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Review

B Cells and Autoantibodies in Multiple Sclerosis

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Abstract: While over the past decades T cells have been considered key players in the pathogenesis of multiple sclerosis (MS), it has only recently become evident that B cells have a major contributing role. Our understanding of the role of B cells has evolved substantially following the clinical success of B cell-targeting therapies and increasing experimental evidence for significant B cell involvement. Rather than mere antibody-producing cells, it is becoming clear that they are team players with the capacity to prime and regulate T cells, and function both as pro- and anti-inflammatory mediators. However, despite tremendous efforts, the target antigen(s) of B cells in MS have yet to be identified. The first part of this review summarizes the clinical evidence and results from animal studies pointing to the relevance of B cells in the pathogenesis of MS. The second part gives an overview of the currently known potential autoantigen targets. The third part recapitulates and critically appraises the currently available B cell-directed therapies.

Keywords: multiple sclerosis; neuromyelitis optica; B cells; autoantibodies; autoantigen; pathogenesis; therapy

1. Introduction

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS). Both experimental and clinical evidence suggest that it is initiated by autoreactive immune cells directed

against components of the CNS, be it the oligodendrocytes, the astrocytes, or the neurons [1]. The pathologic hallmarks are demyelination, gliosis, and axonal loss, the latter of which is thought to contribute most to sustained disability [2]. Despite numerous experimental, genetic, and epidemiological studies, the trigger mechanisms of this autoimmune disorder remain elusive. MS is thought to be caused by a complex interplay of genetic and environmental factors (infections, Vitamin D, gut microbiome, and others) [1,3–6]. One of the potential and most controversially discussed infectious triggers is Epstein-Barr virus infection, which might lead to cross-reactive antibodies targeting CNS autoantigens [7,8]. Having been considered for a long time as a T cell-dominated disease, based on the T cell-driven animal model of experimental autoimmune encephalomyelitis (EAE), B cells have moved into focus over the recent years, inspired by the success of B cell-directed therapies [1,9,10] and emerging experimental evidence of direct B cell involvement extending far beyond their role as mere antibody-producing cells [2,11]. This review summarizes the clinical evidence and results from animal studies pointing to the relevance of B cells in the pathogenesis of MS. It also gives a detailed overview of the currently known potential autoantigen targets. This knowledge provides the basis to understand the rationale behind B cell-directed therapies that are discussed in the third part.

2. The Many Faces of B Cells in MS—Beyond Antibody Production

2.1. Clinical Evidence for B Cell Involvement in MS

Various findings in patients with MS suggest the involvement of B cells in the pathogenesis, including: the presence of oligoclonal bands (OCBs), clonal expansion of B cells in the cerebrospinal fluid (CSF), antigen-dependent affinity maturation of antibodies, immunoglobulin (Ig) and complement deposition in lesions, the presence of B cell follicle-like structures, and a B cell-fostering milieu.

2.1.1. Oligoclonal Bands (OCBs), Clonal Expansion, and Antigen-Driven Affinity Maturation of B Cells

OCBs are one of the few biomarkers used in clinical practice to establish the diagnosis of MS [1,3–6,12]. OCBs are clonally expanded antibodies that are produced intrathecally and are not found in serum [13]. The presence of OCBs is very stable over time, albeit with substantial modulation by a few immunomodulatory treatments [14,15]. To date, several attempts have failed to identify the target antigens of the OCBs [16]. Comparison of the OCB proteome with the transcriptome of B cells in the CSF revealed that rearranged Ig sequences in most B cells in the CSF are represented by peptides found in the OCBs, allowing the conclusion that, indeed, clonally expanded B cells in the CSF contribute to the production of the OCBs [17]. Moreover, the transcriptome of B cells in the CSF overlaps with those in MS lesions, indicating a functional relationship between B cells in the CSF and brain parenchyma [18]. Even more interestingly, molecular analysis of B cells in the CSF and MS lesions revealed not only clonal expansion, but also somatic hypermutation, pointing toward antigen-driven stimulation [19–21]. Several recent studies have shown that in addition to intrathecal clonal expansion and somatic hypermutation of B cells in the CSF, there is trafficking of clonally related B cells between the peripheral and CNS compartments with antigen-driven maturation both in the periphery (cervical

lymph nodes) and CNS [22–25]. All in all, there is increasing evidence for an active axis between the B cells found in the peripheral blood, lymph nodes, CSF, and MS lesions.

