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Review

# Peripheral blood biomarkers in multiple sclerosis

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ABSTRACT

Multiple sclerosis is the most common autoimmune disorder affecting the central nervous system. The heterogeneity of pathophysiological processes in MS contributes to the highly variable course of the disease and unpredictable response to therapies. The major focus of the research on MS is the identification of biomarkers in biological fluids, such as cerebrospinal fluid or blood, to guide patient management reliably. Because of the difficulties in obtaining spinal fluid samples and the necessity for lumbar puncture to make a diagnosis has reduced, the research of blood-based biomarkers may provide increasingly important tools for clinical practice. However, currently there are no clearly established MS blood-based biomarkers. The availability of reliable biomarkers could radically alter the management of MS at critical phases of the disease spectrum, allowing for intervention strategies that may prevent evolution to long-term neurological disability. This article provides an overview of this research field and focuses on recent advances in blood-based biomarker research.



**Contents**



## 1. Introduction

Multiple sclerosis (MS) is an immune-mediated, inflammatory demyelinating and neurodegenerative disease of the central nervous system (CNS). MS has a heterogeneous clinical presentation and course, reflecting complexity in its pathophysiology, and is classified into three main types of clinical courses: relapsing–remitting (RRMS), primary progressive (PPMS), and secondary progressive (SPMS) [1]. In most cases, RRMS turns at one point into a SPMS form, characterized by the irreversibility of the deficits due to progressive neurodegeneration. Meanwhile, PPMS is characterized by a gradual progression of disability from the onset of the disease [1]. Although the etiology of MS is

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unknown, evidence suggests that the disease may result from a complex interaction between the environmental factors, the genetic background that defines individual susceptibility, and the immunological and physiological settings of the individual [2]. The pathological hallmarks of MS are inflammation, demyelination, remyelination, neurodegeneration and glial scar formation, which occur either focally or diffusely throughout the white and grey matter in the brain and spinal cord [3]. These pathological features are present in both RRMS and SPMS, as well as in PPMS, although they vary over time both quantitatively and qualitatively between these three forms of MS and among individuals with the same form of the disease, thus contributing to the heterogeneity in phenotypic expression of the disease and response to therapies [4,5]. As supported by experimental evidence, mainly derived from its principal model experimental allergic encephalomyelitis (EAE), MS is generally considered a predominantly T cell-mediated autoimmune disease. Indeed, inflammatory lymphocytes transmigrate into the CNS and initiate tissue damage and neurological impairment [6]. Even though myelin specific Th1 and Th17 $CD4^+$ T cells are involved in the disease, also other cell types like $CD8^+$ T cells, B cells, macrophages and natural killer (NK) cells contribute to the pathogenesis of MS [7–9]. It is likely that inflammatory responses are the key mediators of early disease in most cases and, over time, there is incremental neurodegeneration correlating with progressive disability. However, current evidence indicates that in all forms and stages of the disease, inflammation seems to drive demyelination and neurodegeneration, and in the progressive stage, in contrast to early stage with BBB compromise, inflammation is partially trapped within the CNS behind the BBB, which makes the current anti-inflammatory treatment to become ineffective [4]. Along these lines, mechanisms of the pathophysiology of MS involve mainly three physiological compartments: 1) the peripheral blood, in which immune processes mainly take place; 2) the blood brain barrier (BBB), which breaks down to a point so that immune cells can pass into the CNS; and 3) the CNS, in which lesions mark acute sites of inflammation and neural damage, leading to the phenotypic displayed symptoms of disability. In each of these compartments, changes in gene expression of a certain set of proteins and cell types are characteristic hallmarks of MS. The clinical disability of MS patients is evaluated using the Expanded Disability Status Scale (EDSS) [10], while the disease activity is evaluated using magnetic resonance imaging (MRI) with gadolinium (Gd)-enhancing lesions, providing the most objective and sensitive tool for assessing the progression and activity of the disease in MS patients.

