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Review

The role of antibodies in multiple sclerosis

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ABSTRACT

B cells, plasma cells, and antibodies are commonly found in active central nervous system (CNS) lesions in patients with multiple sclerosis (MS). B cells isolated from CNS lesions as well as from the cerebrospinal fluid (CSF) show signs of clonal expansion and hypermutation, suggesting their local activation. Plasma blasts and plasma cells maturating from these B cells were recently identified to contribute to the development of oligoclonal antibodies produced within the CSF, which remain a diagnostic hallmark finding in MS. Within the CNS, antibody deposition is associated with complement activation and demyelination, indicating antigen recognition-associated effector function. While some studies indeed implied a disease-intrinsic and possibly pathogenic role of antibodies directed against components of the myelin sheath, no unequivocal results on a decisive target antigen within the CNS persisted to date. The notion of a pathogenic role for antibodies in MS is nevertheless empirically supported by the clinical benefit of plasma exchange in patients with histologic signs of antibody deposition within the CNS. Further, such evidence derives from the animal model of MS, experimental autoimmune encephalomyelitis (EAE). In transgenic mice endogenously producing myelin-specific antibodies, EAE severity was substantially increased accompanied by enhanced CNS demyelination. Further, genetic engineering in mice adding T cells that recognize the same myelin antigen resulted in spontaneous EAE development, indicating that the coexistence of myelin-specific B cells, T cells, and antibodies was sufficient to trigger CNS autoimmune disease. In conclusion, various pathological, clinical, immunological, and experimental findings collectively indicate a pathogenic role of antibodies in MS, whereas several conceptual challenges, above all uncovering potential target antigens of the antibody response within the CNS, remain to be overcome.

1. Introduction

For decades, self-reactive antibodies have been implicated to participate in the pathogenesis of multiple sclerosis (MS). Increased immunoglobulin (Ig) levels in the cerebrospinal fluid (CSF), first described to be suggestive for MS in 1942 by Kabat et al. [1], remain a hallmark finding in the diagnosis of disease. Since then, a plethora of investigations attempted to identify the target antigens which these antibodies may be raised against. Some findings implicated that antibodies within the inflamed CNS may eventually recognize components of the myelin sheath; however, no unequivocal evidence of such CNS reactivity has been established to date. While the occurrence of antibodies in the CSF is thus tightly associated with the diagnosis of MS, it is still under debate whether these newly occurring Ig indeed actively contribute to pathogenesis or progression of the disease. In this review, we will present a variety of pathological and immunological findings supporting a pathogenic role of humoral immune responses in MS. Further, we will provide an overview on the role of antibodies in the animal model experimental autoimmune encephalomyelitis (EAE) and discuss applicability and implication of these experimental findings to human CNS demyelinating inflammatory disease.

2. The role of antibodies in central nervous system autoimmune disease—evidence from human studies

2.1. Antibodies in the central nervous system

Strong evidence for a role of antibodies in MS derives from histopathological studies in which B cells, as well as B-cell-derived plasma cells and antibodies, are found in the central nervous system (CNS). Of importance, molecular analyses of B cells in brain lesions demonstrate an accumulation of clonotypic B cells with preferential use of particular variable (V) heavy (H) chain (VH) genes indicating a restricted local immune response. Furthermore, investigated sequences showed signs of hypermutations reflecting an ongoing and maturating B-cell response to the target antigen [2–4]. After antigen challenge, B cells mature to short-lived plasma blasts and plasma cells, both subsets produce large amount of antibodies. Antibodies are frequently observed in acute lesions of MS patients. In newly diagnosed patients, histopathological studies demonstrate heterogeneity of acute lesions

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between individual patients suggesting at least four distinct patterns of acute demyelinating lesions exist [5,6]. The most frequent pattern is characterized by significant antibody deposits and complement activation. In contrast, in acute lesions of patients with established MS, a more homogenous pattern was observed [7]. Whereas it can be questioned whether these specimen are entirely representative for established disease, all samples tested contained antibodies and complement deposition [7]. Complement activation supports the role of pathogenetic antibodies and antibody-mediated effector functions and is found in areas of demyelination [5,8].

