Review Article

Multiple Sclerosis: Animal Models and Treatment Options

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Abstract

Multiple sclerosis is an inflammatory autoimmune-mediated disease of the Central Nervous System (CNS). Different treatment protocols, based on neurotropic viral infections and/or immunization with CNS proteins, have been implemented. Although there are encouraging outcomes, cure is still far from reach. Here, we discuss some of these treatment options.

Keywords: Multiple sclerosis; Central nervous system

Introduction

In multiple sclerosis (MS), inflammation-induced damage against the axonal myelin sheath, or demyelination, within the central nervous system (CNS), leads to breakdown of saltatory conduction and progressive disability due to neuronal cell death. There is limited endogenous repair of demyelination in the CNS of MS patients. Moreover, the suppressor T cell responses are deficient in MS and higher antibody responses to microbial agents have been found, both of which may also be due to lower production of downregulatory mechanisms [1]. While treatments are available to limit demyelination, no treatments are available to promote myelin repair. In this article, we discuss the variety of treatments that are available at present and the need for suitable treatments, which can lead to remyelination.

Importance of MS around the world

While MS is considered to be a disease of the colder climate, primarily affecting North America and Europe, recent evidence suggests that this disease is prevalent in areas like Japan, China [2] and the Middle East (unpublished observation), countries traditionally considered low-incidence regions. MS is now probably affecting over 2.5 million people worldwide.

The disease starts at a young age of 20-40 and accompanies the patient throughout the life, resulting in a damaging socio-economic impact [2]. Thus even more than other human diseases, MS research needs to develop effective and specific therapies.

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Animal Models of MS

There are two main available experimental models of MS: 1) Viral models, in which demyelination and remyelination are naturally-occurring, and 2) experimental autoimmune encephalomyelitis model (EAE), with symptoms that closely resemble MS symptoms in humans, and are more widely-used to test treatment protocols for MS. These models offer two different insights:

Multiple sclerosis and the viral Models

Pathologically MS is characterized by inflammatory demyelination, a feature similar to viral infections of the CNS [3]. While viruses have been considered as an important etiological agent in MS, no single virus has been consistently isolated from MS patients, to account for a substantial, if not all, cases of MS. However, it should be emphasized that a few neurotropic viruses do cause inflammatory demyelinating diseases similar to the pathological features of MS. The old and well-characterized model of inflammatory demyelinating virus infection in the mouse is Theiler's murine encephalomyelitis (TMEV-IDD) [4].

In few susceptible strains of mice, TMEV initially causes an acute infection, followed by a persistent phase, both resulting in a sustained inflammatory disease eventually causing demyelination. It has been hypothesized that the initial acute infection leads to CNS destruction and release of myelin components in the surrounding microenvironment. Myelin proteins are then taken up by local or infiltrated antigen-presenting cells [5-7] and presented to autoreactive T cells, resulting in their activation to myelin proteins. This process of "bystander activation" leads to "determinant spreading", a popular, previously described concept in autoimmunity [8].

Although TMEV imitates essential pathological features of some forms of human demyelinating diseases, no persistent neurotropic virus has been identified in MS. In practical terms, a MS model of treatment, based on a persistent demyelinating virus is difficult to use: the experimental conditions leading to determinant spreading is technically complicated [5-8], and seems to produce highly variable results. Another less studied CNS virus model is the nonlethal strain, A7-74, of Semliki Forest virus (SFV) that has been used to elucidate