## 2. MS biomarkers

Biomarkers are measurable indicators of normal biological and pathogenic processes, or pharmacological responses to a therapeutic intervention. A good biomarker should be precise and reliable, able to distinguish between MS disease and control, can detect inflammatory activity, as well as the degree of neurodegeneration and demyelination/remyelination, in order to get a more accurate picture of the disease status [11]. Since for many years intensive efforts have been directed toward the identification of biomarkers in body fluids (CSF or blood) associated with various aspects of MS on different levels of the organizational hierarchy of the human body (e.g. DNA, RNA, proteins, cells) [12], the application of more advanced screening technologies has opened up new categories of biomarkers, including gene expression and autoantibody arrays, microRNAs (miRNAs), and circulating microvesicles (MVs). However, despite the large sum of studies provided in a long list of candidate biomarkers, most of them have not been validated, and therefore they are not clinically useful at present. Moreover, the lack of validation is a common problem with biomarkers of complex diseases such as MS, reflecting a bias in statistical analysis or a lack of available data, but it may also indicate difficulties in performing clinical validation studies [13].

## 3. Peripheral blood versus CSF biomarkers

In MS, most studies search for biomarkers within the CSF with the view that this is more likely to reflect CNS disease. However, blood-based biomarkers are of great clinical value, because of the ease with which blood can be obtained in a minimally invasive manner. Blood biomarkers may exist in MS if there is a systemic component of the disease, or if peripheral changes mimic central disease [14]. The biologic events associated with a focal active inflammatory cerebral lesion may not be readily detectable in the peripheral blood. Furthermore, immune abnormalities in the peripheral blood in MS patients may also lack specificity because they may be altered by systemic events, such as viral infections. Despite these limitations, peripheral blood biomarkers can give important information regarding immune triggers of MS, as well as therapeutic efficacy of drugs administered [15]. Additionally, blood has two properties that make it attractive for the search for biomarkers: 1) it is more easily accessible than other body tissues; and 2) the perfusion of blood through different organs and tissues can result in the addition of new proteins, or modification of existing proteins, which may vary according to specific physiological or pathological conditions [16]. Thus, the blood can carry molecules derived from other tissues, reflecting the biological status of the body [17]. Peripheral biomarkers in MS can be categorized into five groups: diagnostic, associated with the conversion to clinically definite MS (CDMS), disease activity, progression and treatment-response (Table 1).

## 4. Diagnostic biomarkers

Diagnostic biomarkers can be used to distinguish patients who have MS from patients with other neurological or autoimmune disorders, or from healthy individuals. Indeed, white-matter lesions typical of MS can be seen in many other neuroinflammatory conditions, such as neurosarcoidosis, neuroborreliosis, Sjögren Syndrome, and systemic lupus erythematosus. For this reason, a set of diagnostic criteria (the revised McDonald's criteria [18,19]) that incorporates clinical, radiologic, and laboratory findings is used to establish a definitive diagnosis of MS. The only validated biomarker for MS diagnosis in clinical practice is the detection of oligoclonal IgG bands (OCGB) in the CSF. Thus, MRI of the brain and spine together with OCGB formation in CSF reflects the inflammatory and demyelinating nature of the disease and is an important tool in the diagnosis of MS [18,20]. Autoantibodies have been documented to be valuable diagnostic biomarkers for several autoimmune diseases. Furthermore, serum antibodies against specific antigens have been established also in several neuro-immunological diseases, such as myasthenia (antibodies against acetylcholine receptor) and paraneoplastic disorders (e.g. anti-Hu, anti-Yo) [21,22]. The importance of autoantibodies as diagnostic biomarkers has been emphasized following the discovery of a serum pathogenic specific antibody targeting the principal water channel of astrocyte aquaporin-4 (termed NMO-IgG or AQP4-Ab), distinguishing neuromyelitis optica (NMO), also known as Devic's disease, from MS [23,24]. Initially, many studies investigated the autoantibodies targeting myelin proteins as biomarkers of the disease, well established in EAE, where anti-myelin antibodies induce CNS demyelination [25]. However, the detection of serum antibodies to myelin basic protein (MBP), myelin-associated glycoprotein, and proteolipid protein has resulted in conflicting data, which in all cases lacked specificity, sensitivity, and reproducibility [26–28]. Among these myelin autoantigens, myelin oligodendrocyte glycoprotein (MOG) has emerged as a promising autoantigen, especially in autoimmune pediatric demyelination in both acute disseminated encephalomyelitis and MS [29]. Meanwhile, the role of MOG antibodies in adult MS patients is still speculative, thus more research is needed to clarify if MOG antibodies can be used for prognosis or classification of