The CSF compartment gives also evidence for a role of antibodies in MS. About 50–60% of all diagnosed MS patients exhibit an intrathecal production of IgG. After separation of CSF Ig by electrophoresis, this IgG fraction appears as oligoclonal IgG bands (OCBs) in the CSF but not in serum where IgG is polyclonal. OCBs extracted from the CNS have a similar pattern as from CSF of the same individuals strengthening the view that the CSF compartment reflects—at least partially—the milieu in the CNS itself. The occurrence of such OCBs in CSF is still the only reliable immunological test supporting clinical and MRI findings in establishing the diagnosis of MS. The oligoclonal IgG pattern reflects local accumulation of restricted IgG specificities and is concomitant with a restricted Ig receptor repertoire in CSF. B cells, mostly IgM−/IgD− memory cells, and plasma blasts are present in the CSF [9]. Interestingly, patients largely differ with respect to the presence of B cells and plasma blasts in CSF [10]. The presence of plasma blasts correlates with acute parenchymal inflammation as determined by MRI [11]. Moreover, in infectious diseases, plasma blast numbers correlate with the viral or bacterial load in the CSF [12,13], suggesting that the presence of these cells reflects acute inflammatory activity.

Analysis of the H and L chain of B cells, plasma cells, and plasma blast in the CSF of MS patients revealed a restricted use of H and L chains with hypermutations in the variable region indicating a focused and ongoing immune response in the CSF of MS patients [14–18] similar to what was observed in brain tissue. The relevance of CSF plasma blasts and plasma cells [19], in the production of OCBs, had been for a long time an open question. In a recent study, Obermeier et al. [20] compared the IgG proteome in CSF and the IgG transcriptome from the B cellular compartment in CSF and found an overlap between both compartments. Furthermore, von Budingen et al. [21] found the same amino acid sequences of H-CDR3 in clonally expanded plasma cells as well as in OCBs using anti-idiotypic antibodies raised against the CDR region. Interestingly, the OCBs, B-cell numbers, and B-cell clonotypes are stable over years in the CSF of MS patients [11,22,23].

Hence, researchers have investigated the relevance of OCBs as potential biomarkers for clinical outcome of patients with MS. OCB-negative MS patients seem to have a more benign disease course [24]. Also, the number of OCBs and the intrathecal IgG synthesis [25] correlated with a more progressive outcome in a retrospective study [26] but not in a more recent study [27]. The presence of IgM OCBs predicts a higher probability for conversion to secondary progressive MS (SP-MS) [28] and intrathecal IgM production predicts a higher progression rate [29]. However, this was not confirmed by an independent study [30].

2.2. Targets of antibodies in multiple sclerosis

OCBs are not specific for MS but are also found in other neuroimmunological CNS diseases like neuroborreliosis, herpes simplex encephalitis, human immunodeficiency virus (HIV) of the CNS, or subacute sclerosing panencephalitis (SSPE). In infectious CNS diseases, the OCBs specifically recognize the disease-causing antigens [31,32].

Although researchers have been searching for the targets of the local immune response in MS for many years, the target antigens of the humoral immune response in MS are still largely unknown. MS lesions are focused on CNS white matter, so that possible antigenic structures where suspected to be within this region. Whereas some data suggest that lipids or carbohydrates may be targets of the humoral response, the main body of research provided evidence that the relevant components may be proteins of the myelin sheath, such as myelin basic protein (MBP), myelin oligodendrocyte glycoprotein (MOG), and proteolipid protein (PLP). The immune response against myelin proteins has been extensively investigated. However, to date, controversial results have been obtained. In MS lesions, antibodies to myelin, especially MOG, were found by immunohistochemical analysis [33] and IgGs extracted from inflamed CNS also recognized MOG [34]. Elevated antibody titers against MBP and/or MOG were also reported in serum and CSF of MS patients [35–37] and in serum of children with the first episode of CNS demyelination [38,39]. Myelin-specific antibodies are, however, not confined to MS. They are also found in different neurological diseases and even in healthy controls [40–42]. Moreover, a recent careful study with antibodies reconstructed from B-cell clonotypes from the CSF of MS patients did not provide any evidence for binding of these antibodies to MOG, PLP, or MBP.

