invariably detrimental, but may even be beneficial. Finally, diffuse alterations indicating general neurodegenerative processes are present throughout the brain of many MS patients, and these alterations are not necessarily due to immune-mediated mechanisms. Hence, there are still many gaps to fill in the "autoimmune hypothesis" of MS.

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2. The "Autoimmune Hypothesis" of Multiple Sclerosis

MS is one of the most common neurological diseases within developed countries. It usually starts in young adults and leads in a chronic relapsing or progressive course over many years to major neurological disability (Noseworthy *et al*., 2000). Genetic factors are important in determining the susceptibility to develop this disease, but within families of MS patients no Mendelian pattern of inheritance is found (Kalman and Lublin, 1999). Furthermore, studies on identical twins show that in addition to genetic factors other pathogenetic triggers have to be involved in disease induction. It is suspected that infections may act as triggers of disease, but so far no MS specific agent has been identified.

MS is believed to be an autoimmune disease, since it can in part be ameliorated or controlled by immunosuppressive or immunomodulatory treatments, and since autoreactive T lymphocytes or antibodies can be found in most patients (Wekerle, 1998; Noseworthy *et al*., 2000). Furthermore, a chronic inflammatory demyelinating disease with close similarities to MS can be induced in many different animal species by active sensitization with brain tissue or specific brain antigens (Wekerle, 1998). However, the concept of autoimmunity in MS is questioned frequently, since no unique, MS-specific autoimmune response has been identified to date. In addition, recent studies show that the disease process in MS is much more complex than previously thought. It includes an interindividual heterogeneity in the pathogenetic mechanisms of lesion formation, and the presence of a chronic neurodegenerative component with unknown relations to immune-mediated processes (Owens, 2003). In this chapter, we summarize current knowledge about the immunology and immunopathology of MS and discuss arguments for or against the "autoimmune hypothesis" of MS.

3. The Multiple Facets of Multiple Sclerosis

3.1. The Clinical Spectrum of Multiple Sclerosis

The clinical course of MS is highly unpredictable (Noseworthy *et al*., 2000). It ranges from benign disease, in which patients only suffer from some relapses without the development of permanent clinical deficit, to acute fulminate courses, which lead to death of the patients within a few months after disease onset. In more than 80% of patients the disease starts with a relapsing course, characterized by episodes of exacerbations followed by remission and recovery (relapsing–remitting multiple sclerosis, RRMS). After several years this relapsing course develops into a disease with a steady and uninterrupted increase of neurological disability, the so-called secondary progressive course of the disease (secondary progressive multiple sclerosis, SPMS). In 15–20% of the patients the relapsing phase of the disease is missing, and the patients follow a progressive course from the onset of disease. This form of MS is called primary progressive MS (PPMS). Using magnetic resonance imaging to follow the lesion development during these different phases of MS, it was shown that during the relapsing phase of the disease new lesions appear in the brain, which are associated with blood–brain barrier damage (Werring *et al*., 2000). This suggests that these lesions are triggered by new waves

of inflammatory cells, reaching the CNS tissue from the circulation by their passage through cerebral vessels. This is in marked contrast to the situation in the progressive phase of the disease (both in SPMS and PPMS), where new lesions are only rarely formed in the brain white matter, and where blood–brain barrier damage is not detected. Instead, profound abnormalities are found in the so-called "normal" white matter. This suggests a diffuse injury affecting the brain as a whole. Such diffuse changes can already be seen in early stages of RRMS and seem to gradually increase with time (Filippi *et al.*, 2003).

3.2. The Pathological Spectrum of Multiple Sclerosis

In pathology MS is defined as an inflammatory demyelinating disease (Lassmann *et al.*, 2001), since focal plaques with primary demyelination, relative axonal sparing, and reactive astroglial scaring are formed in the course of a chronic inflammatory reaction. The inflammatory infiltrates are mainly composed of lymphocytes and activated macrophages or microglia cells. Within the lymphocyte population of chronic inflammatory lesions, MHC class I–restricted CD8$^+$ T cells dominate (Gay *et al.*, 1997). In addition, and more prominent in the chronic progressive stage of the disease, B lymphocytes and plasma cells accumulate, mainly in the meninges and the perivascular spaces. These B cells and plasma cells are responsible for a continuous intrathecal production of immunoglobulins.