the mechanisms of demyelination [9,10] and remyelination in MS [10]. There are several unique aspects of the SFV model: 1) easy initiation of acute CNS disease by peripheral inoculation of SFV, 2) clearance of virus by day 7 Post Infections (pi) with no persistence and 3) transient autoimmune mediated demyelination, in the absence of viral antigens, on days 15-21 pi followed by remyelination, by day 35 pi [10]. The most important feature of the SFV model is that it fully remyelinates, after the autoimmune demyelination. The major surface protein of SFV, the E2 protein, contains its epitopes (E2P1 and E2P2), which evoke antibody responses [11,12] and clear the virus [13,14]. Antibody response to E2P2 was found to correlate with remyelination after SFV infection [15]. A unique feature of SFV is the presence of "molecular mimicry" (3 identical and some partial amino acid homologies) between the E2P2 of SFV and a peptide of mouse myelin basic protein (MBP) [16], and between E2P2 and a peptide of human MBP (unpublished). The role of mimicry was confirmed by the finding that T cells and antibody from SFV-infected mice responded, not only to E2P2, but also to myelin peptides, in particular to mouse MBP peptide [16], Inoculation of mice with the mimicked mouse MBP-E2P2 peptide was not pathogenic in naïve mice (unpublished). Treatment of SFV-infected δ-knock-out mice that made low antibody to E2P2 of SFV, by inoculation with E2P2, induced more robust antibody response, which improved clinical symptoms and reduced widespread demyelination [15]. The remyelinating effect following E2P2 inoculation was most likely due to molecular mimicry between E2P2 peptide and the peptide of mouse MBP, to which the induced anti E2P2 antibody binds, and suggested that anti E2 P2 antibody plays a role in remyelination.

The activation of autoreactive human T cells by viral peptides, and generation of viral specific antibodies that cross-react with constitutive epitopes found within the body have provided evidence for a role of molecular mimicry between viral and autoantigenic peptides in the etiology of human autoimmune diseases [17-19], such as MS [19], diabetes [20] and SLE [21].

MS and EAE Model

MS is thought to be, at least partially, caused by an autoimmune attack on three major proteins of myelin: Myelin Basic Protein (MBP), Proteolipid Protein (PLP) and Myelin Oligodendrocyte Glycoprotein (MOG). In EAE model, animals are injected with myelin antigens to initiate an immune response. EAE provides a model for inflammation and demyelination, two basic processes of MS [22-26]. Encephalitogenic epitopes of MOG-, MBP and PLP-induced EAE models in mice were found to be demyelinating encephalomyelitis resembling MS [23-25]. Adoptive transfer of T-cells, specific for these proteins/peptides [26] provided useful models to study MS, and to test the therapeutic activity of potential treatment protocols. EAE in mice, like MS, targets oligodendrocytes, the myelin-producing cells [27,28]. Myelin-specific T cells cross the compromised blood-brain barrier, attack the myelinated axons in the CNS, and activate and recruit microglia and macrophages which in turn release a plethora of cytokines and chemokines that regulate disease progression [29,30] Some of these cytokines and chemokines promote the disease process, whereas others act to suppress. EAE models are used extensively to test the therapeutic activity of potential treatment protocols. Based on findings in EAE model(s) treatment for MS patients have mainly included immunosuppressive agents and immunoregulatory cytokines that down-regulate the immune responses [31-36]. Inoculation with

myelin peptides to generate suppressor T cells to has also been used to treat EAE and MS [37-40].

Immunoregulation and self-tolerance- role of natural T cells and antibodies

The discovery of auto-reactive T cells in healthy individuals led to the findings of mechanisms maintaining self-tolerance. Early experiments, using MBP specific T cell lines from Lewis rats showed that, when transferred, not only produce EAE but lead to activation of regulatory T cells which inhibit further activation and future induction of EAE in the recipient animals [41]. This protection was mediated by CD8+ T cells [42]. The discovery of these inhibitory T cells provided the basis for using inactivated myelin specific T cells as a vaccine, and is being used as strategies for treatment of MS. Natural antibodies (Ab) utilize germline-encoded genes directed against foreign antigens, self- and altered self-structures [43] and are present in newborns without stimulation by foreign antigens [44]. Natural Abs is polyreactive and binds their antigen with rather low affinity but high avidity. In contrast, conventional Abs undergoes affinity maturation and contains somatic mutations to ensure high affinity antigen binding [45].

Remyelination promoting antibodies

The appearance of natural Abs in vertebrates is presumably the firstline of defense against invading pathogens [45], which opsonize damaged cells in the body for antibody-dependent cellular cytotoxicity. In addition certain types of natural Abs can actively signal in different cell types including cancer and brain cells. In mice, another class of natural Abs, termed remyelination-promoting antibodies, actively promote repair in demyelinated spinal cord areas in virus-infected animals [46,47].