In serum, anti-MOG and -MBP IgM antibodies determined by immunoblot were reported to predict conversion to MS in CIS patients [43]. Unfortunately this finding was not confirmed by others [44,45]. Although antibody reactivities would be attractive for use as biomarkers to predict relapses or progression to MS, no antibody that is specific to MS has been yet identified. This may be in part due to shortcomings in the assays to determine antibody responses to CNS proteins. Especially membrane proteins are highly folded, and the conformational epitope targets of autoantibodies. The conformational epitopes are, however, not preserved in conventional assays such as ELISA or Western blot. This problem was recently overcome by cell-based assays. Using these assays, in which MOG is expressed by a transfected cell line, serum antibodies to native MOG were observed in a subgroup of patients [46,47]. Interestingly, high antibody titers to native MOG were recently reported in two independent studies in pediatric CIS, ADEM, and MS [48,49]. The use of whole myelin particles also revealed a more frequent positive reactivity in MS and CIS patients [50].

Furthermore, MS is very heterogenous with respect to histopathological changes [5], CSF phenotype [10], disease course [51], and response to therapy [52]. Accordingly, different mechanisms may play a role in demyelination. Not all patients might have a prominent antibody response, or specific autoantibodies may characterize distinct clinical entities.

In neuromyelitis optica (NMO), an autoantibody specific for aquaporin-4 (Aqp-4), a water channel protein, was recently found [53,54]. There is accumulating evidence that NMO is pathologically different from MS and represents a distinct disease entity [55]. Transfer experiments have demonstrated that the Aqp-4 antibody can induce astrocyte pathology upon transfer in animals after disruption of the blood–brain barrier [56,57]. Such an astrocyte pathology is also observed in patients with NMO [58]. In addition, the Aqp-4 antibody titer seems to correlate with disease activity, further supporting the concept that Aqp-4 is a major target of the autoimmune reponse in NMO.

Besides the autoimmune hypothesis, it is assumed that infectious agents may play a significant role in the pathogenesis of MS. The antibody reactivities against various numbers of pathogens have been investigated in CSF and serum of MS patients (summarized in Gilden [59]). Most discussed are Epstein–Barr virus (EBV), human herpes virus-6 (HHV-6), varicella zoster virus (VZV), and *Chlamydia pneumoniae*. The hypothesis is still attractive in view of other infectious diseases of the CNS, which cause inflammation and demyelination in humans such as SSPE- or HTLV-I-associated myelopathy [60]. In these disorders, a comparable chronic immune response is observed in the CNS, including the occurrence of OCBs. Interestingly, the intrathecal Ig response and the OCBs contain antibodies specific for the causative agent [61]. Similar to autoantibody studies, many researchers have reported on elevated

antibody titers to a broad range of pathogens in MS patients, although most findings were not confirmed by independent studies. Only in EBV that conclusive data on an increased antibody response were reported.

Since CNS resident proteins might be the target of the antibody response, cDNA expression libraries generated from MS brain lesions were developed and probed with CSF antibodies with little success [62]. Phage display libraries containing random short peptides or peptides derived from MS brain plaques were constructed and displayed on phage surface-enabled large-scale screening of CSF antibodies for identification of binding epitopes or minotopes [63–67]. Using this technology, one group identified a 5-amino acid consensus sequence present in Epstein–Barr virus nuclear antigen and a heat shock protein, alphaB crystallin [65]. Recently, another group identified antibodies to eight novel antigenic targets present in a subgroup of MS patients but not in controls [67]. Using a human brain cDNA expression library combined with epitope mapping, Cepok et al. [68] identified two different EBV proteins, the well-known EBNA-1 and a novel protein BRRF-2, as putative targets of the oligoclonal immune response in MS.