The formation of new and active demyelinating plaques in the white matter (Figure 16.1) is mainly found in the relapsing stage of the disease. This process is associated with pronounced inflammatory infiltration of the whole tissue, accompanied by a profound blood–brain barrier disturbance. Both the structural and the immunopathological features of active MS plaques are different between different patient subpopulations, suggesting an interindividual heterogeneity in the mechanisms of tissue damage (Lucchinetti *et al.*, 2000). In some patients demyelination and tissue injury is mainly associated with cytotoxic T cells and activated macrophages/microglia cells, while in others immunoglobulins and activated complement are deposited at sites of active myelin destruction. In another subgroup of patients the patterns of tissue damage closely resemble hypoxic tissue injury. Furthermore, a small cohort of patients show unusually severe damage of myelin, oligodendrocytes, and/or axons, suggesting problems of the target tissue to cope with the inflammatory insult (Lucchinetti *et al.*, 2000).

In contrast to the relapsing stage of the disease, the formation of new active white matter lesions is rare in the progressive disease. Here, the typical finding is a slow and gradual enlargement of preexisting plaques (Prineas *et al.*, 2001). In addition, a mild but completely diffuse inflammatory process in the whole brain and the meninges is evident. This is associated with diffuse microglia activation and ongoing axonal injury in the "normal" white matter, and with the formation of large areas of cortical demyelination (Kidd *et al.*, 1999) topically related to the inflammatory process in the meninges. It is not clear yet whether this diffuse inflammatory process is the cause of global cortical and white matter damage in progressive MS or whether it occurs as a secondary reaction to the degenerative process in the brain. Is there clear evidence for immune reactions directed against CNS myelin, neurons, or glia cells, i.e., autoimmune reactions, in MS patients?
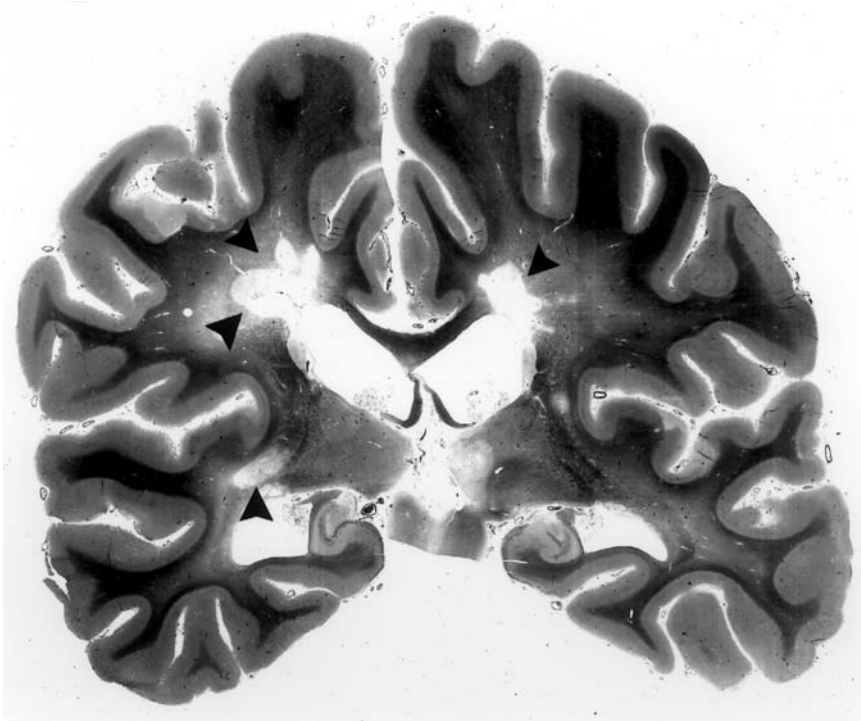
Figure 16.1.   Brain lesions of an multiple sclerosis (MS) patient. The arrows point to large demyelinated plaques in central nervous system (CNS) white matter.

