REVIEW

Autoimmune Versus Oligodendrogliopathy: The Pathogenesis of Multiple Sclerosis

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Abstract Multiple sclerosis (MS) is the most common inflammatory demyelinating disease of the central nervous system (CNS); it affect millions of patients worldwide and the number of patients is on the rise. Current treatment options are fairly limited and there is a strong unmet need for disease-targeted therapies for MS. The most widely accepted hypothesis for the pathogenesis of MS is that it is a primary autoimmune disease in which myelin-specific T cells play a central role in the progression of demyelination. According to this hypothesis, a powerful immune suppression or a reconstruction of the immune system to abrogate disease-specific leukocytes early in the development of the disease is expected to halt or even reverse the disease, since remyelination is an exceptionally efficient regenerative process in the CNS. However, recent neuropathological studies have provided evidence of primary oligodendrogliopathy as a cause of demyelination, suggesting that immune reactions may be a mere secondary event in the course of MS. On the other hand, some recent clinical trial results of new immune-suppressive treatments showed a nearly complete blockade of relapses and significant, albeit incomplete, neurological improvement. Therefore, which hypothesis—autoimmunity or oligodendrogliopathy—lights the correct path to a "cure" for MS?

Keywords Multiple sclerosis · Pathogenesis · Autoimmune · Oligodendrogliopathy

Abbreviations

ADEM	Acute disseminating encephalomyelitis
BBB	Blood–brain barrier
CCL	CC chemokine ligand
CNS	Central nervous system
CSF	Cerebrospinal fluid
EAE	Experimental autoimmune encephalomyelitis
GA	Glatiramer acetate
IFN	Interferon
IL	Interleukin
LT	Lymphotoxin
MR	Magnetic resonance
MS	Multiple sclerosis
MTX	Mitoxantrone
OPCs	Oligodendrocyte precursor cells
PPMS	Primary progressive multiple sclerosis
RRMS	Relapsing-remitting multiple sclerosis
SAS	Subarachnoid space
SPMS	Secondary progressive multiple sclerosis
TNF	Tumor necrosis factor

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Introduction

In 1868, the French neurologist Jean Martin Charcot first described patients with intermittent neurological dysfunctions whose brain and spinal cord white matter showed

multiple perivascular accumulations of inflammatory cells and named this entity *sclérose en plaques disseminées* (Charcot 1868), the disease we now call multiple sclerosis (MS). After more than a century of continuous research, we now know that MS is the most common demyelinating disease of the central nervous system (CNS) as well as one of the primary causes of neurological disability in young adults. Epidemiological studies indicate that more than one million people worldwide suffer from MS, with a higher prevalence in Europe and North America (reviewed in Rosati 2001). Clinically, approximately 80–90% of these patients initially develop a relapsing-remitting form of the disease (relapsing–remitting multiple sclerosis, RRMS) in their 20s and 30s and spontaneous neurological recovery, albeit to a variable degree, is observed quite commonly during the remission. Nonetheless, most of these RRMS patients later develop the secondary-progressive form (secondary progressive multiple sclerosis, SPMS), in which phase functional recovery virtually disappears and neurological dysfunctions increase. The remaining 10–20% of patients develop the primary progressive form (primary progressive multiple sclerosis, PPMS), characterized by no apparent spontaneous recovery from the initial phase.

Currently, there are a limited number of treatment options for MS and available disease-modifying therapies only reduce the annualized relapse rate by 30%; none of them reverse functional outcome in the long term. More disease-specific treatments are needed in order to develop new therapies and ultimately cure this disease. Therefore, what exactly is MS? As clinically shown by gadolinium-enhanced magnetic resonance (MR) images or pathologically proven in a few biopsied cases, the main feature of MS is multi-focal demyelination in the CNS white matter, often associated with localized inflammation. The most widely accepted hypothesis for MS pathogenesis is that it is an autoimmune disease driven primarily by myelin-specific $CD4^+$ T cells. Alternatively, primary oligodendrogliopathy as a cause of demyelination (and in this case immune responses are secondary to demyelination) is gaining favor as a secondary hypothesis. Despite the fact that many clinicians (especially non-MS specialists) tend to believe that MS is already proven to be an autoimmune disease, the causal relationship between demyelination and inflammation is a "chicken and egg" problem and still a matter of debate.