The first successful attempt to stimulate remyelination using natural Abs was performed in the Theiler's Murine Encephalomyelitis Virus (TMEV)-induced model of demyelination [46-48]. TMEV-infected SJL mice were immunized with Spinal Cord Homogenates (SCH) of normal mice to stimulate polyclonal and monoclonal antibody responses directed against a variety of CNS antigens including myelin components. A higher level of remyelination was observed in these, than in non-immunized virus-infected mice. Two monoclonal mouse Abs of the IgM phenotype were identified to be effective in promoting remyelination [49]. Both Abs were able to target mature oligodendrocytes in vitro, and had the features of physiologic natural autoantibodies. Based on this information remyelination-promoting Abs of human origin were present in the sera of patients with monoclonal gammopathies. Cerebellar slice cultures were used in addition to cultured oligodendrocytes for preliminary screening. This resulted in the identification of two serum-derived human remyelination promoting Abs, sHIgM22 and sHIgM46, which stimulated remyelination in vivo and could bind to oligodendrocytes in vitro. The latter Ab has been humanized and has recently been approved by the FDA for phase I clinical trials in MS patients. Identified mouse and human remyelination promoting IgMs stimulate remyelination after TMEV – and lysolecithin- [46-51], but not EAE - induced (unpublished data) demyelination, in mice.

Utilizing SFV as a model to study the pathogenesis of MS, We have shown that treatment of SFV-infected mice, with E2P2 of SFV, induced an antibody response, which improved clinical symptoms and reduced widespread demyelination in SFV-infected mice [15]. Furthermore, inoculation with E2P2, which contained shared viral and

MBP amino acid sequences, induced the production of antibody to the peptide and improved remyelination in the MOG model of chronic progressive EAE [52]. This antibody was capable of binding to cells in the CNS and activating them to produce myelin. In this study, elevated amount of serum anti E2P2 antibody in peptide-treated EAE mice correlated with remyelination in treated compared with untreated EAE mice.

Mechanisms of action of remyelinating antibodies

Studies of IgM remyelinating antibodies [46-51] have proposed two main mechanisms: 1) the direct hypothesis in which antibodies recognize Oligodendrocyte Progenitor Cells (OPCs) and promote the synthesis of new myelin. 2) The indirect hypothesis in which antibodies activate either immune cells or cell types other than cells of the oligodendrocyte lineage within the CNS, which, in turn, stimulate OPCs or oligodendrocytes (e.g. by secreting remyelination promoting factors). Support exists for both hypotheses. Evidence supporting the direct hypothesis is derived from the observation that remyelination promoting IgMs target oligodendrocytes in culture, isolated myelin and myelin tracks in cerebellar slice cultures [53-54]. This could not be supported by in vivo experiments, using immunofluorescence studies. All tested human and mouse remyelination promoting IgMs induce Calcium influx in cells of the OL-lineage, which suggests activation of intracellular signaling pathways potentially important for remyelination [55]. In the SFV model [52], higher number of oligodendrocytes and Oligodendrocyte Progenitor Cells (OPC) in E2P2-treated EAE mice suggested that the production of specific antibodies after peptide treatment could have led to more migration of oligodendrocytes into demyelinated areas and proliferation leading to improved remyelination in treated EAE mice. It has been suggested that for a successful remyelination, OPCs must proliferate, migrate to sites of demyelination and mature into myelinating oligodendrocytes [56,57]. More data is needed, however, to show the exact mechanism of remyelination, and whether remyelination is a direct consequence of activation of oligodendrocytes and OPCs. Our studies also indicated that treatment with E2P2 might be able to further activate the astrocytes, which could indirectly promote remyelinating effect of oligodendrocytes in treated EAE mice [52]. Accordingly, astrocyte-derived factors and chemokines promote OPC migration [56,57], proliferation [58] and maturation [59]. Furthermore, astrocytes-derived factors promote the survival of oligodendrocyte precursor cells [60]. In summary, our studies have shown that treatment with SFV E2 P2, or anti peptide antibody, led to immunomodulation, improvement of clinical disease, and detectable improvement in remyelination, in mice with EAE. The improvement in remyelination appeared to be as a result of increased oligodendrocyte number (and OPC), and oligodendrocyte and astrocyte activation that led to repair and increased remyelination in the CNS of EAE mice.