3.3. Evidence for T Cell–Mediated Autoimmunity

Since MS is an inflammatory demyelinating disease, which is, at least in northern Europe, often associated with the expression of the MHC class II antigen HLA-DR2, the search for autoimmunity was mainly a search for myelin antigens possibly recognized by brain-infiltrating CD4^{+}, MHC class II–restricted T cells. And indeed, T cells specifically recognizing myelin basic protein (MBP), proteolipid protein (PLP), or myelin oligodendrocyte glycoprotein (MOG) (Pette *et al*., 1990; Kerlero de Rosbo *et al*., 1997) could be readily isolated from the blood of MS patients. However, such cells can be isolated from the blood of healthy individuals just as well, indicating that they are normal components of the immune system (Wekerle, 1998). Then, the search was on for quantitative differences (Olsson *et al*., 1990b) in the antimyelin response of T lymphocytes found in the blood of MS patients and healthy controls. Here, simple assays such as testing for primary proliferation responses turned out to be insufficiently sensitive to detect such differences, with the exception of a single study showing stronger proliferative responses against MOG in MS patients than in controls (Kerlero de Rosbo *et al*., 1993). The more sensitive approach using ELISPOT techniques proved to be more rewarding, pointing to increased T cell responses also to PLP and MBP

(Olsson *et al*., 1990b). Then, qualitative differences in the antimyelin response became the focus of intense research. It has been observed that monozygotic twins differ in their anti-MBP response. When both of the twins developed MS, they had a similar epitope recognition pattern, but when only one twin had MS, they differed more in epitope recognition (Utz *et al*., 1993). Other studies revealed that the autoimmune response against MBP can be focused to a narrow, dominant peptide segment in some selected patients—a finding that contrasts with the broad peptide recognition pattern in controls. This narrow epitope pattern may be remarkably stable for several years over the course of the disease (Goebels *et al*., 2000). However, in other patients the epitope recognition pattern radically changes over time. This was best demonstrated in human patients progressing from an isolated mono-symptomatic demyelinating syndrome (IMDS) to clinically definite MS (Tuohy *et al*., 1998). Coinciding with, or appearing soon after the diagnosis of IMDS, PLP-specific T cells from these patients recognized a single, specific PLP peptide. In the course of the disease, the response to this peptide regressed, and responses to other PLP epitopes emerged. This change in T cell reactivity concurred with relapses and the diagnosis of clinically definite MS.

Under normal circumstances, CNS antigen–specific T cells are resting components of the immune system. However, once activated, they can trigger autoimmune reactions within the human CNS. Evidence for such a disease scenario comes from a series of neuroparalytic accidents in humans receiving anti-rabies treatments with killed carbolized virus isolated from infected animal brains. Since these vaccines were contaminated with brain material, CNS antigen–specific T cells of the treated patients were activated and initiated CNS inflammation (for review see Bradl and Hohlfeld, 2003). This discovery paved the way for the development of experimental autoimmune encephalomyelitis (EAE), an animal model widely used to decipher certain aspects of CNS inflammation and demyelination seen in MS patients.

Based on this animal model it is undisputed that activated T cells recognizing antigens from myelin, oligodendrocytes, astrocytes, as well as neurons can induce inflammatory brain disease (Berger *et al*., 1997). However, it became also clear that not every activated CNS antigen–specific T cell will be autoaggressive and hence pathogenic. For example, C57Bl/6 mice harbor PLP-specific T cells in their immune repertoire, but activation of these cells by immunization with PLP fails to provoke CNS inflammation. This is in marked contrast to the situation in SJL mice. With the same treatment regimen, PLP-specific T cells of these animals initiate massive inflammatory lesions in the CNS. The differences between these two strains of mice can be ascribed to variations in the intrathymic expression of tissue-specific self-antigens and tolerance induction (Klein *et al*., 2000).

