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Autoantigens and Autoantibodies in Multiple Sclerosis

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ABSTRACT

Multiple Sclerosis (MS) is an autoimmune disease characterized by recurrent episodes of demyelination and axonal lesion mediated by $CD4^+$ T cells with a proinflammatory T helper (Th)1 and Th17 phenotypes, macrophages, and soluble inflammatory mediators. The overactive pro-inflammatory Th1 cells and clonal expansion of B cells initiate an inflammatory cascade with several cellular and molecular immune components participating in MS pathogenic mechanisms. In this scenario, autoantibodies and autoantigens have a significant role in immunopathogenesis, diagnosis and therapeutic targets of MS. In this review, we try to introduce the autoantigens and autoantibodies and explain their roles in pathogenesis of MS.

Keywords: Alpha B-crystallin; Elonase; Multiple sclerosis; Myelin basic protein; S100 beta Aquaporin-4

INTRODUCTION

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system (CNS) manifested morphologically by inflammation, demyelination, axonal loss and gliosis. The inflammatory lesions are characterized by high infiltration of various populations of cellular and soluble mediators of the immune system, such as T cells, B cells, macrophages and microglia, as well as a broad range of cytokines, chemokines, antibodies, complement and other toxic substances.[1-3]

The cellular components involved in the neuroinflammation and neuroimmune activation in the cerebrospinal fluid (CSF) are brain microglial cells, ependymal cells, macrophages, astrocytes and mast cells.

Microglial cells which constitute around 10% of the CNS are the first to respond to neuronal injury.[1,4,5] MS is considered as an autoimmune disease in which T cell reactivity to self-antigens expressed in the brain, particularly myelin antigens, plays a pivotal role.[6] In this connection, the essential contribution of B cells and autoantibodies have been demonstrated in the pathogenesis of MS, leading to interest in the use of such autoantibodies as diagnostic or prognostic biomarkers.[7] Therefore, autoantibody profiles against epitopes derived from MS brain tissue could serve as diagnostic markers or form the basis for the identification of a subgroup of MS patients.[8] Autoantibadies (IgG and IgM) localized against demyelinated axons and oligodendrocytes and also antibody-antigen immune complexes were detected in foamy macrophages in active lesion areas.[9] These

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observations provide further evidence on the role of antibodies, complement and macrophages in plaque development, and strongly suggest that they can induce axonal injury, an important cause of disability in MS. They may provide novel therapeutic strategies to limit tissue degeneration in the disease. However, detection of antibodies against Myelin basic protein(MBP), Myelin oligodendrocyte glycoprotein (MOG)peptides, and alpha-beta-crystallin, could be used as surrogate markers for the confirmation of MS diagnosis.10 Some autoantigens such as alpha B-crystallin, S100beta and the DM20 isoform of proteolipid protein(PLP) are clearly expressed in the thymus and also in selected peripheral tissues. Whereas, the existence of MOG out of the CNS is not seen.[11] These results indicate that most of the antigens involved in MS are also expressed in the thymus, suggesting a possible role of central tolerance in MS development.[11] In this review, our aim is to show the role of CNS autoantigens and autoantibodie in immunopathogenesis of MS.

Immunopathogenesis of MS

MS, the principal inflammatory demyelinating disease of the CNS is believed to have an immunopathological etiology arising from gene-environment interactions. The initiation factors of the inflammatory response remain yet unknown. However, MS is considered as a complex disease depending on genetic as well as environmental factors.[1,12] Genetic factors have a significant role in susceptibility to MS, such as genes related to interleukin-1 receptor (IL-1R), immunoglobulin Fc receptor, Apo protein E, IL-1β, immunoglobulin heavy chain, T cell receptor, tumor necrosis factor (TNF)-α , MBP, IL-2R, IL-7R and Human leukocyte antigen(HLA) genes.13-18 Through these genes, there are a robust association between HLA locus and susceptibility to MS,[13,19] particularly DR15 haplotype and three alleles of DR2 haplotype, including DRB1*1501, DRB5*0101 and DQB1*0602.[13,20-22] In contrast, HLA-DRB1*01 has a role in disease resistance.[13,23] Moreover, environmental factors such as pathogens and chemical agents have been also suggested. Thus, probably both genetic and environmental factors have a role in the pathogenesis of MS.[1,24]