The Autoimmune Hypothesis

The autoimmune hypothesis (Fig. 1), the most widely accepted hypothesis for MS pathogenesis, proposes that inflammation is the cause of demyelination, initiated by auto-reactive leukocytes. The process begins when naïve myelin-specific $CD4^+$ T cells are primed in the lymph nodes (probably in the CNS-draining cervical lymph nodes; Furtado et al. 2008) by dendritic cells presenting either myelin or myelin cross-reactive epitopes. Th17 cells differentiated from these activated T cells by interleukin (IL)-23 are likely to play a central role in the course of the development of autoimmunity (Cua et al. 2003; Tzartos et al. 2008). These Th17 cells express the CC chemokine receptor 6, a receptor for CC chemokine ligand (CCL)20, whereas CCL20 is expressed by choroid-plexus epithelial cells, which constitute the blood-cerebrospinal fluid (CSF) barrier. As a result, the myelin-specific Th17 cells drain into the CSF in the subarachnoid space (SAS) for CNS immune surveillance (Reboldi et al. 2009). In the SAS, the patrolling T cells are reactivated by MHC class II-expressing macrophages or dendritic cells expressing myelin epitopes, leading to their infiltration into the CNS parenchyma to cause inflammation and consequently stimulate the blood–brain barrier (BBB) (Brown and Sawchenko 2007). After the activation of the BBB, additional T cells contact and crawl on the activated endothelial cells, then penetrate and enter the SAS (Bartholomäus et al. 2009). As T cells enter the parenchyma, together with activated macrophages and glial cells (microglia and astrocytes), they secrete soluble factors that cause demyelination. Tumor necrosis factor (TNF)-α and lymphotoxin (LT)-α are factors thought to be directly responsible for demyelination. Both of these factors bind to TNF receptor (TNFR)1 and TNFR2. Induction of demyelination by TNF-α and LT-α is likely to be dependent on TNFR1 (Eugster et al. 1999). Although it is well recognized that TNF-α and LT-α are secreted by T cells and macrophages, CNS parenchymal cells such as activated microglia (Frei et al. 1987; Pang et al. 2010) and activated astrocytes (Lieberman et al. 1989) also secrete these cytokines and thus may additionally be involved in the demyelination process (Selmaj et al. 1991a).

Importantly, many lines of supportive evidence that form the foundation of the above autoimmune hypothesis were derived from an animal model of MS, i.e. experimental autoimmune encephalomyelitis (EAE), rather than directly from MS patients. EAE is currently the most widely distributed model for MS, probably due to its ease of production and the absence of any other competing models. While some aspects of EAE are indeed similar to those of MS, there are key differences between the two diseases (reviewed in Sriram and Steiner 2005). Therefore, in order to evaluate the validity of the autoimmune hypothesis, the most critical question would be: is EAE really a valid model of MS?

In 1933, Rivers et al. (1933) first described a few monkeys which developed encephalomyelitis characterized by perivascular demyelination after repeated immunization with rabbit brain extracts. Of note, as they clearly state in

