B cells in autoimmune and neurodegenerative central nervous system diseases

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Abstract | B cells are essential components of the adaptive immune system and have important roles in the pathogenesis of several central nervous system (CNS) diseases. Besides producing antibodies, B cells perform other functions, including antigen presentation to T cells, production of proinflammatory cytokines and secretion of anti-inflammatory cytokines that limit immune responses. B cells can contribute to CNS disease either through their actions in the periphery (meaning that they have an 'outside-in' effect on CNS immunopathology) or following their compartmentalization within the CNS. The success of B cell-depleting therapy in patients with multiple sclerosis and CNS diseases with an autoantibody component, such as neuromyelitis optica spectrum disorder and autoimmune encephalitides, has underscored the role of B cells in both cellular and humoral-mediated CNS conditions. Emerging evidence suggests B cells also contribute to the pathogenesis of neurodegenerative diseases, including Alzheimer disease and Parkinson disease. Advancing our understanding of the role of B cells in neuroinflammatory and neurodegenerative diseases could lead to novel therapeutic approaches.

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The central nervous system (CNS) has traditionally been considered an immune-privileged site. However, immune cells are increasingly recognized to access the CNS in both health and disease. Lymphocytes can enter the CNS through several points, including the blood–brain barrier (BBB), the blood–meningeal barrier and the blood–cerebrospinal fluid (CSF) barrier[1,2]. In general, only activated lymphocytes are able to exit postcapillary venules of the BBB into the CNS parenchyma and thereby enter the perivascular space. A subset of B cells can leave the perivascular space and enter the CNS parenchyma. However, under healthy steady-state conditions, B cells are present in very low numbers in the CNS parenchyma (~0.1 cell/cm^2)[3] and CSF, where they account for less than 1% of white blood cells[4]. By contrast, in individuals with CNS inflammation, B cell numbers can increase by at least several orders of magnitude in the CNS parenchyma and perivascular spaces[5] and by severalfold in the CSF[4]. Lymphocytes can also enter the CSF in the subarachnoid space, either by extravasation across subpial venules of the blood–meningeal barrier or by crossing the stroma and epithelium of the choroid plexus (that is, the blood–CSF barrier). To reach the CNS parenchyma from the CSF, lymphocytes must cross the glia limitans, a thin barrier of astrocyte foot processes closely associated with the basal lamina. B cells and T lymphocytes are also present in non-diseased CNS lymphatic vessels[6], supporting their role in immune surveillance. Lymphatic drainage is the primary mechanism of lymphocyte egress from the CNS. Lymphocytes in the CSF drain via nasal or meningeal lymphatic vessels, which ultimately drain into the cervical lymph nodes[1,2,7]. Each of these compartments can serve as a focus for immune pathology in CNS diseases.

B cells, in concert with T cells, constitute the adaptive immune system, which exhibits antigen-specific memory. B cells are capable of performing a variety of cellular and humoral functions depending on their stage of differentiation and activation status (FIG. 1). For example, B cells and their corresponding secreted antibodies recognize distinct antigens through a unique rearranged B cell receptor (BCR). Arising from haematopoietic stem cell precursors, naive B cells expressing IgM and IgD emerge from the bone marrow and circulate in the peripheral blood and lymphoid organs. Following BCR-mediated recognition of their cognate antigen, these B cells become activated and a subset of these activated B cells undergo a germinal centre reaction in secondary lymphoid tissues. In geminal centres, B cells expressing a specific BCR undergo clonal expansion and proliferate rapidly, eventually becoming CD27$^+$ memory B cells, a process reviewed in detail elsewhere[8]. Mature, activated B cells can undergo immunoglobulin class switching, a T cell-dependent process that enables them to express

other antibody isotypes (IgG, IgA or IgE). Class-switched autoreactive B cells can be present at high frequencies in autoimmune CNS conditions[9]. Memory B cells can further differentiate into antibody-secreting CD38$^+$ plasmablasts or long-lived CD138$^+$ plasma cells (FIG. 1). The bone marrow is an important reservoir of plasma cells[10].

Antibody production is the most widely recognized role of B cells. Antigen specificity is conferred by the