As stated above, one of the proposed mechanisms would be binding of anti E2 P2 antibody to glia and direct enhancement of oligodendrocyte proliferation and migration. This binding can result from antigenic similarities between the surface of enveloped SFV particles and glycoproteins of brain cells and components. The significance of findings in SFV to the field of MS, and other autoimmune inflammatory diseases of the CNS, rely on the concept of molecular mimicry that has been proven to be credible in several other autoimmune diseases as well [16-21].

SFV buds from the infected neurons and other cells in the brains of infected mice, incorporating their constituents into the envelopes of virions. Antibody responses to galactocerebrosides have been detected in the sera of SFV-infected mice at 2-4 weeks following infection (unpublished).

Another mechanism for improvement in remyelination, could be an immunoregulatory role of anti-viral antibody, which may have led to production of some cytokines and growth factors that promote immunoregulation and consequently improve remyelination.

What are the available treatments for MS

The predominant treatments that currently exist for MS are immunomodulators that have anti-inflammatory [31,32] or anti-cytokine effects [33], inducers of suppressor T cells and TH2 responses [40,41], and inducers of immunotolerance [37]. Treatments for MS also include immunomodulators [(interferon (IFN) beta] [33,35,36] glatiramer acetate [38-40], immunosuppressants (mitoxantrone) [61] and natalizumab [62,63], a monoclonal antibody that prevents activated lymphocyte transmigration in the central nervous system. IFN beta and glatiramer acetate are effective in reducing clinical relapses and lesions visible on Magnetic Resonance Imaging (MRI) in patients with MS. Natalizumab reduces the short-term risk of increasing disability and the rate of clinical relapse in patients with relapsing MS. Many candidate drugs are being evaluated in relapsing-remitting forms of MS. While their efficacy is encouraging, the potential benefit is offset by toxicity, including severe infections due to immunosuppression.

Therefore, any treatment that induces and improves repair of damaged myelin in the mouse model and may have the potential to repair human myelin, would be an improvement in therapy. This treatment strategy could be used as monotherapy or in conjunction with other proven immunosuppressive therapies (especially in severe MS).

Potential emerging treatments

Growing evidence implies that the normal, mature CNS contains low or non-detectable levels of most Matrix Metalloproteinases (MMPs); the principal cells that express these MMPs are perivascular and parenchymal microglia. On the other hand, studies on the serum, Cerebrospinal Fluid (CSF) and brain tissue of MS patients have shown an increase of MMP-1,-2,-3,-7,-9,-12 and-14 activities, but in many neuroinflammatory conditions, such as encephalitis, meningitis, brain tumours, cerebral ischaemia, Guillain-Barré syndrome, these enzymes are also significantly upregulated. It seems that cells of monocyte group are key contributors to the neuroinflammatory process in MS through a mechanism that involves the high expression of different MMPs, such as MMP-1, -2, -3, -7, -9, -14 and decreased expression of TIMP-1 and TIMP-2. In the damaged sites of the CNS, there are complex and dynamic regulations of MMP expression by different cell types. The imbalance between MMP activity and the inhibitory action of tissue inhibitors of metalloproteinases (TIMPs) are implicated in MS development, as one of the MMP roles may be to facilitate the transmigration of circulating leukocytes into the CNS. Therefore, it is possible that the MMPs attack the basal lamina macromolecules that line the blood vessels, disrupting the BBB's integrity. Therefore, MMPs and their TIMPs play a key role in the immunopathogenesis of MS, and are suggested as potential targets to treatments. Hence, more research in MMPs/TIMPs domain and their roles in immunopathogenesis of disease might be recommended as a therapeutic toll for controlling MS [64]. The recent advances in stem

cell therapies may serve as potential treatments for neurological disorders. There are broad types of stem cells such as neural, embryonic, mesenchymal and hematopoietic stem cells with unprecedented hope in treating many debilitating diseases. Nowadays, Stem cell therapy in axonal demyelination and neurological disability (Specially MS) has been accelerated by growth in animal models, as well as by clinical studies in human patients. A new way that promotes this procedure is tissue engineering, which uses synthesis of natural polymer that simulates extra cellular matrix for better response of body to grafted cells. The results of these new studies may pave the road for the utilization of stem cells for the treatment of MS [65].