Fig. 1 The autoimmune hypothesis. In the autoimmune hypothesis, inflammation (initiated by auto-reactive T cells) is the cause of demyelination. See main text for the details. *Ab* antibodies, *OPCs* oligodendrocyte precursor cells, *SAS* subarachnoid space, *T* T cells
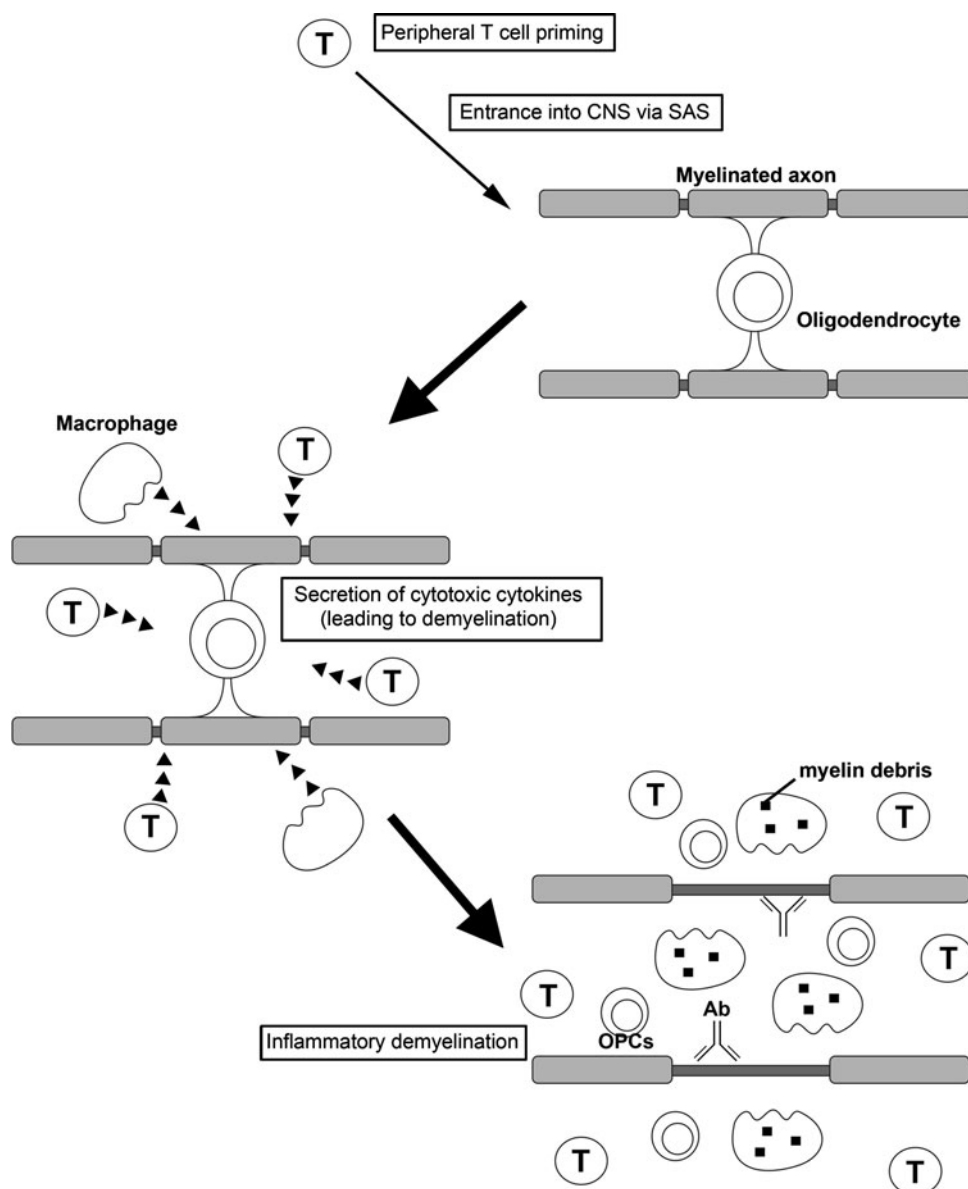
their original article, the experiment was carried out to produce a model of human acute disseminating encephalomyelitis (ADEM) that occurred occasionally after immunization with vaccine virus, and not to create an experimental model of MS. In the late 1950s, EAE was proposed as a useful animal model of MS. Elizabeth Roboz-Einstein, one of key opinion leaders involved in the distribution of EAE as a model of MS, wrote in her article in 1959 (Roboz-Einstein 1959): "Despite these objections we believe that allergic encephalomyelitis may be used as an experimental model because of its close relationship to multiple sclerosis." The inflammation observed in MS lesions was initially hypothesized to be an immune reaction against microbial infection. While enormous efforts were made to transmit this disease from man to animals, even

the famous microbiologist Hideyo Noguchi failed to fulfill Koch's postulates. These failures made researchers reconsider the possibility that the inflammation may be a non-infectious dysregulated immune reaction against autoantigens. In contrast, Philip Paterson succeeded in transmitting EAE to healthy animals by injecting them with lymphocytes of diseased rats (Paterson 1960). Together, these findings brought us to consider MS as a "possible" autoimmune disease and making EAE an attractive "possible" model of the disease.