In general, MS begins with the formation of acute inflammatory lesions characterized by disruption of the blood brain barrier (BBB). Breakdown of the BBB usually lasts for about a month and then resolves, leaving a site of damage that can be investigated by conventional magnetic resonance imaging (MRI). The pathological features of MS plaques are BBB leakage, destruction of myelin sheaths, oligodendrocyte damage and cell death, axonal damage and axonal loss, glial scar formation and the presence of inflammatory infiltrates that mainly consist of lymphocytes and macrophages.[25-27] Despite major advances in the current understanding of pathogenesis of MS, exact details of the inflammatory cascade of MS remain unknown. It has been demonstrated that axonal degeneration is the major feature of irreversible neurological disability in MS patients. Axonal injury initiates the disease onset and correlates with the degree of inflammation within lesions.[25,28,29] Four different patterns of pathology with resulting demyelination have been identified in MS lesions: Type I is T cell mediated where demyelination is macrophage mediated, directly or by macrophage toxins. In type II lesions, both T cells and antibodies are involved and are the most common pathology observed in MS lesions. In this pattern, demyelination occurs through specific antibodies and complement. Type III is related to distal oligodendropathy, degenerative changes which occur in distal followed by apoptosis. Type IV results in primary oligodendrocyte damage followed by secondary demyelination. The latter pattern is seen only in a small subset of primary progressive MS patients.[25,30,31]

Both subgroups of T helper cells (Th1 and Th2) are involved in pathogenesis of MS, although it is evident that the role of Th1 is more prominent in comparison to Th2.[1,32-35] The presence of cytotoxic T lymphocytes (CTLs) in pathogenesis of MS has been also reported.[1,36] On the other hand, perivascular immunoglobulin and complement deposition within the MS lesions, robustly declares the role of humoral responses in the pathogenesis of disease.[1,37] Th17 cells which generate inflammatory cytokines such as IL-17 and IL-21 are also involved in neuroinflammation.1,38,39 It has been also shown that mice with fewer Th17 cells are less susceptible to Experimental autoimmune encephalomyelitis (EAE).1,40,41 Surprisingly, it has been reported that the microRNAs also have roles in the pathogenesis of MS. Du et al. showed that increased expression of miR-326 promotes progression of EAE and Th17 differentiation. They demonstrated that miR-326 inhibits translocation of Ets-1 mRNA, which is the

inhibitor of Th17 differentiation.[1,42,43] In addition, the activation of regulatory T cells in MS is decreased, due to reduction in FoxP3 (essential transcription factor for regulatory T cells) levels.[1,44] Other cell types that are presented in inflammatory lesions are astrocytes, which produce extracellular matrix molecules that are components which provide framework in the CNS. In addition, they maintain ion homeostasis by producing neurotrophic factors and clearing diffused neurotransmitters. A role for astrocytes in regulating immune responses in the CNS has been suggested on the basis of production of transforming growth factor-β (TGF-β) and its ability to induce apoptosis of T cells.[1,45]

It seems that the macroscopic lesions and normal appearing white matter damage occur mainly during the earliest clinical stages of MS, whereas pathological features of gray matter may be a hallmark of the late progressive stage of the disease.[1,46] Recently, many autoantigens in the CNS have been introduced as immunopothogenic factors in MS disease. The produced autoantibodies against autoantigens are able to precede the neurodegenerative reactions in the CNS.

Autoantigens and Autoantibodies

Alpha- Enolase

Enolase, a key glycolytic enzyme, belongs to a novel class of surface proteins which through an unknown mechanism are transported on the cell surface. Enolase is a multifunctional protein, and it has a significant role in the intravascular and pericellular fibrinolytic system because of its ability to serve as a plasminogen receptor on the surface of a variety of hematopoetic, epithelial and endothelial cells.[47] Enolases include three subunits: a (46kDa), b (44kDa), and g (46kDa). The a-subunit is expressed in most tissues and the b-subunit only in muscle. The g-subunit exists primarily in neurons, in normal and in neoplastic neuroendocrine cells.[48] In autoimmune and inflammatory diseases, anti-alpha-enolase antibodies could induce endothelial injury through the generation of immune complexes and activation of the complement classical pathway, inhibition of the binding of plasminogen to alpha-enolase with perturbations of the intravascular and pericellular fibrinolytic system, and induction of cell death through an apoptotic process.[49] Serum autoantibodies against the glycolytic enzyme enolase have been reported in a diverse range of inflammatory, degenerative, and psychiatric disorders,[50] and have also previously been reported in MS patients. The T-cell response to these antigens, however, has not been established.[51] These antibodies have been involved in autoimmune retinopathy. Anti-enolase antibodies are likely an epiphenomenon of autoimmune disease, and are not causing retinopathy in MS patients with normal visual acuity.[52]