2.1.2. Ig and Complement Deposition in Lesions and B Cell Follicle-Like Structures

The presence of Ig and complement deposition in at least a subtype of acute demyelinating MS lesions (Type II lesion) is a well-recognized phenomenon [26,27], and more recently, B cell follicle-like structures have been described in the meninges of patients with (mainly progressive) MS [28–31]. Furthermore, it has been shown in patients with progressive MS that these extra parenchymal meningeal B cell clones are related to those in the parenchyma and that the immunoglobulin G (IgG) repertoires of the brain lesion also connect to those in the CSF [18,32]. While until now the brain was considered as an "immune privileged organ", it has only been shown very recently that lymphatic vessels are indeed present in the CNS and drain directly into cervical lymph nodes where CSF-derived dendritic cells are mainly clustered in B cell follicles [33,34]. Future research will have to show how MS lesions and B cell follicle-like structures relate to these newly discovered lymphatic vessels.

2.1.3. B Cell Fostering Milieu: The BAFF/APRIL System

There is ample evidence of the presence and clonal relationship of B cells in the brain parenchyma, the meninges, and the CSF, and the chronic persistence of these cells presupposes a B cell fostering milieu. The B cell survival factor tumor necrosis factor (TNF) superfamily 13b (BAFF), the B cell-attracting chemokine (CXCL13), and the Chemokine (C-C motif) ligand 19 (CCL19) have been identified in the CSF and lesions of MS patients and are proposed to be key attractants [35–37]. In a relapsing experimental autoimmune encephalomyelitis (EAE) model, intracerebral expression of BAFF and CXCL13 led to the formation of lymphoid follicle-like structures in the meninges [38]. Increased CXCL13 and CCL19 levels were also linked to intrathecal immunoglobulin production as well as the presence of B cells, plasmablasts, and T cells in MS patients [36,37]. Interestingly, expression of CXCL13 in CSF of MS patients was correlated with future inflammatory disease activity, thereby indirectly linking B cell recruitment and MS disease activity [39].

2.2. Experimental Evidence for B Cell Involvement in MS

A growing body of evidence for B cell involvement in MS from both clinical and human tissue-based studies, and more recently, animal models, is starting to shed light on the diverse functions of B cells, particularly the capacity of B cells to prime and regulate T cell responses in MS.

2.2.1. B Cells as Antigen-Presenting Cells and Pro-Inflammatory Mediators

While the experimental model for MS, *i.e.*, the adoptive transfer of activated encephalitogenic T cells leading to demyelination, promoted the notion that MS is a T cell-mediated disease for a long time, it was recently elegantly shown that the B cell antigen-presenting (APC) function is crucial for the induction of myelin oligodendrocyte glycoprotein (MOG)-induced EAE. This was done by creating mice with a selective deficiency of major histocompatibility complex (MHC)II on B cells (B-MHC II(-/-)) [40]. B cells of these mice could still produce autoantibodies but were not able to stimulate T cells anymore.

This reduced stimulatory capacity led to resistance to EAE induction. Moreover, it was shown that CNS-resident B cells can fuel inflammation, which is mediated by the release of pro-inflammatory cytokines namely TNF, lymphotoxin and interleukin-6 (IL-6), by re-activating infiltrating T cells. This effect is partly alleviated by B cell-depleting therapy [41–43].

2.2.2. Regulatory and Anti-Inflammatory Capacities of B Cells

The involvement of B cells gets even more complex when one considers their capacity to down-regulate immune responses. This regulatory function involves both cell-mediated mechanisms and the secretion of anti-inflammatory cytokines such as IL-10 and IL-35 [43–46]. In mice, regulatory B cells have been phenotyped as immunoglobulin M (IgM)-positive, CD138-high, TNF receptor superfamily 13b-positive, CXC receptor-4-positive, CD1d-intermediate, and hepatitis A virus cellular receptor (T-cell mucin 1)-intermediate (IgM^+, $CD138^{hi}$, $TACI^+$, $CXCR4^+$, $CD1d^{int}$, and $TIM1^{int}$) [45]. Moreover, the generation of regulatory B cells in mice has been shown to depend in particular on the presence of IL-21 and T cell interaction via CD40/CD40L [47].