Recently, monoclonal recombinant antibodies (rAbs) were generated from clonally expanded and therefore most likely disease-relevant CSF IgG-secreting plasma cells and B cells of MS patients. This strategy allows to produce an unlimited amount of relevant Igs for large-scale screening of antibody binding using various antigens and tissues [21,69,70]. Immunofluorescent staining of MS lesions tissue with rAb revealed reactivity to areas of myelin degradation [21] or axons [71]. However, specific reactivity of rAB to myelin epitopes could not be confirmed by immunostaining of MOG-, MBP-, and PLP-transfected cell lines or immunostaining of brain tissue sections [69]. Screening of rAB reactivities to a larger number of different antigens, cells, and tissues will be the next step to determine the specificity of these rAbs.

2.3. Effector mechanisms of antibodies in multiple sclerosis

Beside the prevalence of specific antibodies in MS, it will be crucial to demonstrate a biological consequence of antibodies and their participation in one effector function leading to demyelination. In general, antibodies may exert their effector function through various mechanisms.

1. A mechanism called antibody-dependent cellular cytotoxicity (ADCC) in which cells of the innate immune system, e.g., NK cells recognize and bind the gamma chain of the antigen-bound antibody complex through the Fc-gamma receptor expressed on the effector cell. The binding leads to the release of inflammatory components by the effector cell mediating cytotoxicity and lysis of the target. Cell lines transfected with the candidate antigen are an appropriate tool for the measurement of antigen-specific ADCC [46,69].
2. Opsonization and phagocytosis is an additional effector mechanism of antibodies. Here, antibodies specifically bind and opsonize the antigen, e.g., myelin for recognition through the Fc-gamma receptor expressed on phagocytotic cells like macrophages leading to the phagocytosis of the antigen–antibody complex and destruction of the tissue. In MS lesions and EAE brain tissue, phagocytotic cells containing Ig and myelin proteins have been found [33], supporting the hypothesis of cell-induced demyelination.
3. Complement activation by binding to antibodies is an additional possible mechanism leading to demyelination. In this pathway, complement components bind to structures of antibodies leading to activation of the complement cascade and the assembly of the membrane attack complex and destruction of the target [72]. Complement deposition was found in several studies associated with macrophages in acute demyelinating lesions, suggesting an antibody- and complement-mediated demyelination [7,8]. CSF IgG of MS patients contain mainly IgG1 and IgG3. Both subclasses are potent in the activation of the complement cascade. The potential for demyelination by binding of antibodies against MOG and MBP was shown to be related to the ability to fix complement [73].
4. Beside the activation of effector cells or complement pathway the antibody binding itself might be able to induce demyelination. Marta et al. investigated the signalling of anti-MOG antibody binding to MOG and found that crosslinking of anti-MOG–MOG complexes resulted in the phosphorylation of specific proteins related to cellular stress response and cytoskeletal stability providing a possible biochemical mechanism of antibody induced demyelination [74,75]. Antibodies were also shown to modulate synaptic transmission [76].
5. Finally, antibodies have the capacity to neutralize antigens, mostly relevant in neutralisation of circulating pathogens. In this mechanism, antibodies prevent by antigen opsonization the ability of pathogen to spread and disturb cells of the host.
6. Furthermore, the pathogenicity of antibodies can be investigated by transfer of human serum to animal disease models. Likewise, serum from patients with high anti-MOG antibody titers stained white matter myelin in rat brain and enhanced demyelination as well as axonal damage when transferred to animals with ongoing EAE [46]. Typical NMO-like lesion formation was observed in EAE after transfer of human anti-Aqp-4-positive serum [57].