Another example is provided by MOG-reactive T cell lines isolated from Lewis rats. While all of these T cell lines vigorously proliferated in response to "their" specific peptides, only cells reactive to MOG_{1-20} or MOG_{35-55} were encephalitogenic and hence able to induce CNS inflammation, while T cells specific for MOG_{60-79} were incapable of mediating an inflammatory response within the CNS (Adelmann *et al*., 1995). Based on this information, reports about the presence, expansion, or proliferation of myelin-specific T cells in the repertoire

of MS patients should be critically evaluated, as long as the encephalitogenic potential of the described T cells remains unclear. There have been attempts to clarify this issue.

Human myelin-specific T cells have been transferred into SCID mice or rhesus monkeys, but the results of these studies were inconclusive (for review see Bradl and Flügel, 2002). At around the same time, a humanized mouse model has been created using transgenic animals expressing three human components involved in T cell recognition: (a) a T cell receptor derived from an MBP-specific T cell clone of an MS patient, which recognizes an MBP epitope that is conserved between mouse and man, (b) an MHC class II antigen associated with MS (HLA-DR2), and (c) the human coreceptor CD4. When the humanized MBP-specific T cells in these animals were activated, CNS inflammation ensued (Madsen *et al.*, 1999).

As seen above, it turned out to be extremely difficult to prove that the myelin-specific T cells found in the immune repertoire of MS patients are directly involved in the initiation and/or progression of an autoimmune reaction within the CNS. Other groups did not use the "*in vivo* approach" to solve this problem. Instead, they concentrated on the inflammatory lesions of MS patients and reasoned that they should be able to find CNS antigen–specific T cells in the plaques, provided that the lesions were initiated by these cells. And indeed, characterization of the T cell receptor usage of T cells found in MS plaques revealed the presence of T cells with similar complementary-determining region-3 sequences to those found in MBP-reactive T cell lines (Oksenberg *et al.*, 1993). In addition, MBP–MHC class II complexes have been found on antigen-presenting cells within MS plaques, indicating that MBP epitopes could be presented by local antigen-presenting cells (Krogsgaard *et al.*, 2000).

Taken together, while several reports describe the presence and the reactivity/receptor usage of CD4$^+$, myelin-specific T cells in MS patients (a recent search in Medline revealed more than 140 entries), there is little evidence for an active role of such CNS antigen–specific T cells in the induction of MS (see above).

Even less is known about the dominant T cell population in the MS plaque, the CD8$^+$ T cells. According to a recent publication, CD8$^+$ T cells in MS lesions represent an oligoclonal population (Babbe *et al.*, 2000). CD8$^+$ T cells are enriched at sites of actively demyelinating lesions, and there is evidence for a direct cytotoxic interaction between CD8$^+$ T lymphocytes and target cells in the CNS (Neumann *et al.*, 2002). However, it remains unclear whether these cells actually recognize myelin proteins and mount an autoimmune response to CNS antigens, or whether they recognize other, probably viral, target structures. The situation is further complicated by the fact that there are only few studies available so far that show that class I–restricted myelin-specific T cells can induce brain inflammation in experimental animals (Huseby *et al.*, 2001; Sun *et al.*, 2001). Unfortunately, these models are not developed to such an extent, that their validity as models for MS can be judged.

Moreover, most, if not all CNS-specific proteins, and even glycolipids (De Libero, 2004) may be targets of encephalitogenic, autoreactive T cells. Hence, T cell–mediated autoimmunity in MS patients may be directed against many dif-

ferent CNS antigens, which may be different between individual patients. It may, thus, not be surprising that a common MS-specific autoimmune response has so far not been identified.

3.4. Evidence for B Cell– or Antibody-Mediated Autoimmunity

There is no doubt about chronic B cell responses and a persistent immunoglobulin production in the CNS of MS patients. This is best exemplified by the diagnostically useful determination of intrathecal immunoglobulin synthesis, and by the presence of oligoclonal immunoglobulin in the cerebrospinal fluid. More recent studies, using new molecular technologies, showed extensive somatic mutations in the immunoglobulin variable genes of B cells isolated from the lesions or the cerebrospinal fluid of affected patients (Owens *et al*., 1998; Qin *et al*., 1998). These data also suggest that the B cell and plasma cell populations in the brain of MS patients are derived from the expansion of few individual B cell clones, possibly driven by local antigenic stimulation.