In a study, statistically significant difference between MS patients and controls in the rod-cone b-wave implicit time (p<0.005) and autoantibodies against alpha-enolase in 38% of MS patients and 11% of controls (p=0.02) has been reported.[52]

Alpha B-crystallin

Alpha B-crystallin, a major protein of the vertebrate lens, is found in the CNS and is a major protein component of Rosenthal fibers, and intracytoplasmic inclusions within astrocytes.[53] In fact, It is expressed on astrocytes, oligodendrocytes and occasionally on demyelinated axons.[54] This protein is not normally expressed in the brain, but is induced in response to the injuries inflicted on nerve cells in MS. Essentially, crystallin has anti-apoptotic and neuroprotective[8] functions.[55] Furthermore, alpha B-crystallin is a chaperone protein (heat shock protein [Hsp] B5) and a potential myelin antigen for human T cells in MS. It has been labeled as autoantigen in MS based on humoral and cellular responses found in humans and animal models.[56] On the other hand, it has been demonstrated that EBV-induced expression of alpha B-crystallin in B cells leads to HLA-DR-restricted presentation of the protein and activation of proinflammatory alpha B-crystallin-specific Th cells.[57] Moreover, Western blot analysis showed the presence of high molecular weight alpha B-crystallin in CSF, and also it was observed in the CSF of all MS patients and 88% of neurological controls without MS.[58] It should be noted that in a study by Jeffrey *et al,* in 3 of 10 active MS lesions, alpha B-crystallin could be detected inside phagocytic vesicles of perivascular macrophages, colocalizing with myelin basic protein and MOG.[59] In addition, some studies have reported that alpha B-crystallin inhibited inflammation in the brain and terminated relapses as remissions in MS.[60]

Beta- Arrestin

Beta-arrestins are cytosolic proteins that form complexes with seven- transmembrane receptors after

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agonist stimulation and phosphorylation by the G protein-coupled receptor kinases.[61] They compete with G proteins for binding to activated phosphorylated receptors, initiating receptor internalization, and activating additional signaling pathways.[62] In addition, the role of beta-Arrestin regulation in ever increasing number of signaling molecules, including the mitogen activated protein kinases ERK, JNK, and p38 as well as Akt, PI3, kinase, and RhoA has been demonstrated.[63] Furthermore, the receptor-specific or homologous for desensitization of beta 2-adrenergic receptors is thought to be affected via phosphorylation of the receptor by the beta-adrenergic receptor kinase (beta ARK), followed by binding of beta-arrestin.[64] Basically, beta-arrestin 1 is critical for $CD4^+$ T cell survival and is a factor in susceptibility to autoimmunity.[65] G protein-coupled receptor (GPCR) kinases (GRKs) and arrestins mediate desensitization and control GPCR signaling; hence, regulate further signal reproduction through G proteins. Recent evidence suggests that the GRK-arrestin desensitization machinery fulfills a vital role in regulating inflammatory processes. First, GRK/arrestin levels are dynamically regulated in immune cells in response to inflammatory reactions. Second, in animals with targeted the deletion of GRKs or arrestins, the progression of various acute and chronic inflammatory disorders, such as autoimmunity, is profoundly affected. Third, chemokine receptor signaling seems to be tightly regulated by the GRK/ arrestin machinery, so that the small changes in GRK/ arrestin expression can have a marked effect on cellular responses to chemokines.[66] In the study by Wojciech et al using immunoblot analysis, MS sera mainly revealed 46-kD antigen, 41-kD antigen, retinal arrestin and to a smaller extent also 70-, 56-, 43-, and 36-kD proteins. Patients whose sera showed the highest reactivity with 41- and 46-kD antigens showed deficiencies in visual acuity, visual fields, ophthalmoscopy, and electroretinograms.[67]