2.4. Evidence from therapeutic approaches in multiple sclerosis

B-cell-derived antibodies against CNS autoantigen may be important in the pathogenesis of certain MS subtypes [3,15,35,77]. Based on this assumption, plasma exchange has evolved as a therapeutic strategy to remove or reduce self-reactive antibodies in treatment of acute MS relapses. In a small observational study in patients with severe optic neuritis refractory to conventional pulsed steroid therapy, plasma exchange was associated with an improvement of visual acuity in 7 out of 10 patients [78]. Another clinical trial investigated plasma exchange in patients with recently acquired severe neurological deficits from attacks of inflammatory demyelinating disease, who failed to recover after treatment with intravenous corticosteroids. Substantial clinical improvement in neurological disability was observed in 42.1% of active treatment courses compared with 5.9% in sham treatment [79]. A larger trial dating back to 1989 also studied the effectiveness of plasma exchange in acute MS exacerbations. In this trial, 116 patients were assigned to receive 11 treatment cycles of plasma exchange or sham exchange during 8 weeks. In addition, both groups received corticotropin (ACTH) and cyclophosphamide. During the treatment period, patients receiving plasma exchange clinically improved, whereas no clear long-term benefit was observed. Interestingly, the respective MS subtype appears to be a predictor for the achievable benefit from plasma exchange. In a recent clinical trial with MS patients undergoing an acute relapse, therapy-responsive patients could be identified to be histopathologically defined by antibody deposition and enrichment of B cells within the CNS [80,81]. First, these data demonstrate the urge for intravital biomarkers distinguishing individual MS subtypes. Second, although it needs to be noted that all patients included did not respond to initial steroid treatment, which may cause a bias towards patients with severe relapses, this finding strongly supports that in a subgroup of patients CNS-directed autoantibodies indeed contribute to MS pathogenesis.

Another approach that may indirectly decrease titers of self-reactive antibodies is therapeutic depletion of CD20-positive B cells. Anti-CD20 (rituximab, Rituxan®) was initially developed to treat non-Hodgkins B-cell lymphoma and has shown promising results in treatment of CNS demyelinating diseases. In a small open-label pilot study evaluating B-cell depletion in neuromyelitis optica (NMO), seven out of eight patients receiving rituximab experienced substantial improvement of neurologic function over 1 year [82]. In relapsing–remitting MS, a recent placebo-controlled phase II trial revealed that MS patient receiving rituximab exerted a substantial reduction in development of newly emerging inflammatory brain lesions. Despite the short

period of the trial, the same study at least suggested a reduction in clinical attack frequency [83]. Mechanistically, it remains to be elucidated elimination of which B-cell function may correlate best with a potential benefit of B-cell depletion in CNS autoimmune disease. It can be speculated that rituximab immediately abolishes cellular B-cell functions, such as B-cell antigen presentation, whereas myelin-specific antibody titers appear to decrease with a substantial delay because antibody-secreting plasma cells no longer express CD20. Based on this assumption, it appears likely that the immediate benefit of B-cell depletion in T-cell-mediated autoimmune disease may indeed relate to an impaired activation of T cells. In this regard, a recent study demonstrated that in MS, anti-CD20 mediated depletion of B cells was correlated with an altered response of T cells to unspecific activation [84]. An experimental study revealed that activation and proinflammatory differentiation of autoreactive T cells are impaired in the absence of myelin-activated B cells [85]. Detailed longitudinal studies are about to more thoroughly investigate the impact of B-cell depletion on T-cell activation and whether a later decrease in self-reactive antibody titers may contribute to long-term clinical stabilization of patients receiving anti-CD20 therapy.

3. The role of antibodies in central nervous system autoimmune disease—implications from animal models

The animal model of MS, EAE, is thought to be predominantly mediated by pro-inflammatory, self-reactive T cells [86]. Strong evidence for this assumption derives from the fact that adoptive transfer of encephalitogenic T cells is sufficient to induce EAE in susceptible mice [87] and that EAE can be actively induced in B-cell-deficient mice [88]. Nevertheless, in addition to infiltrating T cells and macrophages, B cells, plasma cells, and antibodies are found in areas of myelin breakdown in EAE similar to active CNS lesions in some MS patients [33,89,90]. Whereas it is clear that these antibodies alone are not capable of initiating inflammation in brain and spinal cord, certain EAE studies suggest that they might facilitate CNS damage and promote disease progression.

