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Review

# B cells and antibodies in progressive multiple sclerosis: Contribution to neurodegeneration and progression☆

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ABSTRACT

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS) characterized by demyelination, axonal degeneration and gliosis. The progressive form of MS is an important research topic as not much is known about its underlying mechanisms and no therapy is available. Although progressive MS is traditionally considered to be driven by neurodegeneration, compartmentalized CNS inflammation is currently accepted as one of the driving processes behind neurodegeneration and progression. In this review, the involvement of B cells and antibodies in progressive MS is discussed. The identification of meningeal ectopic B cell follicles in secondary progressive MS (SPMS) patients and the successful use of B cell-depleting therapy in primary progressive MS (PPMS) patients have underlined the importance of B cells in progressive MS. Proof is also available for the role of antibodies in neurodegeneration and progression in MS. Here, oligoclonal immunoglobulin M (IgM) production and autoreactive antibodies are described, with a focus on antibodies directed against sperm-associated antigen 16 (SPAG16). Further research into the role of B cells and autoantibodies in MS progression can lead to novel prognostic and theranostic opportunities.



**Contents**



## 1. Introduction

Multiple sclerosis (MS) is a debilitating disease in which chronic inflammation occurs in the central nervous system (CNS), leading to myelin loss, axonal pathology and neurodegeneration [1]. Progressive MS remains one of the greatest challenges in the MS field, which has led to the foundation of the International Progressive MS Alliance, dedicated to accelerating the development of treatment for progressive MS. Gradual disability progression is a major characteristic of progressive MS that occurs from the start of the disease in primary progressive MS (PPMS) or following a disease course with alternating periods of relapse and remission (relapsing–remitting MS, RRMS) in secondary progressive MS (SPMS). Both SPMS and PPMS can be designated as active or not active depending on the occurrence of clinical relapses and/or activity on magnetic resonance imaging (MRI), defined by the presence of

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contrast-enhancing lesions or new and enlarging T2 lesions [2]. At the pathological level, gray and white matter atrophy, axonal loss, cortical demyelination and changes in the normal-appearing white matter (NAWM) contribute to neurodegeneration [3].

B cells are important contributors to the chronic inflammatory processes in MS pathogenesis. Oligoclonal immunoglobulin bands (OCB) are found in the cerebrospinal fluid (CSF) of more than 90% of MS patients, pointing to an intrathecal antibody production [4]. Various autoantigens have been suggested as targets of these autoantibodies, although specificity and pathologic potential remain controversial [5,6]. Clonal B cell proliferation has been noted both in the CNS and in the periphery [7,8]. B cells are further implicated in MS pathology by stimulation of pro-inflammatory T cell responses and the production of pro-inflammatory cytokines, including lymphotoxin (LT), tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6) [9].

As most current immunomodulatory therapies for RRMS did not meet endpoints in trials of progressive MS, neurodegeneration instead of inflammation has traditionally been considered as the main driver of progression in MS. However, evidence is now available for the involvement of inflammation in progressive MS. The absence of blood–brain barrier (BBB) leakage in cases of perivascular inflammation in progressive MS has suggested the entrapment of CNS inflammation behind the BBB [10]. Post-mortem brain tissue from different MS subtypes further showed pronounced inflammation in SPMS and PPMS with a positive association between inflammation and axonal injury [11]. In addition, comparable numbers of activated intrathecal B cells and T cells were indicated in progressive MS (SPMS and PPMS) and RRMS patients [12]. In this review, the involvement of B cells and antibodies in inflammation in progressive MS (both SPMS and PPMS) is discussed in more detail (Fig. 1). SPMS and PPMS are discussed together, as it was suggested that both MS subtypes do not have pathophysiologically distinct features [2].

## 2. B cells in neurodegeneration and progressive MS

A first indication for B cell involvement in progressive MS came from the identification of ectopic B cell follicles in the meninges of SPMS patients [13,14]. This local B cell proliferation pointed to the sustainment of inflammation in progressive disease. Ectopic B cell follicles were associated with early disease onset, cortical demyelination, microglia activation, loss of neurites and irreversible disability [15]. Further, cortical lesions with B cell rich infiltrates were described, while high B cell to monocyte CSF ratios were associated with more rapid disease progression in SPMS patients [16,17].

