

Mini Review

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Relevance of Catalytic Autoantibodies to Myelin Basic Protein (MBP) in Autoimmune Disorders

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Abstract

Catalytic autoantibodies with proteinase enzymatic activity against myelin basic protein (MBP) are a distinctive feature of several autoimmune disorders. These autoantibodies, named abzymes (Abz), have both antibody and proteinase activity in a single molecule. Abz targeting MBP (MBP Abz) are commonly found in sera from multiple sclerosis (MS) and systemic lupus erythematosus (SLE) patients, and only recently have been identified in sera from autism spectrum disorder (ASD) patients. Their activities and specificity are similar in MS and SLE; however, although they recognize the same substrate, MBP, the catalytic activity of the Abz from autism spectrum disorder patients is controlled by different proteinase inhibitors. MBP Abz are generated as part of a process started by loss of compaction of myelin due to changes in charge after deamination of arginyl residues in MBP by the enzyme peptidylarginine deiminase. This exposes a normally hidden surface of MBP to T-cells initiating the autoimmune response. A large body of evidence suggests that MBP Abz play an important role in the pathogenesis not only of MS and SLE, but also of ASD. Many autoantibodies found in MS and SLE are also observed in healthy individuals at ranges usually considered pathological; however, clinical signs of the disease are not manifested, suggesting that expression of single autoantibodies may be inconsequential to develop the disease. However, it is the expression of hundreds of different autoantibodies, in addition to MBP Abz, that collectively lead to the clinical development of MS and SLE.

Introduction

Antigen-specific catalytic autoantibodies have been identified in several autoimmune diseases and their repertoire includes antibodies whose antigen binding sites may recognize external as well as autologous antigens and may structurally resemble the active site of enzymes displaying enzymatic activity¹. Under normal physiological conditions, B cell clones that produce antibodies with catalytic activity are negatively regulated; however, their expression is enhanced following active immunization, or if the regulatory mechanisms controlling the catalytic antibody-producing B cell clones are perturbed, as is the case during the course of autoimmune diseases². Catalytic autoantibodies or Abz possess both antibody and enzymatic activity in a single molecule and they are an important pathogenic factor in the progression of clinical autoimmune disorders³. One specific antigen, MBP, a component of the myelin sheath of neurons in the peripheral nervous system and central nervous system (CNS)⁴, is a target of Abz in several autoimmune disorders including MS⁵, SLE^{6,7} and ASD⁸.

The degradation of MBP is a central feature of MS⁹. MBP, is usually compacted within the myelin sheath; however, in patients with immune disorders, MBP becomes accessible to catalysis by peptidyl arginine deiminase, which converts arginine residues into citrulline, decreasing

both its charge and compact structure¹⁰. The loss of compaction facilitates access to the protein and proteolytic generation of immunodominant MBP peptides which sensitize T-cells for the autoimmune response to MBP^{11,12}. Autoantibodies against MBP are also found in sera from patients with Alzheimer's disease (AD)¹³ and patients with advanced stages of rheumatoid arthritis (RA)¹⁴; however, MBP Abz catalytic activity in sera from AD and RA patients has not been reported. Therefore, we will focus this mini review mainly on the pathogenic and clinical relevance of MBP Abz in MS, SLE and ASD.