3.1. Autoreactive antibodies in EAE—pathogenic involvement or epiphenomenon?

Whereas MS is likely to be a heterogenous disease with differential involvement of inflammation throughout its progression, autoimmune T- and B-cell responses against CNS antigens remain a central component in the current view of MS pathogenesis. Myelin antigens are the prevalent putative targets studied in the field due to the often primarily demyelinating nature of inflammatory CNS lesions. Within candidate myelin antigens, MOG is probably the one that is most investigated due to its extracellular location on the outermost myelin lamellae, which makes it an exposed target accessible to an initial autoimmune attack against properly myelinated axons. The full-length MOG protein is constituted of 218 amino acids and is exclusively expressed within the CNS. Most importantly, MOG is highly encephalitogenic in the murine as well as in the marmoset EAE model.

Regarding the possible contribution of myelin-reactive antibodies to EAE pathogenesis Schluesener et al. [91] reported more than 20 years ago that a monoclonal antibody directed against MOG exacerbated clinical and histological EAE in a rodent disease model. The authors demonstrated convincingly that the intravenous administration of this myelin-reactive antibody enhanced CNS demyelination and induced fatal relapses in recipient mice. Notwithstanding this seminal observation, it appears necessary to be noted that the antibody was injected into already EAE-diseased mice at a quantity that is unlikely to be produced endogenously. Experiments in B-cell-deficient mice indicate indeed that B cells or antibodies are not required when the short encephalitogenic T-cell-determinant peptide (p)35–55 is used to immunize mice in an active EAE induction protocol [92]. A crucial step in disease induction by active immunization is the presentation of the administered CNS autoantigen to naïve encephalitogenic T cells by antigen-presenting cells (APC) in the context of major histocompatibility complex (MHC) class II. Short peptides, such as MOG p35–55, are known to be most efficiently phagocytized and presented by dendritic cells and macrophages [93,94], so that B-cell encounter with the peptide antigen rarely occurs. This results in two key features of this model of CNS autoimmune disease: B-cell antigen presentation does not play a crucial role for EAE induction by MOG peptide and low anti-MOG antibody titers, if any, are generated.

B cells and antibodies may however be required for EAE induced by the recombinant (r) extracellular domain of MOG, as genetically B-cell-deficient mice were found to be resistant to active immunization with human rMOG [88]. Reconstitution with the antigen-specific antibody was sufficient to restore EAE susceptibility, suggesting a crucial role for antibody-mediated antigen recognition in this model [92]. Unfortunately, the question whether B cells are required for MOG protein-induced EAE appears to be more complex though and is still debated lively. Oliver et al. [95] reported that immunization with either rat or human MOG leads to comparable titers of anti-MOG antibodies. However, only human (but not rat) MOG was reported to induce a B-cell-dependent EAE model as evaluated by active immunization of B-cell-deficient mice. The sequence of human MOG differs from rat MOG only at a few residues, including a proline for serine substitution at position 42, which encodes within the dominant T-cell determinant of MOG p35–55. Substituting this amino acid with serine in human MOG p35-55 (resulting in the rat MOG sequence) substantially increased its encephalitogenicity [95]. Further, exchanging the same residue within human MOG protein appears to be sufficient to restore EAE susceptibility in B-cell-deficient mice [72], suggesting that B cells or B-cell-derived products are specifically required to recognize human MOG protein due to the presence of proline at position 42 within the three-dimensional protein.