3. Autoantigen Candidates in MS—The Ongoing Treasure Hunt

3.1. In Vitro and in Vivo Evidence for Autoantibody Involvement in MS

While the cellular effects of B cells have only shifted into focus recently, it has been assumed for a long time that autoantibodies contribute to the pathogenesis of MS. *In vivo*, antibody and complement deposition has been shown to be present in a subset of MS lesions [27] both in chronic disease and early active lesions [48]. In addition, it has been shown that it is only those patients with evidence of antibody deposition in lesions that respond to plasmapheresis [49]. *In vitro*, studying the effect of serum antibodies from MS patients in myelinating cultures revealed induction of demyelination and, more rarely, axonal injury [50].

3.2. Antigen-Screening Approaches

A variety of antigen-screening approaches with antibodies from serum and CSF have been conducted, including immunohistochemical staining of brain sections, western blotting of one- or two-dimensionally separated proteins, immunoprecipitation of brain tissue or cell lysates, peptide and protein microarrays, and phage display and immunofluorescent labeling of transfected cells by flow cytometry [51,52]. Various aspects complicate the quest for the autoantigen target(s): first, it has been shown that not only the native conformation of the protein is crucial for the detection of disease-specific antibodies, but also that the various posttranslational modifications (glycosylation, phosphorylation, citrullination, and others) complicate the autoantigen identification; second, the pathogenic autoantibodies constitute only a minor part of the autoantibody repertoire, which has been experimentally approached by enriching for potential pathogenic autoantibodies from MS lesions or generating monoclonal antibodies from CNS-resident cells [16,53,54]. However, despite the vast effort that has been expended over the last decades in the field, the search for the antigen(s) in multiple sclerosis is still open.

3.3. Potential Autoantigen Targets

3.3.1. Myelin Oligodendrocyte Glycoprotein (MOG) and Aquaporin-4 (AQP4)

The best-studied autoantigen in the field is MOG. MOG is a myelin glycoprotein that is located at the uttermost lamellae of the myelin sheath, making it easily accessible to potential autoantibodies. While the pathogenic role of anti-MOG antibodies in EAE is undisputed, the role of anti-MOG antibodies in MS patients has been controversially discussed over decades [55,56]. This has been fueled by the use of various different assays using recombinant, non-conformational MOG. More recently, with the use of different cell-based assays, anti-MOG antibodies could be identified in a subgroup of pediatric ADEM (acute disseminated encephalomyelitis), CIS (clinically isolated syndrome), or MS [57–69] and were shown to correlate with the disease course [63,70]. Moreover, it was shown that these antibodies are of the complement-activating IgG1 isotype [58,63], were able to exhibit complement-dependent cytotoxicity on MOG-expressing cells [71], and have a functional effect on the oligodendrocyte cytoskeleton [72], suggesting that these antibodies are potentially pathogenic. Analysis of the recognized epitopes revealed that the antibodies are directed against distinct epitopes without intramolecular epitope-spreading during disease course [73]. The fact that the presence of anti-MOG antibodies was negatively related to age [63] tempts one to speculate that the age of disease onset, *i.e.*, an ongoing myelination process in children, influences the autoantigen target.

Even more recently, anti-MOG antibodies have also been identified in a subgroup of AQP4-seronegative pediatric and adult patients with neuromyelitis optica spectrum disorder (NMOSD) presenting with a distinct and more benign clinical phenotype with strong correlation to uni-/bilateral recurrent optic neuritis [68,71,72,74–78]. Transfer of these antibodies to the mouse brain revealed reversible lesions fitting into the clinical picture of a reversible clinical demyelinating syndrome [79]. Future studies are needed to further study the pathogenic relevance of the antibodies and to address the question of whether these MOG-seropositive patients represent a unique disease entity [80].