Indeed, EAE successfully served as an MS model in some respects, especially in the development of certain disease-modifying treatments, namely glatiramer acetate (Copaxone®), mitoxantrone, and an antagonistic antibody against $\alpha 4\beta 1$ integrin (natalizumab; Tysabri®) (reviewed in

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Steinman and Zamvil 2006). Glatiramer acetate (GA) is a random copolymer of glutamate, tyrosine, alanine, and lysine and in a phase III trial in RRMS the drug showed a 29% reduction in relapse rate compared with placebo (Johnson et al. 1995). There are several mechanisms proposed to explain the clinical efficacy of GA in MS (reviewed in Schrempf and Ziemssen 2007), although its competition with myelin peptide (especially myelin basic protein) for binding to MHC molecules is thought to be the principal mechanism, leading to the inhibition of peripheral T cell priming. Mitoxantrone (MTX) is a small-molecule cytotoxic anti-neoplastic agent which acts on both healthy and cancerous cells by inhibiting topoisomerase II, leading to altered DNA synthesis and repair. MTX can cross the BBB and enter the CNS parenchyma to act as an immune-suppressive agent. Two randomized placebo-controlled trials in RRMS and SPMS showed that MTX reduced relapse rates by nearly 60% compared with placebo (Hartung et al. 2002; Millefiorini et al. 1997). Natalizumab is a monoclonal antibody against $\alpha 4\beta 1$ integrin. Since $\alpha 4\beta 1$ integrin expressed on lymphocytes binds to endothelial receptors on blood vessels within the CNS and thus helps the lymphocytes enter the parenchyma, natalizumab inhibits the migration of lymphocytes across the BBB by blocking $\alpha 4\beta 1$ integrin-mediated lymphocyte attachment. A randomized placebo-controlled trial in RRMS showed that natalizumab reduced relapse rates by 68% compared with placebo (Polman et al. 2006) and an additional 55% reduction rate when combined with interferon (IFN)-β 1a compared to IFN-β 1a alone (Rudick et al. 2006). All of these drugs were developed on the basis of their efficacy in EAE animals.

On the other hand, there are many more agents that can successfully treat EAE which have failed to show any beneficial effect in MS (and some of them exacerbated the disease; reviewed in Sriram and Steiner 2005). Probably, the two most disappointing results were the therapeutics that were directed against CD4 and TNF-α, both of which are critically involved in (either in the onset or the progression of) the aforementioned hypothesis. According to the autoimmune hypothesis, CD4$^+$ T cells are the critical player in the pathogenesis of MS and indeed anti-CD4 antibody prevented the onset of EAE or even reversed EAE in paralyzed animals (Waldor et al. 1985). Nonetheless, no beneficial clinical effect was observed in a phase II trial in RRMS and SPMS patients, despite a substantial decrease in the number of CD4$^+$ cells in the treated patients (van Oosten et al. 1997). TNF-α is thought to directly induce demyelination in the final course of the autoimmune hypothesis. In agreement with this theory, anti-TNF antibody or soluble TNFR1 (to antagonize TNF-α) inhibited the development of demyelination without interfering in the induction phase of EAE (Ruddle et al. 1990; Selmaj

et al. 1991b; Selmaj et al. 1995). However, a randomized placebo-controlled phase II trial on the effect of anti-TNF antibody in RRMS showed that it exacerbated MS (The Lenercept Multiple Sclerosis Study Group and The University of British Columbia MS/MRI Analysis Group 1999). Another study indicates that even the onset of MS may be associated with the inhibition of TNF (Sicotte and Voskuhl 2001). As a result, anti-TNF therapy, which shows significant effect in other autoimmune diseases (e.g. rheumatoid arthritis), is currently contraindicated in MS.

The above facts suggest that EAE is certainly a useful animal model that gave us vast pathophysiological information regarding CNS–immune relationships and that EAE would be a suitable animal model to test anti-autoimmune drugs targeting the CNS. Nonetheless, as for MS, EAE is an incomplete model and the results provided by EAE cannot be directly applied to MS. Most importantly, given the failure of clinical trials, MS and EAE should be considered to have some different pathophysiological characteristics, and the autoimmune hypothesis remains to be rigorously proven.

The Oligodendrogliopathy Hypothesis

If EAE animals do not reflect the true pathogenesis of MS, we have to go back to the beginning and reanalyze data from MS patients themselves to solve the hidden mystery of its pathogenesis. Although MR images have emerged as a powerful clinical tool to visualize live human brains, they are still unable to elucidate the mechanism behind lesion formation. However, histopathological studies on MS are reported far less frequently than those using EAE, largely due to the difficulty of obtaining appropriate MS specimens.