Further, not all MOG-specific antibody responses are thought to be pathogenic which can be determined by their antigen recognition. In general, pathogenic MOG-specific antibodies recognize conformation-dependent MOG epitopes that are only available within the intact protein. Antibodies that are specific for linear determinants, although they may recognize antigens following tissue injury, are not thought to contribute to disease initiation in a pathogenic manner [96–98]. Further, in EAE it appears that immunization with either rat or human MOG leads to a considerable development of anti-MOG antibodies, whereas only immunization with human rMOG generates a pathogenic, EAE-enhancing MOG antibody response [74]. The gold standard to prove potential antibody pathogenicity has become a cell-based assay, in which MOG is expressed by a transfected cell line [46,47]. Through measurement of cell lysis, these assays allow determining whether antibodies are capable to target conformationally folded, cell membrane-embedded MOG. Using this technique, one study was able to demonstrate higher IgG antibody titers to native MOG in the serum of MS patients compared with non-MS control groups [46]. Most intriguingly, serum from patients with high anti-MOG antibody titers stained white matter myelin in rat brain and enhanced demyelination and axonal damage when transferred to animals with ongoing EAE. Along the same lines, a transgenic mouse engineered to express the rearranged heavy chain of a pathogenic antibody recognizing a conformational determinant of MOG (8.18-C.5) developed more severe EAE with greater inflammation and demyelination compared with wild-type mice [99]. Following a physiological B-cell development, the MOG-recognizing antibody was expressed in these mice as membrane-bound B-cell receptor as well as secreted by B-cell-derived plasma cells. The combination of the fact that serum from these mice bound specifically to native, brain-derived MOG and the observed enhancement of CNS demyelination these studies may indicate a pathogenic role for plasma cell-secreted myelin-specific antibodies. Alternatively, although not mutually exclusive, accelerated EAE severity may reflect a pathogenic role for myelin-specific B cells in processing and presentation of myelin antigen to encephalitogenic T cells.

3.2. The role of B cells and antibodies in spontaneous EAE models

As EAE induced by active immunization with self-antigen or passive transfer of encephalitogenic T cells is unlikely to fittingly reflect MS pathogenesis characterized by chronic inflammation and the lack of an apparent disease trigger, recent efforts have been focused on developing EAE models which do not require their active induction. All of these models have in common, that B cells, T cells, or both are genetically engineered to recognize CNS antigens at a higher frequency than mouse strains susceptible to induced EAE. While it is debatable whether "spontaneously" occurring EAE in these transgenic mice reflects MS pathogenesis more closely, these models undoubtedly provide an excellent tool to study the interaction of self-reactive T cells, B cells, and antibodies.

One of the first of these spontaneous EAE models has been described after the above-mentioned transgenic mice, in which a high frequency of B cells express a pathogenic antibody against MOG (MOG B-cell knockin), were crossed onto a line of transgenic mice in which a majority of T cells responds to MOG p35–55. While it needs to be noted that approximately 40% of these single-transgenic MOG T-cell receptor transgenic mice were already affected by optic neuritis, they rarely revealed symptoms of spontaneous paralysis [100,101]. In contrast, in the double-transgenic mice containing in addition a high frequency of MOG recognizing B cells, approximately 60% spontaneously developed a severe form of EAE with meningeal and parenchymal lesions [100,102]. Interestingly, inflammatory lesions remained restricted to the spinal cord and optic nerves, not unlike in NMO or Devic's syndrome, which selectively affects optic nerves and spinal cord, but spares the brain [103,104]. In NMO, however, accumulating evidence suggests that a serum antibody against Aqp-4 may have the central pathogenic impact. It is thus unlikely that the selective appearance of spinal and optic nerve inflammatory lesions in B-cell/T-cell double-transgenic mice indicates a true parallel to NMO pathogenesis. Nevertheless, this model suggests that the myelin specificity of B cells and T cells is, in principle, sufficient to trigger spontaneous CNS autoimmune disease. It remains to be determined in further studies whether this spontaneous model primarily relates to the abundance of myelin-specific antibodies or, alternatively, to the fact that MOG-specific B cells serve as efficient APCs for the activation of MOG p35–55-specific T cells in these mice.