Interestingly, a recent phase III clinical trial of the B cell depleting anti-CD20 monoclonal antibody (mAb) ocrelizumab (ORATORIO) in PPMS met both primary (confirmed disability progression after 12 weeks of treatment) and secondary (confirmed disability progression after 24 weeks of treatment, timed walk, T2 lesion volume and total brain volume) endpoints [18]. As ocrelizumab demonstrated clinical effectiveness, the importance of B cells in inflammation in PPMS has become evident. Moreover, intrathecal rituximab administration in a single SPMS patient led to reduced inflammation and neurodegeneration as indicated by reductions in inflammatory markers such as tumor necrosis factor (TNF), interleukin-2 (IL-2) and neurofilament light [19].

More descriptive evidence for the role of B cells in neurodegeneration and progression has come from observation studies. While plasmablasts, DC-SIGN$^+$ B cells and CD83$^+$ B cells were all increased in the peripheral blood of SPMS patients, DC-SIGN$^+$ B cells correlated with disease progression [20]. Thus, activated B cells (DC-SIGN$^+$) and B-T cell interactions (CD83) are involved in SPMS. Further, MS patients with high neurodegeneration showed an increased B cell activation status (elevated CD80 and CD86 expression) compared to MS patients with low neurodegeneration [21].

## 3. Antibodies in neurodegeneration and progressive MS

The occurrence of autoantibodies has been associated with progression and axonal loss in progressive MS. We describe oligoclonal IgM production and autoreactive antibodies, with a focus on anti-SPAG16 antibodies.

### 3.1. Intrathecal oligoclonal IgM antibodies

The finding of oligoclonal IgM bands (OCMB) in the CSF is an unfavorable prognostic marker in MS [22]. These intrathecal IgM antibodies are mostly directed against myelin lipids, preferentially phosphatidylcholine. Patients with lipid-specific OCMB (LS-OCMB) suffered from more aggressive disease with higher relapse rate and increased

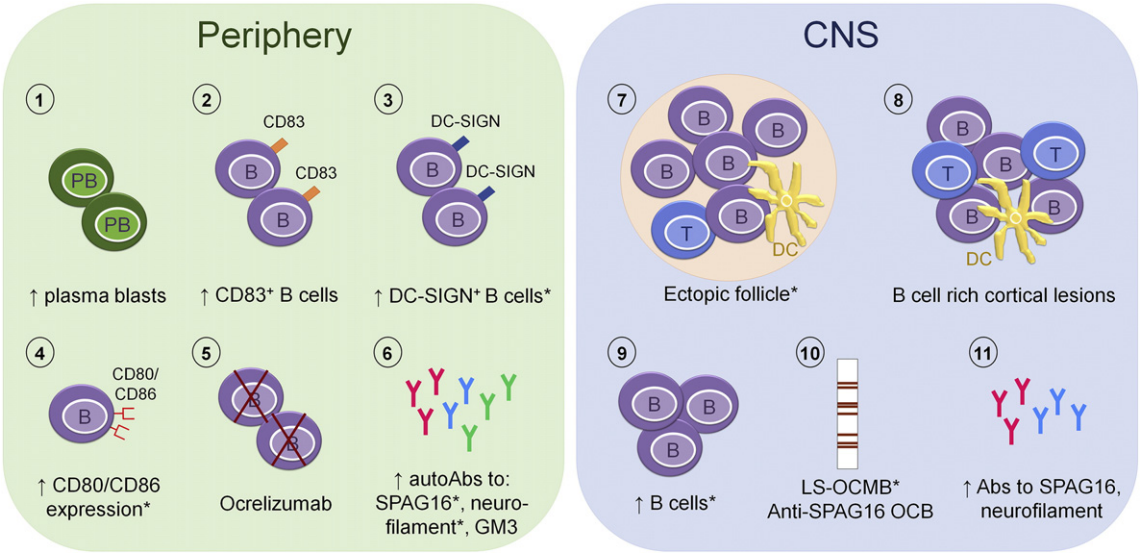


**Fig. 1.** Current proof for the involvement of B cells and antibodies in neurodegeneration and progression. In the peripheral blood of SPMS patients, increased numbers of plasma blasts (1), CD83$^+$ B cells (2) and activated DC-SIGN$^+$ B cells (3) were present. Elevated B cell CD80/CD86 expression was shown in MS with high neurodegeneration (4). Positive clinical results were obtained using ocrelizumab (5) and increased serum/plasma autoantibodies were found (6). In the CNS, ectopic follicles (7) and B cell-rich cortical lesions (8) were identified. Progressive MS CSF demonstrated increased B cell numbers (9), LS-OCMB and anti-SPAG16 OCB (10) together with increased autoantibodies (11). * indicates an association with neurodegeneration or progression. PB, plasma blast; B, B cell; Abs, antibodies; T, T cell; DC, dendritic cell; LS-OCMB, lipid-specific oligoclonal IgM bands.