While the role of anti-MOG antibodies in the pathogenesis of demyelination is still to be determined, the presence and diagnostic significance of AQP4 antibodies in NMOSD is undisputed [81–85]. In animal models, it has been shown that AQP4 antibodies can bind to astrocytes and lead to characteristic pathological features reminiscent of NMO (AQP4 and astrocyte loss, granulocytic infiltrates, T cells and activated macrophages/microglia cells, extensive immunoglobulin and complement deposition on astrocyte processes of the perivascular and superficial glia limitans) [84,86]. In fact, the discovery of AQP4 as a biomarker has marked a breakthrough in the understanding of the pathogenesis of the disease, being identified as the first confirmed autoantigen in a CNS demyelinating disease.

3.3.2. Neurofascin and Contactin-2

The node of Ranvier has more recently received attention as the "Achilles heel" of the CNS [87]. Evidence for the perturbation of the nodal region was motivated by biomarker and pathological studies [88–90]. Two potential autoantigen targets, neurofascin and contactin-2, have been identified by a two-dimensional western blot approach with myelin glycoproteins derived from post-mortem human brain samples [91,92].

Neurofascin (NF) is a glycoprotein expressed both in the central and peripheral nervous systems. It exists in two isoforms: neurofascin 155 (NF155) is a myelin protein localized at the paranodal axo-glial junction, whereas NF186 is a neuronal protein exposed on the surface of myelinated axons at the axonal initial segment and node of Ranvier [93]. The neuronal isoform of neurofascin 186 exposed at the node is crucial for sodium channel clustering, while the glial isoform NF155 at the paranode is necessary for proper paranodal junction formation [94]. Autoantibodies against NF were detected in a subgroup of multiple sclerosis patients and, more recently, also in patients with combined central and peripheral demyelination [95]. *In vivo*, recombinant antibodies to NF were shown to induce axonal injury paralleled by reversible clinical deterioration in an experimental autoimmune encephalomyelitis model [91].

Contactin-2 is expressed both by glial cells and axons at the juxtaparanode. Contactin-2-specific T cells induced inflammatory cuffs in the gray matter of the spinal cord and the cortex in an animal model [92].

Both antigens provide a possible mechanism for axonal and gray matter injury which have been recognized only recently to be contributing to pathology early on during disease in parallel to demyelination [96,97].

3.3.3. Inward-Rectifying Potassium Channel (KIR4.1)

Recently, antibodies against the inward rectifying potassium channel KIR4.1 were reported to be present in 47% of adult patients with MS and CIS and in an even higher proportion of pediatric patients, but in no healthy controls, using an enzyme-linked immunosorbent assay (ELISA) with either full-length KIR4.1 protein or peptide (amino acids 83–120) [98,99]. Subsequent independent studies using peptide ELISAs or a cell-based approach have failed to replicate these findings [100–102]. Future studies using the identical method as originally described need to be conducted to validate or refute the findings [103,104].

3.3.4. Glycolipid-, Sulfatide-Specific, and Other Antibody Targets

In addition to the above-mentioned target antigens, numerous other antigen candidates have been described in MS patients including viral, microbial, and self-antigens [51,105,106]. More recently, there has been increasing evidence for (glycol-)lipid and sulfatide-specific antibodies [107,108].

4. B Cell-Directed Therapies—Towards Personalized Treatment

While substantial evidence for B cell involvement in MS comes from animal studies, the success of B cell-directed therapies illustrates a triumphant example of how translational medicine promotes basic findings into clinical applications, allowing for more diverse and personalized treatment options for MS patients. A variety of currently available treatments such as natalizumab, fingolimod, and alemtuzumab, as well as several anti-CD20 and anti-CD19 therapies currently being tested in clinical trials (anti-CD20: rituximab, ocrelizumab, ofatumumab; anti-CD19: MEDI-551; anti-BAFF-R: VAY736), have a substantial targeting effect on B cells (Table 1).

Although natalizumab exhibits its primary effect on the reduction of T cells in the CNS by blocking their egress into the CNS via alpha 4-integrin blockade, it has also been shown to reduce B cell counts in the CNS of MS patients [109]. In contrast, the effect of fingolimod is most pronounced in the

peripheral blood, leading to a marked decrease of circulating B cells by sequestration in the secondary lymphoid organs, and it also directly alters proportions of B cell subpopulations in treated patients with MS [110]. Alemtuzumab, which has been recently approved for the treatment of active multiple sclerosis, is a monoclonal anti-CD52 antibody with a direct depleting effect on both B and T cells [111,112].