Through careful histopathological examination of MS lesions from 51 biopsies and 32 autopsies, Lucchinetti et al. (2000) provided four major patterns, each of them possibly reflecting a different pathogenesis. In type 1 (T cell-mediated autoimmune encephalomyelitis) and type 2 (T cell-plus antibody-mediated autoimmune encephalomyelitis) lesions, sharply demarcated active demyelination was frequently observed perivenously, associated with inflammation consisting mainly of T cells and macrophages, with (in type 2) or without (in type 1) pronounced antibody and complement deposition. Importantly, primary oligodendroglial apoptosis was absent in these two types of active lesions and the reappearance of oligodendrocytes in inactive plaques and remyelinated shadow plaques were frequently observed. In type 3 (primary oligodendroglial apoptosis) and type 4 (primary oligodendroglial dystrophy) lesions, either ill-defined (in type 3) or sharply demarcated (in type 4) active demyelination was frequently observed. Although these type 3 and 4 lesions were associated with T cells and macrophages, no typical association with veins

or venules was observed. In both these lesions, oligodendroglial death was prominent not only in active, but also in inactive lesions and shadow plaques were absent. Oligodendroglial apoptosis, as shown by nuclear condensation and fragmentation, was observed in type 3 lesions, whereas oligodendroglial death without these morphological features of apoptosis was frequently observed in type 4 lesions. Lucchinetti et al. reported that type 4 lesions were exclusively found in PPMS and type 1 lesions were rather infrequent compared with the other two types. Type 2 lesions were most frequently observed in RRMS or SPMS with various lengths of disease duration, whereas type 3 lesions were observed primarily in patients with a short disease duration (less than a couple of months before biopsy or autopsy). The most surprising finding provided by Lucchinetti et al. was that the type of lesion was homogeneous between different lesions within the same patient, although heterogeneous between different patients. The study thus suggested that there were at least four types of MS; type 4 presented exclusively in PPMS while types 1–3 were found in RRMS/SPMS patients. Types 1 and 2 differ with respect to the involvement of humoral immunity in demyelination, although both types may be explained in general by "autoimmunity", similar to that observed in various EAE animals. Type 3, which shows primary oligodendrocyte apoptosis, has never been described in the autoimmune hypothesis or in EAE animals and thus has brought a novel hypothesis of MS pathogenesis: oligodendrogliopathy. Of note, about a half of patients who were proven to have type 3 lesions by biopsy at the onset of disease are reported to have developed clinical RRMS in later follow-ups. If the lesion type remains "homogeneous" in the long course of the disease in the same patient (which was not proven in the study), then oligodendroglial apoptosis may well be "relapsing-remitting" and these patients are unlikely to be responsive to immune-suppressive therapies.

Although Lucchinetti et al. only included tissues with evidence of on-going inflammatory demyelination and assessed for the total disease duration before biopsy or autopsy, it was difficult to tell "how early" each lesion was. In other words, although active demyelination appeared to be present histopathologically, it is inconclusive as to when the trigger leading to demyelination occurred. Thus, the possibility remains that the four different pathological findings may reflect the timing of biopsy or autopsy after the onset of lesion formation rather than types that reflect differences of the trigger.

In rare cases, a relapse may be lethal, especially when a new lesion is formed in the brainstem or upper spinal cord. Barnett and Prineas (2004) analyzed 12 such cases, with the earliest case being only 17 h the onset of symptoms. In the 17-h fatal lesion, they found that myelin sheaths showed only a slight reduction in Luxol fast blue staining, whereas extensive apoptosis associated with shrunken nuclei and condensed chromatin was observed in oligodendrocytes, but not in any other cells within the lesion. Strikingly, they found no inflammatory cells (e.g. macrophages, T cells, or activated astrocytes) within the lesion with the exception of increased microglia showing signs of a very early phase of activation. Barnett and Prineas analyzed several other cases with the duration of episode ranging between 60 h and 42 days and together concluded that new MS lesion formation follows a time-line; (1) within hours, oligodendrocytes become apoptotic (only ramified microglia with thick processes increase, while no T cells or macrophages are observable within the lesion and myelin phagocytosis is yet to begin), (2) within 1–2 days, oligodendrocytes disappear (presumably phagocytosed by now activated amoeboid microglia in the lesion) and myelin becomes edematous and degenerated, (3) after that, myelin phagocytosis occurs in association with T cells and macrophages while oligodendrocyte precursor cells (OPCs) begin to appear, and (4) within 1–2 weeks, differentiated oligodendrocytes reappear (possibly for remyelination). If their observations reflect the true pathogenesis of MS, then inflammation is not the cause, but a mere result of oligodendroglial apoptosis and myelin degeneration, suggesting that inflammation (infiltration of T cells and macrophages) may be driven by demyelination as the normal immune response to remove degenerated myelin sheaths. The lesion formation that Barnett and Prineas described resembles the so-called type 3 lesion in the Lucchinetti study, suggesting that the type 3 lesion represents the true pathology of a very early stage of lesion formation. MS is a disease of oligodendrogliopathy rather than of autoimmunity.