Are the antibodies synthesized intrathecally by these B cell populations directed against autoantigens? This question is still unresolved, since detailed studies aiming to define the antigen specificity of oligoclonal immunoglobulins in MS patients were so far inconclusive. Nevertheless, antibodies in the circulation and the cerebrospinal fluid (CSF) of MS patients may be directed against a large number of different autoantigens (Archelos and Hartung, 2000). Most extensively studied are antibodies against MBP and MOG (Berger *et al*., 2003). They are found in higher frequencies in MS patients than in controls, and their serum titers at the time of the first clinical presentation may predict how fast the disease will convert to definite MS. However, the presence of antibodies against MOG or MBP is not unique for MS patients, but can be also found in patients with other inflammatory or noninflammatory CNS diseases. Hence, such antibodies may rather represent a secondary response of the immune system to brain damage, rather than being pathogenic by themselves.

Is there evidence for pathogenic autoantibodies responsible for the induction of demyelination or tissue injury? One requirement of an autoantibody to be directly pathogenic is that its target antigen is accessible in the intact tissue. Thus, the respective target antigen has to be located either on the cell surface or on extracellular matrix components. In contrast, most antibodies detected in MS patients are reactive with intracellular antigens such as MBP or neurofilament. The situation is different with MOG, which is a small immunoglobulin-like molecule expressed on the surface of myelin sheaths or oligodendrocytes (Linington *et al*., 1988). Most anti-MOG antibodies detected in MS patients are pathogenetically irrelevant, since they are directed against linear epitopes hidden within the folded molecular structure (Brehm *et al*., 1999). However, in a small subgroup of MS patients the antibodies recognize the conformational epitope of MOG, which is accessible on the surface of intact oligodendrocytes (Haase *et al*., 2001) and myelin sheaths. Since such antibodies drive demyelination in animal models of EAE (Linington *et al*., 1988), it is likely that they are also truly pathogenic in humans, leading to antibody- and complement-mediated demyelination

characteristically found in active lesions in a subset of MS patients (Lucchinetti *et al*., 2000).

Other antibodies that may be pathogenetically relevant are those directed against AN-2, a surface molecule expressed on glial progenitor cells (Niehaus *et al*., 2000). Again, these antibodies are only found in a subset of MS patients. Since these antibodies may initiate the destruction of glial progenitor cells, they could be responsible for the failure of myelin repair in some patients. Taken together, autoantibodies directed against cell surface antigens of CNS cells or components of the extracellular matrix of the brain are potentially pathogenic in MS. The target structures of these antibodies may vary between individual patients, but a common, MS-specific autoantibody has not been described yet.

3.5. Evidence for Autoimmunity from Immunotherapies of Multiple Sclerosis

As described above, there is strong, but always indirect, evidence for an immunopathogenesis of MS (Figure 16.2), and different autoimmune mechanisms might operate in different patients or at different stages of the disease. Several immunotherapies provided further evidence for the presence of autoimmune reactions in MS patients, in particular on the level of MBP-specific T lymphocytes. For example, MBP-reactive T cells suspected to be involved in the pathogenesis of MS were depleted by subcutaneous inoculations with irradiated autologous MBP-reactive T cells ("T cell vaccination"). This treatment regimen resulted in the induction of $CD8^+$ T cells that specifically suppressed the MBP-reactive T cells (Zang *et al*., 2000). It led, at least for an observation interval of 24 months, to a 40% reduction of the relapse rate (as compared to the pretreatment rate), and to a stabilization in lesion activity (Zhang *et al*., 2002). Other immunotherapies used altered peptide ligands for MBP in MS patients. In these studies, T cells recognizing the putative target epitope for an autoimmune response, MBP_{83-99}, were targeted with peptides differing from the peptide normally recognized by one or two amino acids, in the hope to modulate the T cell response to the native peptide antigen. The outcome of these trials was inconclusive. One group described the induction of regulatory type 2 helper T cells, and a reduction in the volume and the number of lesions (Kappos *et al*., 2000). Another group found exacerbations of MS directly linked to the activation of MBP-specific T cells in a subgroup of patients (Bielekova *et al*., 2000). In sum, both of these immunotherapies provide evidence for a role of myelin-specific T cells in the disease. However, there is no evidence that these cells are directly involved in the initiation of MS.