The course of disease in MS includes a relapsing, and often eventually progressive, which is heterogeneous; confidant prediction of long-term individual prognosis is not yet possible. However, because revised MS diagnostic criteria that incorporate neuroimaging data facilitate early diagnosis, most patients need to make important long-term treatment decisions, and selection of disease-modifying therapy. Currently, there are several such approved treatments with varying degrees of efficacy for reducing relapse risk and preserving neurological function, but their long-term benefits remain unclear [66]. Nevertheless, the place of these disease-modifying therapies within the context of several different MS management strategies, including those currently in use (sequential monotherapy, escalation therapy, and induction and maintenance therapy) and others that may soon become feasible (combination approaches and "personalized medicine") have been reviewed. Although, there is no clear indication for using vitamin A as a treatment for MS, there is some evidence [67] that should encourage clinical trials with vitamin supplementation as a potential treatment or as an add-on option. It has been suggested that vitamin A decreases inflammation and increases tolerance in autoimmunity; it may also help in brain protection in multiple sclerosis (MS). Vitamin A acts in synergy with vitamin D, and the immunological homeostasis ensured by these vitamins should not be unbalanced in favor of only one of them [67].

References

1. Lassmann H, Brück W, Lucchinetti C (2001) Heterogeneity of multiple sclerosis pathogenesis: implications for diagnosis and therapy. Trends Mol Med 7: 115-121.

2. Compston A, Contavreux C (2006) The distribution of multiple sclerosis in McAlpines multiple sclerosis (Compston, A. et al eds.) pp 71-111. Churchill Livingston Elsevier.

3. Fazakerley JS, Amor A Nash, W Russell (1997) Animal Model Systems of MS in Molecular Biology of Multiple Sclerosis., C. Wiley, Editor: Chichester.

4. Brahic M (2002) Theiler's virus infection of the mouse, or: of the importance of studying animal models. Virology 301: 1-5.

5. Tsunoda I, Fujinami RS (1996) Two models for multiple sclerosis: experimental allergic encephalomyelitis and Theiler's murine encephalomyelitis virus. J Neuropathol Exp Neurol 55: 673-686.

6. Wekerle H, Lassmann H (2006) Immunology of inflammatory demyelinating disease in McAlpines multiple sclerosis (Compston, A. et al eds.) pp 491- 546. Churchill Livingston Elsevier.

7. Ercolini AM, Miller SD (2006) Mechanisms of immunopathology in murine models of central nervous system demyelinating disease. J Immunol 176: 3293-3298.

8. McMahon EJ, Bailey SL, Castenada CV, Waldner H, Miller SD (2005) Epitope spreading initiates in the CNS in two mouse models of multiple sclerosis. Nat Med 11: 335-339.

9. Fazakerley JK (2002) Pathogenesis of Semliki Forest virus encephalitis. J Neurovirol 8 Suppl 2: 66-74.

10. Mokhtarian F, Swoveland P (1987) Predisposition to EAE induction in resistant mice by prior infection with Semliki Forest virus. J Immunol 138: 3264-3268.

11. Snijders A, Benaissa-Trouw BJ, Oosterlaken TA, Puijk WC, Posthumus WP, et al. (1991) Identification of linear epitopes on Semliki Forest virus E2 membrane protein and their effectiveness as a synthetic peptide vaccine. J Gen Virol 72 : 557-565.

12. Fernández IM, Snijders A, Benaissa-Trouw BJ, Harmsen M, Snippe H, et al. (1993) Influence of epitope polarity and adjuvants on the immunogenicity and efficacy of a synthetic peptide vaccine against Semliki Forest virus. J Virol 67: 5843-5848.