Table 1. Biological drugs targeting B cells or B cell-activating factors.

Biologic	Species & Isotype	Target
Rituximab	chimeric (murine/human) monoclonal IgG1	CD20
Ocrelizumab	humanized monoclonal IgG1	CD20
Ofatumumab	human monoclonal IgG1	CD20
MEDI-551	humanized monoclonal IgG1	CD19
VAY736	human monoclonal IgG1	BAFF-R
Atacicept	recombinant fusion protein TACI-Fc	BAFF/APRIL
Alemtuzumab	humanized monoclonal IgG1	CD52

Rituximab, ocrelizumab, and ofatumumab are different anti-CD20 depleting agents, which are currently in phase II and III trials with promising effects [113–116]. Two monoclonal antibodies targeting CD19 or B cell-activating factor-receptor (BAFF-R) on B cells, MEDI-551 [117] (ClinicalTrials.gov identifier: NCT01585766) and VAY736 (ClinicalTrials.gov identifier: NCT02038049), are currently enrolling patients in phase II trials.

A different approach with the soluble receptor atacicept (TACI-Fc) was based on inhibiting the B cell survival factors BAFF and APRIL (a proliferation-inducing ligand) (TNFSF13), which promote their function by binding to the transmembrane receptor TACI on B cells. Unexpectedly, treatment of MS patients led to disease exacerbation in the atacicept-treated groups [118] and had to be stopped. However, the mechanisms by which atacicept leads to disease exacerbation up to now remain elusive. In contrast to the other mentioned B cell-targeted therapies, atacicept additionally targets plasma cells, which are spared by CD19- and CD20-depleting antibodies, suggesting that protective regulatory plasma cells might have been the reason for the worsening of disease activity. Moreover, expression of BAFF receptor on neurons was described, allowing the speculation that atacicept also limits neuronal survival by decreasing BAFF levels [119]. Also, BAFF was shown to lead to the induction of IL-10-producing regulatory B cells [120], which might have been impaired by atacicept. Very recent studies investigating the function of TACI found that endogenous soluble TACI (sTACI) existed *in vivo*, which shares the decoy function of atacicept, suggesting that atacicept could interfere in the equilibrium between sTACI and BAFF involved in fine-tuning the balance between effector B cells and regulatory B cells [121].

5. Conclusions

During the last years, the understanding of the role of B cells in MS has progressed tremendously. Having been initially considered as antibody-producing cells with a contributing function in the pathogenesis, they are now recognized as main players in conjunction and close interplay with T cells, exhibiting stimulatory, regulatory, and pro- and anti-inflammatory capacities. Further characterization of diverse B cell phenotypes and their different functions in the initiation, propagation, and maintenance

of inflammation is needed and will potentially pave the way for new treatment strategies. The identification of disease-specific autoantibodies against AQP4 and MOG in a subgroup of patients has not only advanced our pathogenic understanding, but it provides a valuable tool for clinical stratification. The search for other autoantigen targets is in progress, paving the way for the development of more specific, customized immunomodulatory/-suppressive treatments.

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Anne-Katrin Pröbstel, Nicholas S. R. Sanderson and Tobias Derfuss wrote and revised the manuscript.

Conflicts of Interest

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Abbreviations

ADEM: acute disseminated encephalomyelitis; APC: antigen-presenting cell; APRIL: a proliferation-inducing ligand; AQP4: aquaporin-4; BAFF: B cell activating factor; CCL19: chemokine (C-C motif) ligand 19; CIS: clinically isolated syndrome; CNS: central nervous system; CSF: cerebrospinal fluid; EAE: experimental autoimmune encephalomyelitis; EBV: Epstein-Barr Virus; ELISA: enzyme-linked immunosorbent assay; Ig: immunoglobulin; IL: interleukin; MHC: major histocompatibility complex; MOG: myelin oligodendrocyte glycoprotein; MS: multiple sclerosis; NMO: neuromyelitis optica; NMOSD: NMO spectrum disease; OCBs: oligoclonal bands; TNF: tumor necrosis factor.

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