4. The Triggers for Autoimmune Reactions in MS Patients

The studies described above have clearly shown that autoimmune reactions occur and that they appear to be more abundant and pronounced in MS patients compared to controls. Furthermore, some studies indicate that MS may be asso-
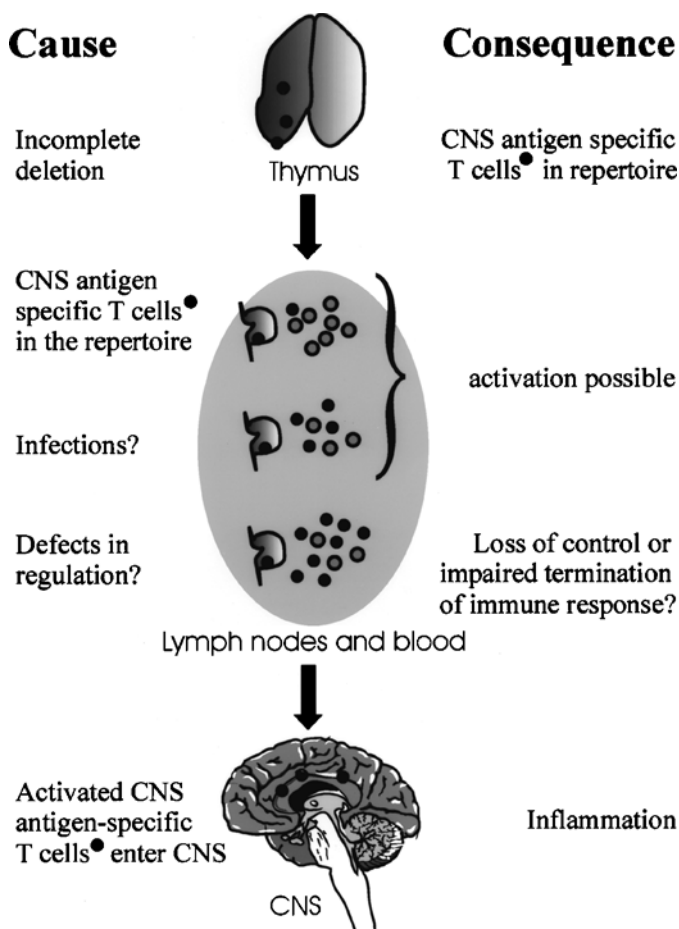
Figure 16.2. Possible causes and consequences of the presence of central nervous system (CNS) antigen–specific T cells in the immune repertoire of multiple sclerosis (MS) patients.

ciated with an increased risk to develop other autoimmune diseases (Henderson *et al.*, 2000). What triggers autoimmune reactions in MS patients?

4.1. Autoimmune Reactions Caused by a Defect in Immune Regulation

A small number of transgenic mice carrying an expanded population of encephalitogenic T cells in the immune repertoire spontaneously develop EAE. If, however, other lymphocytes are genetically ablated, the disease incidence increases to 100% (Lafaille *et al.*, 1994). These data point to the presence of regulatory T cells in the immune system, which may prevent or terminate autoimmune reactions. In MS patients, immune-regulatory processes might act in at least two

different situations: in the termination of acute disease episodes or in the global control of autoimmunity.