Anti-Arrestin

Anti-arrestin antibody is frequently found specifically in adult patients with MS and uveitis and also serial examinations reported that the serum anti-arrestin antibody titer is well correlated with the disease activity.[68] Furthermore, a prominent protein band at 48 kDa stained with MS sera was revealed by immunoblot analysis of bovine rod outer segments. This antigen was purified from bovine retinal outer segments and identified as arrestin.[69] Additionally, a reaction between sera from MS patients and purified beta-arrestin 1 is found in various tissues. The recognition site(s) for antibodies in sera of MS patients was identified at a dominant immunogenic site on arrestin located at the C-terminal region of the molecule, by using competitive ELISA test with a synthetic peptide.[69]

Proteasom

The proteasome-dependent protein degradation participates in multiple essential cellular processes.[70] Indeed it is the key step in the production of Major Histocompatibility Complex class I-restricted epitopes and therefore its activity could be an important element in the activation and regulation of autoreactive CD8+ T cells in MS.[71] In the ubiquitin-proteasome pathway, proinflammatory cytokine mixtures induced upregulation of several genes, notably ubiquitin D (Ubd/FAT10), ubiquitin ligase and several proteasomal proteins.[72] Furthermore, enhancement of proteasome activity through inhibition of USP14 (a proteasome-associated deubiquitinating enzyme) may offer a strategy to reduce the levels of aberrant proteins in cells under proteotoxic stress.[73] Some studies have been reported that the activities of the three peptidases of the 20S proteasome (i.e. chymotrypsin-like, caspase-like and trypsin-like) in both MS-brain white matter and MS-brain gray matter are greatly reduced.[74] In addition, the accumulation of carbonylated (and potentially toxic) proteins are caused by an impaired 20S proteasome in the central nervous system of chronic EAE mice and MS patients. Carbonylated (oxidized) proteins were noticed to be collected in the brain of patients with MS and in the spinal cord of rats with acute EAE.[75] It should be noted that the pharmacologic double inhibition of the ubiquitin proteasome system (UPS) by IFN-beta-1b occurs in MS patients and contributes to improvement of clinical course and reduction in MRI activity.[76] Moreover, proteasome, a ubiquitous protease complex composed of 14 different subunits, is a target for autoantibody (IgG and IgM classes) production in the serum (66%, 73 out of 110) and in the CSF (61%, 16 out of 26) of patients with MS. Therefore, the proteasome might be a major autoantigen in MS.[77] The recombinant proteasomal subunits have induced specific autoantibodies against subunits C2, C8, C9 and C5 which have been detected in MS patients.

S100-Beta

S100 beta protein is a soluble calcium binding protein such as calmodulin and troponin C. S100A is a heterodimere protein with an alpha and beta chains whereas S100B is a homodimeric protein with two beta chains. It exists in melanocytes, nerve cells, and their tumors and also in the antigen presenting cells such as the Langerhans cells and interdigitating reticulum cells in the paracortex of lymph nodes. It is not only expressed by astrocytes in the CNS, but also in many other tissues such as thymus, spleen and lymph nodes. In contrast with this tissue distribution, which was expected to induce a strong status of self-tolerance to S100 beta, the Lewis rat showed a notable T cell response to this autoantigen.[78] S100 beta- and glial-fibrillary-acidic-protein-specific T cells mediated particularly severe inflammatory reaction in the gray matter.[78] Additionally, it has been reported S100-beta as a neurotrophic factor could promote neurotic maturation and outgrowth during development. This protein also plays a role in axonal stability.[79] The pathogenicity of T cell response was demonstrated by the adoptive transfer of S100 beta-specific T cells which induced an inflammatory response in the CNS and eye of naive syngeneic recipients.[80] Indeed, the adoptive transfer of autoreactive S100 beta-specific T cells induces the autoimmune panencephalomyelitis and uveoretinitis in the Lewis rat, mimicking the distribution of lesions seen in a subset of patients with MS.[81] Moreover, it induces an intense inflammation not only in the spinal cord, but throughout the entire CNS and also in the uvea and retina of the eye.[82] According to some assessments, there was a significant trend for increasing S100B levels from primary progressive to secondary progressive to relapsing remitting MS so that, the S100-B was significantly higher in relapsing remitting MS than in control patients (p=0.01).[83]

Aquaporin-4 (AQP4)