Lucchinetti et al. argued against the Barnett and Prineas theory that all MS lesions begin with type 3, as they could not find any correlation between the pathological pattern and episode duration (between the onset of symptoms to the time of biopsy) (Barnett and Prineas 2004; Lucchinett et al. 2004). Breij et al. (2008) then added another important insight from histopathological analysis. They analyzed actively demyelinating lesions (as determined by the presence of myelin phagocytosing macrophages, and thus not including "very early" lesions like those described in Barnett and Prineas 2004) from 27 unselected autopsied MS cases with median disease duration of 22 years. They found that all the actively demyelinating lesions were consistently associated with large depositions of complement activation products and immunoglobulin, suggestive of the type 2 lesions as classified by Lucchinetti et al.

Recently, Henderson et al. (2009) provided further evidence to support the Barnett and Prineas theory. Using a thorough analysis of oligodendroglial apoptosis and the

distribution of inflammatory cells in various MS lesions, they provided evidence that oligodendroglial death and microglial activation are the initial events in MS lesion formation, followed by immune responses to scavenge dead myelin. Importantly, they showed that T cells, B cells, and IgG-positive plasma cells only started to accumulate in the lesions after myelin phagocytosis was completed by macrophages (although this does not imply that macrophages that phagocytosed myelin are cleared from the lesion) and occurred simultaneously with the reappearance of differentiated oligodendrocytes, suggesting that these immune responses are not toxic to oligodendrocytes, but rather permissive for oligodendroglial regeneration.

Taken altogether, the following hypothesis for MS pathogenesis can be drawn (Fig. 2). Lesion formation begins when oligodendrocytes become apoptotic (the type 3 lesion). Due to oligodendroglial death, myelin become degenerated and macrophages are recruited to scavenge and clear-up the degenerated myelin. Subsequently, immune reactions involving T cells and B cells begin (the type 2 lesion) simultaneously with oligodendroglial regeneration and remyelination. This hypothesis is consistent with findings in experimentally demyelinated animals that myelin debris impairs remyelination (Kotter et al. 2006) and activation of Toll-like receptor (to stimulate the phagocytosis of dead myelin) enhances remyelination (Setzu et al. 2006); thus myelin-scavenging processes (or what we considered "autoimmune demyelination") may be beneficial for restoring neural functions through remyelination after oligodendroglial death. Some natural autoantibodies were reported to be beneficial for remyelination (reviewed in Rodriguez et al. 2009), which also reasonably explains the necessity of inflammation after myelin degeneration.

If oligodendrogliopathy is the primary event in MS pathogenesis and immune reactions are mere secondary phenomena that may well be beneficial for the regenerative process that follows, the remaining key question is: what is the cause of oligodendrogliopathy? The two articles which described oligodendroglial apoptosis in newly forming MS lesions provide no conclusive evidence as to the cause of this apoptosis (Barnett and Prineas 2004; Henderson et al. 2009). Possible contributions of oxidative damage, glutamate toxicity, cytokines, mitochondrial injury, or certain autoantibodies have been proposed as possible causes of oligodendroglial death (reviewed in Bradl and Lassmann 2010), although evidence from human MS is yet to be provided.

Alternatively, some indications for the mechanism of primary oligodendroglial apoptosis may be provided by the histopathological study of remyelination failure. Unlike neurons, oligodendrocytes are highly capable of regeneration and remyelination is a very effective process in the CNS, as observed clinically in patients with ADEM or in experimentally demyelinated animals. However, remyelination is a rather inconsistent process in MS, making remyelination failure one of the key characteristics observed in chronic MS cases (reviewed in Nakahara et al. 2009a). Remyelination failure in MS is not due to lack of appropriate cells to be recruited for remyelination, as numerous OPCs, immature cells capable of differentiating into myelinating oligodendrocytes, are observable in many chronic MS lesions (Chang et al. 2000; Nakahara and Aiso 2006; Scolding et al. 1998; Wolswijk 1998). Remyelination failure is rather attributable to the differentiation arrest of OPCs into myelinating cells (Kuhlmann et al. 2008). We recently demonstrated that the differentiation block is attributable to over-expressed TIP30, a physiological inhibitor of nucleocytoplasmic transport (i.e. nuclear transport of transcription factors required for differentiation) within the preserved OPCs in MS lesions (Nakahara et al. 2009b). TIP30 is also well known as a pro-apoptotic protein (reviewed in Nakahara et al. 2009a), and we indeed observed massive apoptosis when TIP30 was over-expressed in OPCs in vitro (Nakahara et al. 2009b). Although possible TIP30 expression in the very early MS lesion remains to be analyzed, the observation in chronic MS lesions suggests by analogy that oligodendrocytes or OPCs may have intrinsic functional defects that lead to demyelination. If this is the underlying mechanism, transplantation of new oligodendrocytes may ultimately be necessary for the "cure" of this disease.