Early studies showed reduced suppressor activity of peripheral leucocytes in MS patients during active disease (Antel *et al*., 1979), which was related to reduced numbers of CD8^{+} T cells in the circulation (Reinherz *et al*., 1980). This implicated that "suppressor" cells might play a major role in regulating the relapsing remitting course of MS. However, subsequent studies found a much less clearcut correlation between disease activity and loss of suppressor function (Antel *et al*., 1985) or changes in peripheral CD8^{+} T cell numbers (Hughes *et al*., 1988). Reduced numbers of NK1 T cells with putative regulatory function, observed within inflammatory infiltrates in MS lesions, also suggest a defect in the termination of local immune responses (Illés *et al*., 2000).

A more global defect of immune regulation in MS patients was postulated following the observation that the numbers of regulatory CD4^{+}CD25^{high} T cells in the circulation of MS patients are lower than in controls (Viglietta *et al*., 2004), possibly provoked by an impaired release of these cells from the thymus (Hug *et al*., 2003). This finding is not typical for all MS patients, since another study failed to detect such differences (Putheti *et al*., 2004).

Finally, the low incidence of asthma in MS patients (Tramlett *et al*., 2002) suggests a general bias of the immune response toward Th1 cells or cytotoxic T lymphocytes, which are polarized to the production of Th1 cytokines. Indeed, therapeutic strategies, which are believed to shift the immune response from Th1 to Th2 reactions, show some beneficial effect, in particular in patients with acute or relapsing disease (Neuhaus *et al*., 2000). Taken together, there are only few studies addressing the question of possible regulatory defects in MS patients, and the results of these studies are, at present, far from being conclusive. Hence, the concept of a general defect in immune regulation in MS patients remains an attractive hypothesis, which has to be proven in future large-scale clinical studies.

4.2. Autoimmune Reactions Caused by Infections

Based on extensive studies it became clear that chronic inflammatory demyelinating diseases reminiscent of MS can be induced in experimental animals by several different viruses causing, for example, Theiler's virus-induced encephalomyelitis (Drescher *et al*., 1997), corona virus–induced demyelinating encephalitis (Nagashima *et al*., 1978), and canine distemper virus encephalitis (Summers and Appel, 1994). In most of these models the disease starts with a panencephalitis, affecting both the gray and the white matter, which leads to injury of glia cells and neurons. While the infection is gradually cleared from the CNS gray matter, it may persist in the white matter and may cause a slowly progressive inflammatory demyelinating disease culminating in the formation of focal plaques of demyelination (Dethlefs *et al*., 1997). Tissue damage is mediated by both CD4^{+} and CD8^{+} T cells: while class I–restricted T cells appear to be particularly important in the induction of axonal damage and clinical deficit, both T cell populations seem to be involved in the induction and progression of demyelination (Murray *et al*., 1998). An important lesson from these animal models is that viral infections

can induce autoimmune reactions against components of the CNS tissue, which may be involved in the propagation of chronic disease, possibly by antigen or determinant spreading (Croxford *et al.*, 2002). This implicates a contribution of autoimmune T cells to the chronicity of the inflammatory reaction and to the induction of tissue injury. Since the virus is not completely eliminated from the CNS of the experimental animals, it remains unclear whether virus-induced autoimmunity alone, in the absence of viral persistence in the CNS, could maintain a long-lasting chronic inflammatory demyelinating disease.

There is little doubt that infections are unusual precursors to the *onset* of MS, but that they frequently precede the *relapses and progression* of MS. Moreover, oligoclonal IgG bands in the CSF, a diagnostic hallmark of MS, are otherwise almost exclusively found in infectious diseases of the nervous system (e.g., mumps, meningitis, neurosyphilis, cryptococcal meningitis, subacute sclerosing panencephalitis, and chronic rubella panencephalitis) (Gilden, 2002). Do such infections trigger autoimmune reactions, or do stress reactions associated with infections lead to the reactivation of human viruses from sites of latency in the CNS, which may in turn start immune reactions directed against viral structures? Research programs addressed both these scenarios.