13. Boere WA, Benaissa-Trouw BJ, Harmsen M, Kraaijeveld CA, Snippe H (1983) Neutralizing and non-neutralizing monoclonal antibodies to the E2 glycoprotein of Semliki Forest virus can protect mice from lethal encephalitis. J Gen Virol 64 : 1405-1408.

14. Smith-Norowitz TA, Sobel RA, Mokhtarian F (2000) B cells and antibodies in the pathogenesis of myelin injury in Semliki Forest Virus encephalomyelitis. Cell Immunol 200: 27-35.

15. Safavi F, Feliberti JP, Raine CS, Mokhtarian F (2011) Role of $\gamma\delta$ T cells in antibody production and recovery from SFV demyelinating disease. J Neuroimmunol 235: 18-26.

16. Mokhtarian F, Zhang Z, Shi Y, Gonzales E, Sobel RA (1999) Molecular mimicry between a viral peptide and a myelin oligodendrocyte glycoprotein peptide induces autoimmune demyelinating disease in mice. J Neuroimmunol 95: 43-54.

17. Fujinami RS, Oldstone MB (1985) Amino acid homology between the encephalitogenic site of myelin basic protein and virus: mechanism for autoimmunity. Science 230: 1043-1045.

18. Ercolini AM, Miller SD (2006) Mechanisms of immunopathology in murine models of central nervous system demyelinating disease. J Immunol 176: 3293-3298.

19. Ercolini AM, Miller SD (2009) The role of infections in autoimmune disease. Clin Exp Immunol 155: 1-15.

20. Miyazaki I, Cheung RK, Gaedigk R, Hui MF, Van der Meulen J, et al. (1995) T cell activation and anergy to islet cell antigen in type I diabetes. J Immunol 154: 1461-1469.

21. Mamula MJ, Fatenejad S, Craft J (1994) B cells process and present lupus autoantigens that initiate autoimmune T cell responses. J Immunol 152: 1453-1461.

22. Sobel RA, Greer JM, Kuchroo VK (1994) Minireview: autoimmune responses to myelin proteolipid protein. Neurochem Res 19: 915-921.

23. Greer JM, Sobel RA, Sette A, Southwood S, Lees MB, et al. (1996) Immunogenic and encephalitogenic epitope clusters of myelin proteolipid protein. J Immunol 156: 371-379.

24. Amor S, Groome N, Linington C, Morris MM, Dornmair K, et al. (1994) Identification of epitopes of myelin oligodendrocyte glycoprotein for the induction of experimental allergic encephalomyelitis in SJL and Biozzi AB/H mice. J Immunol 153: 4349-4356.

25. Kerlero de Rosbo N1, Mendel I, Ben-Nun A (1995) Chronic relapsing experimental autoimmune encephalomyelitis with a delayed onset and an atypical clinical course, induced in PL/J mice by myelin oligodendrocyte glycoprotein (MOG)-derived peptide: preliminary analysis of MOG T cell epitopes. Eur J Immunol 25: 985-993.

26. Mokhtarian F, McFarlin DE, Raine CS (1984) Adoptive transfer of myelin basic protein-sensitized T cells produces chronic relapsing demyelinating disease in mice. Nature 309 356-358.

27. Raivich G, Banati R (2004) Brain microglia and blood-derived macrophages: molecular profiles and functional roles in multiple sclerosis and animal models of autoimmune demyelinating disease. Brain Res Rev 46: 261-281.

28. Hanisch UK, Kettenmann H (2007) Microglia: active sensor and versatile effector cells in the normal and pathologic brain. Nat Neurosci 10: 1387-1394.

29. Steinman L (1996) Multiple sclerosis: a coordinated immunological attack against myelin in the central nervous system. Cell 85: 299-302.

30. Steinman L (2000) Multiple approaches to multiple sclerosis. Nature Med 6: 15-16.

31. Kanwar JR (2005) Anti-inflammatory immunotherapy for multiple sclerosis/experimental autoimmune encephalomyelitis (EAE) disease. Curr Med Chem 12: 2947-2962.