Recent Clinical Trial Results and their Implications

An important question that remains to be answered is, even if MS lesion formation begins pathologically when oligodendroglial apoptosis occurs, whether the same apoptotic cell death is repeated in the clinical course of RRMS or the secondary immune reaction (that was initially driven to clear up dead myelin for regeneration) has some contribution to clinical, if not pathological, "relapses". In the real world, we still do not know if all of the clinical attacks (acute symptoms) reflect new lesion formation or whether all the MS symptoms begin with oligodendroglial apoptosis or with the initiation of "secondary" inflammation (which may cause brain edema as well). Thus, even if it may not be a cure, immune-suppressive treatments may still be beneficial to MS patients.

From this perspective, it is very promising to observe that several new immune-suppressive drugs recently showed tremendous effects on reducing clinical relapses. For example, alemtuzumab is a humanized monoclonal antibody targeting glycoprotein CD52 that is present on all mature lymphocytes. Administration of alemtuzumab

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Fig. 2 The oligodendrogliopathy hypothesis. In the oligodendrogliopathy hypothesis, oligodendroglial apoptosis (by some undetermined causes) is the cause of demyelination and inflammation is a mere secondary event to clear up the degenerated myelin. See main text for the details. *Ab* antibodies, *B* B cells, *OPCs* oligodendrocyte precursor cells, *T* T cells
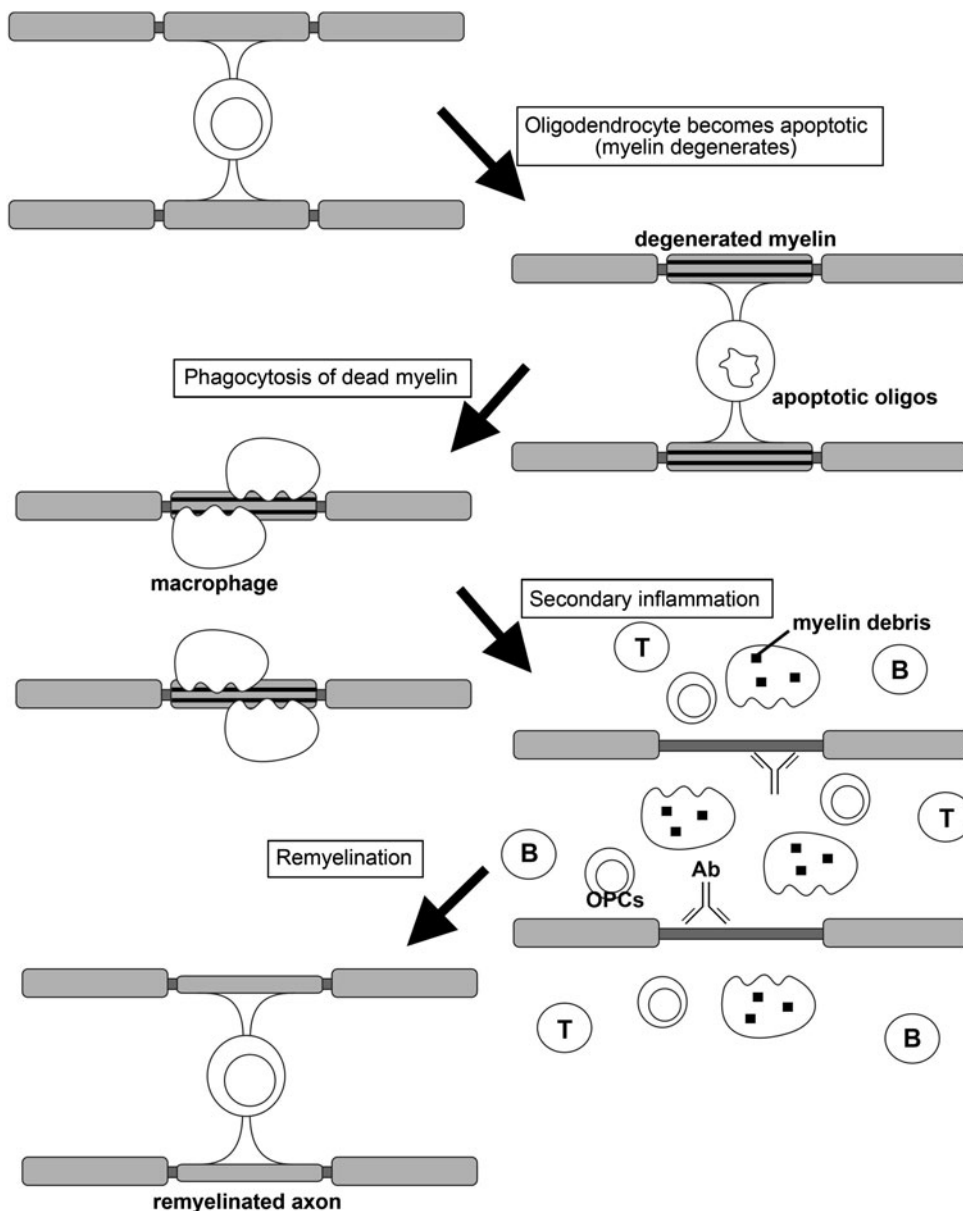
depletes mature T cells as well as B cells, which are thought to be key players in the immune reactions during demyelination. After the treatment, the immune system recovers, but theoretically without the auto-reactive lymphocytes. The results of a phase II clinical study of alemtuzumab in MS patients showed a striking clinical effect of this drug in the suppression of relapses (Coles et al. 2008). In the study, alemtuzumab was administered once yearly to 334 patients with early MS [with a baseline expanded disability status scale (EDSS) score of 1.9/10 on an average]. Over a period of 36 months, the annualized relapse rate was reduced to as low as 0.10 in the alemtuzumab-treated group compared with 0.36 of the IFN-β 1a-treated group, suggesting that alemtuzumab can theoretically reduce relapse occurrence to once in 10 years.