Catalytic Autoantibodies to MBP in Multiple Sclerosis

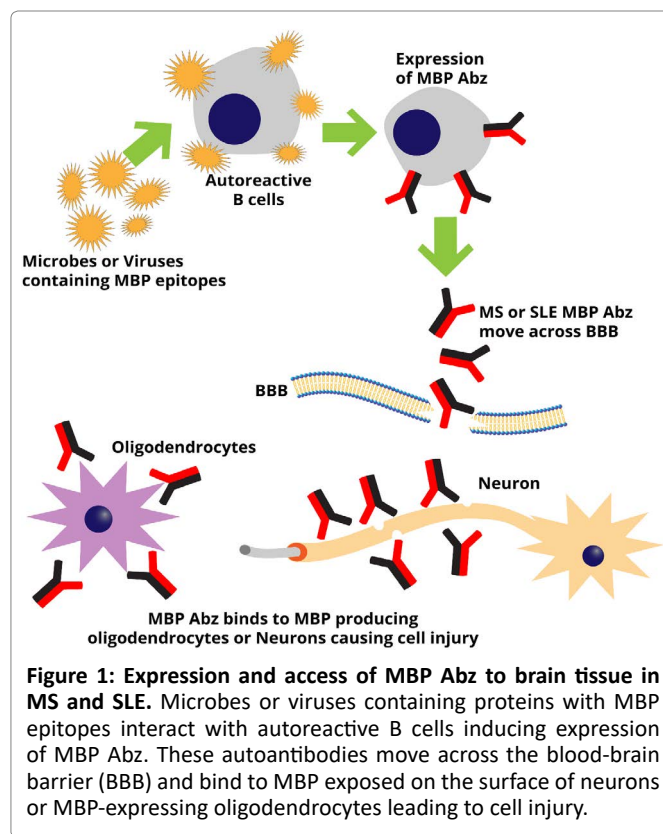
MS is a chronic disease of the CNS characterized by loss of motor and sensory function, that result from immune-mediated inflammation, demyelination and subsequent axonal damage¹⁵. It is widely accepted that the inflammatory process in MS is caused by an autoimmune cascade, involving T-cells which target myelin self-antigens¹⁶, via a mechanism possibly involving molecular mimicry between cross-reactive antigens expressed by viruses and myelin components¹⁷. MBP Abz of the IgA, IgG and IgM classes are found in sera from MS patients^{18,19} and their catalytic activities correlate with the levels of disability observed in these patients²⁰. The MS Abz cleave MBP at six preferential sites¹⁶, all of them located at the immediately COOH-terminal sides from basic amino acids, arginine and lysine, and positioned in the immunodominant MBP region Gln81-Gly103²¹. The mechanism of the MS MBP Abz catalysis is similar to that of serine proteinases; however, its activity is not inhibited by the serine proteinase inhibitor aprotinin, suggesting that this lack of inhibition makes the antibody-mediated catalysis an important factor in the neurodegeneration observed in MS²². For these reasons, MBP Abz found in MS are biomarkers of disease progression.

Catalytic Autoantibodies to MBP in Systemic Lupus Erythematosus

SLE is a systemic autoimmune disease characterized by disorganization of conjunctive tissues resulting from damage to skin and visceral capillaries and the presence of a wide variety of autoantibodies²³. The clinical and serological heterogeneity of SLE makes it difficult to diagnose at the very early stage, when an inadequate number of symptoms are present²⁴. The most widely used classification criteria for SLE are those proposed by the American College of Rheumatology, published in 1971 and revised in 1997²⁵ (for an updated review see ref. 23).

SLE and MS share many of the clinical, biochemical and immunological features including the presence of MBP Abz. These SLE MBP Abz, mainly of the IgG class, show a high specificity for MBP alone⁶, and hydrolyze this protein at the same four immunodominant sites recognized by MS MBP

Abz⁷. The immune systems of SLE patients can generate a variety of MBP Abz with different catalytic properties, which can attack MBP of myelin-proteolipid shell of axons⁷. MBP Abz are part of the intrinsic immune response observed in SLE²⁶, and they play an important role in the diagnostic index of MS²⁰; however, their pathogenic role in SLE remains inconclusive⁷. In addition to MBP Abz, SLE is associated with more than 100 different autoantibodies²⁷. Many of these autoantibodies have been found in asymptomatic individuals²⁸, suggesting that their presence is not pathological per se, and raises the possibility that autoreactivity is an important feature of a normal immune response²⁹. The presence of autoreactivity in the B-cell population of healthy individuals is normally present and can be stimulated in vitro to produce pathogenic autoantibodies such as those found in SLE, suggesting that expression of autoantibodies by autoreactive B cells is an early step towards disease development³⁰. Several factors that trigger expression of autoantibodies have been suggested including oestrogens, pesticides, bacterial superantigens, and viral³¹. In this context, the immune response to the MBP peptide Gln81-Gly103 is major target of both T and cell responses to MBP, a region with structural similarities in sequences found in peptides of several viruses including human papillomavirus^{7,13,40}, cytomegalovirus, herpes simplex, Epstein-Barr virus, influenza A, hepatitis A and human adenovirus³². We constructed a model (Figure 1) showing a hypothetical exposure of autoreactive B cells to agents containing antigens with structural homology to the MBP



peptide Gln81-Gly103. This interaction stimulates expression of specific MBP Abz which move across the blood-brain barrier (BBB) and infiltrate the protective myelin sheath of brain neurons, leading to tissue injury. As observed in MS³³, such mechanism may also function in SLE.