32. Sloane E, Ledeboer A, Seibert W, Coats B, van Strien M, et al. (2009) Anti-inflammatory cytokine gene therapy decreases sensory and motor dysfunction in experimental Multiple Sclerosis: MOG-EAE behavioral and anatomical symptom treatment with cytokine gene therapy. Brain Behav Immun 23: 92-100.

33. Pachner AR (1997) Anticytokine antibodies in beta interferon-treated MS patients and the need for testing: plight of the practicing neurologist. Neurology 49: 647-650.

34. Skurkovich SV, Skurkovich B, Kelly JA (2002) Anticytokine therapy--new approach to the treatment of autoimmune and cytokine-disturbance diseases. Med Hypotheses 59: 770-780.

35. Vandenbroeck K, Urcelay E, Comabella M (2010) IFN-beta pharmacogenomics in multiple sclerosis. Pharmacogenomics 11: 1137-1148.

36. Airas L, Niemelä J, Yegutkin G, Jalkanen S (2007) Mechanism of action of IFN-beta in the treatment of multiple sclerosis: a special reference to CD73 and adenosine. Ann N Y Acad Sci 1110: 641-648.

37. Warren KG, Catz I, Ferenczi LZ, Krantz MJ (2006) Intravenous synthetic peptide MBP8298 delayed disease progression in an HLA Class II-defined cohort of patients with progressive multiple sclerosis: results of a 24-month double-blind placebo-controlled clinical trial and 5 years of follow-up treatment. Eur J Neurol 13: 887-895.

38. Miller CE, Jezewski MA (2006) Relapsing MS patients' experiences with glatiramer acetate treatment: a phenomenological study. J Neurosci Nurs 38: 37-41.

39. Munari L, Lovati R, Boiko A (2004) Therapy with glatiramer acetate for multiple sclerosis. Cochrane Database Syst Rev 2004: CD004678.

40. Wolinsky JS, Narayana PA, O'Connor P, Coyle PK, Ford C, et al. (2007) Glatiramer acetate in primary progressive multiple sclerosis: results of a multinational, multicenter, double-blind, placebo-controlled trial. Ann Neurol 61: 14-24.

41. Ben-Nun A, Wekerle H, Cohen IR (1981) Vaccination against autoimmune encephalomyelitis with T-lymphocyte line cells reactive against myelin basic protein. Nature 292: 60-61.

42. Sun D, Qin Y, Chluba J, Epplen JT, Wekerle H (1988) Suppression of experimentally induced autoimmune encephalomyelitis by cytolytic T-T cell interactions. Nature 332: 843-845.

43. Coutinho A, Kazatchkine MD, Avrameas S (1995) Natural autoantibodies. Curr Opin Immunol 7: 812-818.

44. Avrameas S, Selmi C (2013) Natural autoantibodies in the physiology and pathophysiology of the immune system. J Autoimmun 41: 46-49.

45. Avrameas S, Ternynck T (1993) The natural autoantibodies system: between hypotheses and facts. Mol Immuno 30: 1133-1142.

46. Rodriguez M, Oleszak E, Leibowitz J (1987) Theiler's murine encephalomyelitis: a model of demyelination and persistence of virus. Crit Rev Immunol 7: 325-365.

47. Rodriguez M, Lennon VA, Benveniste EN, Merrill JE (1987) Remyelination by oligodendrocytes stimulated by antiserum to spinal cord. J Neuropathol Exp Neurol 46: 84-95.

48. Rodriguez M, Lennon VA (1990) Immunoglobulins promote remyelination in the central nervous system. Ann Neurol 27: 12-17.

49. Warrington AE, Asakura K, Bieber AJ, Ciric B, Van Keulen V, et al. (2000) Human monoclonal antibodies reactive to oligodendrocytes promote remyelination in a model of multiple sclerosis. Proc Natl Acad Sci U S A 97: 6820-6825.

50. Warrington AE, Bieber AJ, Ciric B, Pease LR, Van Keulen V, et al. (2007) A recombinant human IgM promotes myelin repair after a single, very low dose. J Neurosci Res 85: 967-976.