AQP4 is the first specific molecule which has been defined as a target for the autoimmune response in any form of MS. It is also the first example of a water channel being the target of any autoimmune disorder. This molecule is concentrated in membranes in the precise site where spinal cord inflammation is found in Neuromyelitis Optica (NMO) patients.[84] The AQP4 water channel, a part of the dystroglycan protein complex is located in astrocytic foot processes at the BBB.[85] In addition, AQP4 autoimmunity is a distinctive recurrent and widespread inflammatory CNS disease in children.[86] NMO is an inflammatory demyelinating disease that selectively affects optic nerves and spinal cord. It is seen in the severe variant of MS, and frequently is misdiagnosed as MS, but prognosis and optimal treatments differs. NMO may be the first example of a new class of autoimmune channelopathies.[87] In NMO, disease attacks preferentially involve the optic nerves and spinal cord (hence the name), but neurological signs in the initial attack of AQP4 autoimmunity in children commonly involves the brain, while the pathogenetic role of the AQP4 in NMO remains yet unknown.[88,89]

Anti-AQP4

In the past, NMO affected only the optic nerves and spinal cord. However, the discovery of highly specific anti-AQP4 antibody for NMO enabled us to identify more diverse clinical manifestations.[90] NMO-IgG is a disease-specific autoantibody for NMO and its target antigen is AQP4 waterchannel.[91] Preliminary experiments demonstrate that NMO-IgG can modulate AQP4 function and fix complement, characteristics that suggest it has the potential to be pathogenic in NMO.[92]

Patients with anti-AQP4 have the distinct clinical presentation of NMO and these patients often harbour other autoimmune responses.[93] In a study for evaluating the anti-AQP4-Ab level in Japanese MS patients, the presence of optic-spinal MS (OSMS) without long spinal cord lesions and anti-AQP4 antibody were reported.[94]

MOG

MOG is localized at the outermost surface of myelin in the CNS and has been the focus of extensive research for more than 30 years. Its role as a significant autoantigen for T cells and as a target of demyelinating autoantibodies has been established in several variants of EAE.[95] MOG is quantitatively a minor component of CNS myelin (less than 0.05% of all CNS myelin proteins) but its localization on the outermost surface of myelin[95-98] makes it accessible for antibodies. The exact function of MOG remains unclear but its structure and localization suggest a role as an adhesion molecule, possibly gluing CNS myelin fibers together.[95,99] Essentially, MOG is able to bind the complement component C1q and might therefore regulate the classical complement pathway.[95,100] A recent study[95,101] showed that MOG might also function

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as a host cell receptor for the rubella virus. To state, it can be involved in CNS autoimmunity in principally two different ways. First, MOG-specific T cells evoke CNS inflammation. Second, anti-MOG antibodies lead to the induction of demyelination. Demyelination is a characteristic feature of MS lesions indicated by the presence of naked demyelinated axons.[95]

Anti-MOG

Antibody against MOG is seen in patients with different disease entities such as childhood MS, acute demyelinating encephalomyelitis (ADEM), anti-AQP4 negative NMO, and optic neuritis, but hardly in adult MS.[102] It has recently become clear that only antibodies recognizing conformation-dependent epitopes of MOG have a demyelinating potential in EAE.[103] Basically, using purified MOG from human brain white matter, anti-MOG antibodies were detected in the CSF of a subset of MS patients and also in the control groups.[95] For example, using native full-length mouse MOG from transfected mammalian cells, anti-MOG antibodies in both MS patients and healthy controls were detected and it was demonstrated that the levels of IgM antibodies were higher in patients with a first demyelinating event, as compared with MS patients with a relapse or healthy controls.[104] Anti-MOG antibodies were isolated by affinity chromatography to MOG coupled agarose and the binding of these antibodies to synthetic MOG peptides was then assessed by ELISA method.[105] IgG from the CNS parenchyma of autopsy samples from MS patients were isolated and their binding to refolded *E. coli* MOG in solid phase and to *in vitro* translated human MOG in solution phase was assessed.[106,107] Antibodies against correctly folded MOG are preferably found in pediatric MS and ADEM patients. In adult MS patients, the anti-MOG antibodies are rarely detected. The reason for this phenomenon is yet uncertain, but the different pathogenesis of these two CNS disorders (ADEM and MS) might play a role.[95,108]