Catalytic Autoantibodies to MBP in Autism Spectrum Disorders

ASD are a heterogeneous group of neurodevelopmental conditions characterized by unusual repetitive behaviors and impaired social and communication skills³⁴. Although the etiology of ASD is complex, increasing evidence suggests that immune dysfunctions and the presence of autoantibodies to brain proteins are associated with behaviors observed in ASD³⁵, as reflected by the high correlation between the titers of serum antibodies against brain proteins and the severity of the ASD³⁶. Autoantibodies from individuals with ASD react with a wide variety of proteins in different regions of the brain³⁷, and one of these autoantibodies targets MBP³⁸. ASD patients show IgA and IgG class autoantibodies to MBP, but not of the IgM class⁸. An evaluation of their specificity revealed that the IgA autoantibodies against MBP exhibit the catalytic activity of a serine proteinase and are able to hydrolyze MBP *in vitro*⁸. Unlike the MBP Abz found in MS, the ASD MBP Abz activity is inhibited by the serine proteinase inhibitor aprotinin⁸. The ASD MBP Abz of the IgA class induces a decrease in long-term potentiation (LTP) in models of brain synaptic plasticity in isolated rat hippocampal slices perfused *in vitro* with the antibody or in an *in vivo* model of hippocampal slices from rats injected with the ASD IgA for 10 days⁸. A hypothetical model (Figure 2) depicts how ASD MBP Abz move across the BBB and reach the brain causing

synaptic dysfunctions which cause the decrease in synaptic plasticity (lower LTP) observed in the rat animal model⁸. Table 1 shows a summary of the biochemical properties of MBP Abz in MS, SLE and ASD.

Conclusions

MBP Abz able to hydrolyze MBP have been found in MS, SLE and ASD. These Abz have been extensively studied in both MS and SLE; however, their presence in ASD have been identified only recently. The experimental data from MS and SLE permits the inclusion of them as important players in the pathogenesis of these two disorders. Many autoantibodies found in MS and SLE are also observed in healthy individuals at ranges usually considered pathological; however, their toxicity was not manifested, suggesting that expression of single autoantibodies may be inconsequential to develop the disease. However, there are hundreds of antigens affected by the immune response in these diseases, which in addition to MBP Abz, may collectively affect the clinical development of MS and SLE. Future studies should help to strengthen the understanding of the mechanisms involving MBP Abz in the pathogenesis of MS, SLE and ASD and improve the efficacy of new therapeutic strategies.

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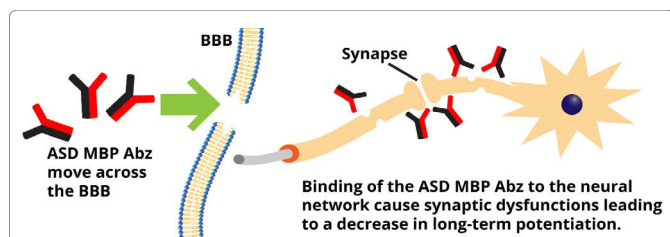


Figure 2: Access of MBP Abz to brain tissue in ASD. MBP Abz produced in the central nervous system move across the blood-brain barrier (BBB), reach brain tissues and bind to neurons. This interaction causes synaptic dysfunctions that affect synaptic plasticity inducing a decrease in long-term potentiation (LTP).

Table 1: Biochemical properties of catalytic autoantibodies to MBP in autoimmune diseases

Function	MS	SLE	ASD
Autoantibodies of the IgA, IgG and IgM class	+++ ^{18, 19}	+++ ⁶	+++ ⁸
Recognition of the MBP region N ⁸¹ -G ¹⁰³	+++ ²¹	+++ ⁷	N.D.
Cleavage of MBP	+++ ^{16, 21}	+++ ⁷	+++ ⁸
Correlation of titers with disability levels	+++ ²⁰	N.D.	N.D.

N.D. non-determined

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