The first line of research followed observations in transgenic mice carrying murine, encephalitogenic T cell receptors. The fact that these animals remained healthy when they were kept under specific pathogen-free conditions but developed spontaneous CNS inflammation when they lived in a normal environment (Goverman *et al.*, 1993) led to the suggestion that the activation of T cells before their entry into the CNS may result from the action or recognition of bacterial/viral proteins. A similar, systemic trigger was also postulated for patients with early relapsing/remitting MS, since lesions appear concurrently in the brain and the spinal cord (Thorpe *et al.*, 1996). Clear evidence for an activation of CNS antigen–specific T cells by infectious agents came from the pioneering work of Wucherpfennig and Strominger (1995). They demonstrated that MBP-specific T cell clones derived from MS patients can be activated by peptides derived from herpes simplex virus, Epstein–Barr virus, influenza virus, or Pseudomonas—and the list of such viral or bacterial peptides increased ever since (Hemmer *et al.*, 1997).

The second line of research was stimulated by the isolation of an MS-associated retrovirus from the choroid plexus or from B lymphocytes of MS patients (Perron *et al.*, 1997). This virus was related to a novel family of human endogenous retroviruses, human endogenous retrovirus type W (HERV-W) (Perron *et al.*, 1997). A complete HERV-W provirus is present on chromosome 7, in a region associated with susceptibility to MS (Charmley *et al.*, 1991). We recently detected HERV-W retroviral antigens in neurons, axons, and endothelial cells of active MS lesions (unpublished observation). However, their expression in inactive lesions was low or absent. It will have to be determined in the future whether this virus is activated in response to the stressful environment of an MS lesion or whether immune responses to such retroviruses cause the development of MS and/or the propagation of lesions. Thus, attractive as a viral/bacterial trigger of autoimmune reactions in MS patients may be, there is no known infection that provokes the onset of the disease.

5. Protective Autoimmunity

Autoreactive T cells and autoantibodies directed against components of the CNS are part of the normal immune repertoire. Since MBP-specific T cells can also be activated by viral/bacterial peptides, and because the response to such peptides might be as high, or even higher than the response to MBP (Wucherpfennig and Strominger, 1995), it seems fair to assume that the risk to develop autoimmune diseases is the price to pay for an efficient and fast immune response against pathogens. Moreover, inflammation should not always be considered an undesirable reaction. In fact, research in animal models of traumatic or excitotoxic brain lesions convincingly demonstrated that inflammatory T cells may serve beneficial functions by limiting tissue injury and stimulating tissue repair, an observation that even led to the concept of "protective autoimmunity" (Moalem et al., 1999).

Activated lymphocytes and macrophages are potent sources of growth factors and neurotrophins (Moalem et al., 2000), e.g., brain-derived neurotrophic factor (BDNF), which is able to rescue neurons in vitro (Kerschensteiner et al., 1999). Interestingly, neurons and glia cells at the active edge of demyelinating inflammatory MS lesions express receptors for BDNF (Stadelmann et al., 2002). Moreover, leukocyte-derived neurotrophins are also essential in the recruitment of oligodendrocyte progenitor cells and the induction of remyelination (Franklin, 2002).

Protective autoimmunity is not only a feature of self-antigen-specific T cells; it is also observed with autoantibodies. For example, murine and human antibodies of the IgM isotype, which recognize antigens on the surface of oligodendrocytes, may promote remyelination in the CNS (Asakura et al., 1996). These observations should be a point of concern when extensive immunosuppression in MS patients is planned: Such a treatment could not only reduce or limit possible deleterious consequences of CNS inflammation, but could also impair remyelination and repair.

6. What Remains of the "Autoimmune Hypothesis" of Multiple Sclerosis?

From all the data discussed above it seems that MS patients have just one feature in common: they share the presence of autoreactive T cells in the immune repertoire. However, they share this with healthy subjects just as well. All other features of the disease seem to be rather patient-specific: the trigger of the disease, the disease course, the pathological characteristics of the MS plaque, the contribution of the immune system to the pathological changes in the CNS, the (auto?)antigens recognized by T cells and/or antibodies, and even the response to treatments. There is evidence that autoimmune processes could be involved in every single aspect mentioned above. Bringing all these aspects together to a uniform picture of MS remains a challenge for the future.

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