Another recently described spontaneous EAE model apparently also relies on the interaction of myelin-specific B cells and/or antibodies and T cells [105]. In this model, T cells are genetically engineered to recognize MOG peptide 92–106 resulting in spontaneous relapsing–remitting EAE on the otherwise wild-type SJL/J background. Backcrossing these T-cell transgenic mice to a line expressing the MOG binding antibody 8.18-C.5 on B cells led to an earlier onset of an even more severe spontaneous EAE disease course. In single T-cell transgenic mice with later disease onset, myelin-specific B cells were shown to be recruited and expanded from the endogenous repertoire, which results in the development of pathogenic anti-MOG antibody titers comparable to those in wild-type mice actively immunized with rMOG. In both single- and double-transgenic mice, anti-CD20-mediated B-cell depletion could abrogate spontaneous EAE development, proving that endogenously recruited or transgenically engineered myelin-specific B cells or antibodies were indeed mandatory for initiation of spontaneous disease. Counterintuitively, myelin-specific B cells obtained from these mice were, however, unable to recognize the transgenic T-cell determinant 92–106. Further, spontaneous disease was not observed when MOG p92-106 T-cell receptor transgenic mice were crossed onto a MOG-deficient background. Collectively, these findings indicate that in this model, activation of abundant MOG p92–106-specific T cells requires prior encounter of B cells with endogenous MOG. Similar to the spontaneous EAE model described in the paragraph above, it remains yet unclear whether spontaneous CNS autoimmune disease in these mice relies primarily on cellular function of myelin-specific B cells or B-cell-derived myelin-specific antibodies.

4. Conclusions

Several lines of evidence indicate that B cells, plasma cells, and, in particular, antibodies contribute to development and progression of MS. The analysis of B cells and B-cell-derived cells within CNS lesions, but also within the CSF, revealed a very restricted clonal expansion of particular B-cell entities. Together with signs of hypermutation, these findings are indicative of a local activation and maturation of these B cells within the CNS itself. A recent study comparing the CSF IgG proteome with the IgG transcriptome of cells from the B-cell lineage within the CNS demonstrated a substantial overlap between both compartments. These findings suggest that commonly found OCBs in the CSF of MS patients may indeed be produced by successors of B cells activated within the CNS itself. The central question remains, however, whether such local activation and consequential production of the respective antibodies derives from B-cell antigen recognition within the CNS. While in NMO, the pathogenic antibody response could be identified to be directed against astrocytic Aqp-4, to date, no conclusive understanding exists on possible CNS target antigens against which the antibody response may be raised in MS. Empirical support for a pathogenic role of antibodies derives from the therapeutic approach of plasma exchange, which was found to be beneficial in a subgroup of MS patients with severe therapy-refractory relapses and antibody deposition within inflammatory CNS lesions. These data suggest that, in a subgroup of patients, peripherally produced CNS-directed antibodies may indeed contribute to MS pathogenesis.

Besides these findings in MS patients, several observations derived from experimental CNS autoimmunity suggest that B cells and CNS-reactive antibodies contribute in a pathogenic manner. B cells, plasma cells, and antibodies accumulate in areas of myelin breakdown in EAE not unlike inflammatory CNS lesions in MS patients. EAE induction by immunization with myelin protein involves B-cell activation leading to development of myelin-specific antibodies. Transfer of antibodies against myelin into mice with ongoing EAE enhances CNS demyelination and exacerbates clinical EAE symptoms, suggesting that myelin-specific antibodies accelerate EAE pathogenesis. Further, such evidence derives from mice that are genetically engineered to express a myelin-reactive B-cell receptor on a high percentage of B cells and to secrete the corresponding antibody by B-cell-derived plasma cells. Immunization of these mice revealed an exacerbation of EAE severity with augmented CNS inflammation and demyelination. When these B-cell receptor knock-in mice were crossed with transgenic mice in which a majority of T cells also recognizes myelin antigen, the resulting mouse line developed spontaneous EAE with a high disease incidence. Another spontaneous EAE model similarly demonstrated that myelin-recognizing B cells and/or antibodies are required for EAE induction in transgenic mice with a high frequency of myelin-specific T cells. Taken together, these experimental findings suggest that myelin-reactive B cells and antibodies—although not required for active induction of EAE—enhance CNS pathology in conventional EAE and support myelin-reactive T cells to induce disease in recently developed spontaneous EAE models.

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