51. Bieber AJ, Warrington A, Asakura K, Ciric B, Kaveri SV, et al. (2002) Human antibodies accelerate the rate of remyelination following lysolecithin-induced demyelination in mice. Glia 37: 241-249.

52. Mokhtarian F, Safavi F, Sarafraz-Yazdi E (2012) Immunization with a peptide of Semliki Forest virus promotes remyelination in experimental autoimmune encephalomyelitis. Brain Res 1488: 92-103.

53. Sommer I, Schachner M (1981) Monoclonal antibodies (O1 to O4) to oligodendrocyte cell surfaces: an immunocytological study in the central nervous system. Dev Biol 83: 311-327.

54. Asakura K, Miller DJ, Pease LR, Rodriguez M (1998) Targeting of IgM kappa antibodies to oligodendrocytes promotes CNS remyelination. J Neurosci 18: 7700-7708.

55. Paz Soldán MM, Warrington AE, Bieber AJ, Ciric B, Van Keulen V, et al. (2003) Remyelination-promoting antibodies activate distinct Ca2+ influx pathways in astrocytes and oligodendrocytes: relationship to the mechanism of myelin repair. Mol Cell Neurosci 22: 14-24.

56. Belmadani A, Tran PB, Ren D, Miller RJ (2006) Chemokines regulate the migration of neural progenitors to sites of neuroinflammation. J Neurosci 26: 3182-3191.

57. Mi S, Miller RH, Tang W, Lee X, Hu B, et al. (2009) Promotion of central nervous system remyelination by induced differentiation of oligodendrocyte precursor cells. Ann Neurol 65: 304-315.

58. Valerio A, Ferrario M, Dreano M, Garotta G, Spano P, et al. (2002) Soluble interleukin-6 (IL-6) receptor/IL-6 fusion protein enhances in vitro differentiation of purified rat oligodendroglial lineage cells. Mol Cell Neurosci 21: 602-615.

59. Zhang Y, Taveggia C, Melendez-Vasquez C, Einheber S, Raine CS, et al. (2006) Interleukin-11 potentiates oligodendrocyte survival and maturation, and myelin formation. J Neurosci 26: 12174-12185.

60. Nair A, Frederick TJ, Miller SD (2008) Astrocytes in multiple sclerosis: a product of their environment. Cell Mol Life Sci 65: 2702-2720.

61. Martinelli Boneschi F, Rovaris M, Capra R, Comi G (2005) Mitoxantrone for multiple sclerosis. Cochrane Database Syst Rev: CD002127.

62. Stüve O, Marra CM, Jerome KR, Cook L, Cravens PD, et al. (2006) Immune surveillance in multiple sclerosis patients treated with natalizumab. Ann Neurol 59: 743-747.

63. Vennegoor A, Wattjes MP, van Munster ET, Kriekaart RL, van Oosten BW, et al. (2011) Indolent course of progressive multifocal leukoencephalopathy during natalizumab treatment in MS. Neurology 76: 574-576.

64. Mirshafiey A, Asghari B, Ghalamfarsa G, Jadidi-Niaragh F, Azizi G (2013) The Significance of Matrix Metalloproteinases in the Immunopathogenesis and Treatment of Multiple Sclerosis. Int J Hematol Oncol Stem Cell Res 7: 15-33.

65. Ardeshiry Lajimi A, Hagh MF, Saki N, Mortaz E, Soleimani M, et al. (2013) Feasibility of Cell Therapy in Multiple Sclerosis: A Systematic Review of 83 Studies. Int J Hematol Oncol Stem Cell Res 7: 15-33.

66. Mirshafiey A, Asghari B, Ghalamfarsa G, Jadidi-Niaragh F, Azizi G (2014) The Significance of Matrix Metalloproteinases in the Immunopathogenesis and Treatment of Multiple Sclerosis. Sultan Qaboos Univ Med J 14: e13-13e25.

67. Fragoso YD, Stoney PN, McCaffery PJ (2014) The evidence for a beneficial role of vitamin a in multiple sclerosis. CNS Drugs 28: 291-299.