Even more strikingly, EDSS scores improved in the alemtuzumab-treated group, but not in the IFN-β 1a-treated group, although the data indicated that the improvement was most obvious during the first 6 months after the initiation of alemtuzumab therapy and the improvement remained as little as 0.32 on the EDSS, suggesting that although alemtuzumab does promote functional recovery, it is somewhat self-limiting.

Another recent study evaluated the effect of autologous non-myeloablative hematopoietic stem cell (peripheral blood stem cell) transplantation in 21 RRMS patients who did not respond to IFN-β, with baseline EDSS of 3.2/10 on average (Burt et al. 2009). Although there were several limitations to this study (e.g. small sample size, uncontrolled single-center design, selection bias (unresponsiveness to

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IFN-β), and the use of alemtuzumab in the conditioning regimen in 17 out of 21 patients), after a mean of 37 months' observation, 16 out of 21 patients were relapse-free and, most importantly, 81% of the patients had improvement on their EDSS scores at least by 1 point.

Further analysis is necessary to determine the factors that contributed to the EDSS improvement, although the results from these studies imply that inflammatory reactions during demyelination, even if it was a secondary event, are to some extent harmful to patients and may be related to clinical symptoms or relapse.

Conclusion

In this review, we have briefly outlined and compared the two major hypotheses of MS pathogenesis: autoimmunity versus oligodendrogliopathy. Although recent histopathological evidence suggests that primary oligodendrogilopathy is central to MS pathogenesis and immune reactions may be only a secondary phenomenon, recent clinical trial results indicate that modification of the immune system is beneficial for modifying the clinical course of MS. Although there have been enormous advances recently in understanding MS pathogenesis, further studies are required to draw up a uniform theory to explain the entire disease course of MS. Finally, it is important to note that the diagnosis of MS is made by a simple clinical picture: CNS demyelination that is multiple in time and space. Thus, we should also be aware that clinical MS may be heterogeneous diseases with several different possible characteristic pathologies.

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