PLP

Myelin PLP is a major protein of mammalian CNS myelin and a member of the PLP gene family (pgf). Also, it is an evolutionarily conserved polytopic integral membrane protein and a potential autoantigen in MS disease.[109] PLP is a component of oligodendritic glial sheaths of neuronal processes that is specifically expressed in the CNS.[110] In the pathogenesis of MS, autoimmune T cells reactive with PLP may play a crucial role, which is linked with HLA-DR2, w15.[111,112] In other words, equal numbers of CD4+ T cells recognizing MBP and PLP are found in the circulation of normal individuals and MS patients.[113] To be more precise, PLP 95-116 and 105-124 specific T cells were more frequently established from DR2 MS than from non-DR2 MS, indicating that the DR2 restricted T cells recognizing these determinants are involved in MS pathogenesis.[114] By a new assay, it was decided to be investigated the mechanism by which heterogeneous nuclear ribonucleoprotein (hnRNP) H and F regulate PLP/DM20 alternative splicing and reduced expression of hnRNPH/F in differentiated oligodendrocytes.[115] A highly selective polyclonal antibody was developed directed against an epitope present in the full-length PLP protein, but absent from the developmentally regulated splice variant DM-20.[110] Furthermore, widespread anti-PLP mAb recognition of neurons suggests a novel potential pathophysiologic mechanism in MS patients, so that anti-PLP antibodies associated with demyelination might simultaneously recognize pgf epitopes in neurons, which thereby affecting their functions.[116]

MBP

MBP is a suspected target autoantigen since it induces EAE.[117] It has been studied as a potential autoantigen in inducing disease because of its role as a post-viral encephalomyelitis and also due to its presence in the blood of MS patients following *in vivo*-activated T cells reactive to MBP.[118] T cell clones that react with MBP can be isolated from the peripheral blood of MS patients using the hypoxanthine guanine phosphoribosyltransferase (hprt) clonal assay.[119] In addition, results of an assay showed that (1) in MS patients both the DR2a and DR2b products of the DR2Dw2 haplotype function as restriction elements for the myelin autoantigen hMBP, (2) the DR2a molecule presents at least five different epitopes to hMBP-specific T lymphocytes, and (3) anti-hMBP T-cell lines derived from individual donors can differ in their antigen fine specificity and in their HLA restriction.[120] Fundamentally, it has been recently documented that the antigen-based therapies are mainly aimed at tolerizing T-cell responses against MBP and have shown only modest or no clinical benefit so far.[102]

Anti-MBP

To date, it is reported that there are at least two immunologically distinct forms of MS, i.e., a common form highly associated with anti-MBP and more frequent prominent inflammatory characteristics in CSF and CNS, and an infrequent form associated with anti-PLP in CSF and CNS tissue with less abundant inflammation.[121]

These autoantibodies were specifically bound to disintegrating myelin around axons in the lesions of acute MS and the marmoset model of allergic encephalomyelitis.[122] In other words, specific myelin protein autoantibodies intervene target membrane damage in demyelinating disease of CNS. Frequencies and titres of the serum anti-MOG-Ig in later MS stages are comparable with early MS. In contrast, the frequency of anti-MBP antibodies is low in MS-R0 (12%) whereas, it increases during disease progression in relapsing–remitting (32%) and chronic progressive MS(40%), suggesting that anti-MBP responses accumulate over time.[123]

The various assessments have shown that autoantigens and autoantibodies have a basic role in immunopathogenesis of MS. Based on recent data, the localized autoantibodies against demyelinated axons and oligodendrocytes and also existing antibody-antigen immune complexes,[9] could be regarded further evidence on the role of antibodies and complement in plaque development, suggesting that they can induce axonal injury, an important cause of disability in MS. Therefore we can focus on them as therapeutic targets to limit tissue degeneration in the disease. Furthermore, the assessment of antibody levels against detected autoantigens could be used as surrogate markers for the confirmation of MS diagnosis.[10] Until now, an appropriate study has not been done about the role of autoantigens and autoantibodies in pathogenesis and diagnosis of MS. We think that by collecting data from autoantigens and autoantibodies, it can be decided which one of them have more effective role in treatment of MS. Collectively, we recommend that the use of antibody against autoantigens might be a new interesting approach for MS diagnosis.

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