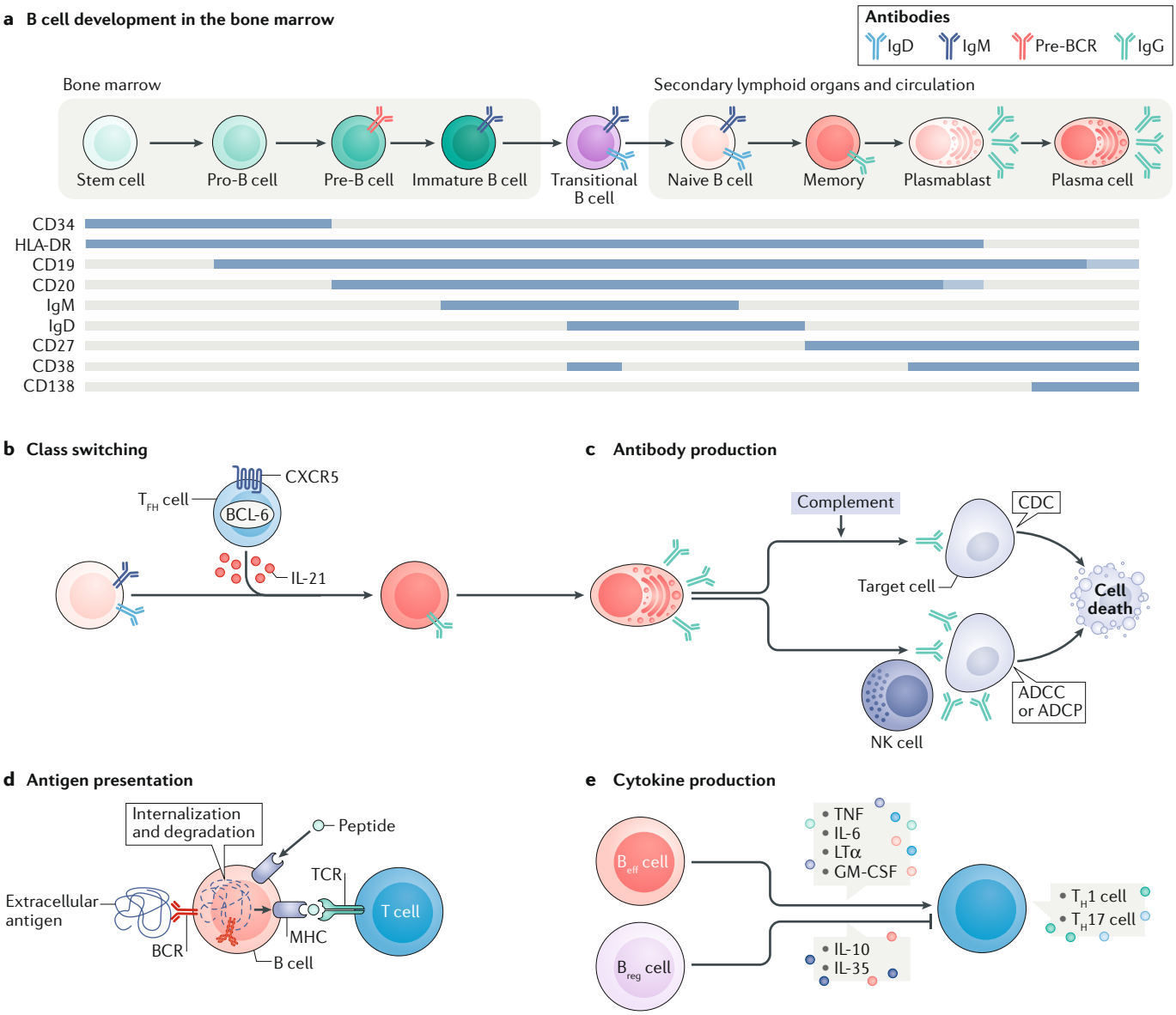


Fig. 1 | **B cell lineages and functions. a** | B cells originate from stem cells in the bone marrow and undergo B cell receptor (BCR) rearrangement and upregulation of CD34 and HLA-DR cell-surface proteins. Pre-B cells express a BCR consisting of a rearranged heavy chain and a surrogate invariant light chain (pre-BCR). Immature B cells begin to express IgM and exit the bone marrow, becoming transitional B cells, which express IgM with or without IgD. Naive B cells co-express IgM and IgD, and can either remain in the circulation or migrate to secondary lymphoid organs. On encountering antigens, naive B cells undergo further differentiation to memory cells or plasmablasts and finally plasma cells. Each differentiation stage is associated with specific changes in protein expression. Although class-switched memory B cells are typically CD27$^+$IgD$^-$ B cells, other memory B cell subtypes can be generated (including outside germinal centres), such as CD27$^+$IgD$^+$ B cells (unswitched memory cells) and CD27$^-$IgD$^-$ B cells (double-negative B cells)[309]. **b** | In lymphoid tissue, T follicular helper cells (T$_{FH}$ cells) promote activation and class switching of naive B cells through secretion of IL-21. **c** | Activated B cells can become memory B cells, some of which become long-lived plasma cells. Both memory B cells and plasma cells produce antibodies, which bind to antigens on cellular targets and cause complement-dependent cytotoxicity (CDC), antibody-dependent cellular phagocytosis (ADCP) or antibody-dependent cellular cytotoxicity (ADCC). ADCC mainly involves natural killer (NK) cells, but macrophages, neutrophils and eosinophils also participate. **d** | B cells present antigen to T cells through BCR-mediated internalization of extracellular antigens, which are then processed and presented by major histocompatibility complex (MHC) class II molecules to T cells. Alternatively, free peptide fragments can bind directly to MHC class II and can be presented to T cells without the need for internalization and processing. **e** | B cells secrete a variety of proinflammatory cytokines, leading to type 1 T helper cell (T$_H$1 cell) or IL-17-secreting T helper cell (T$_H$17 cell) polarization. B regulatory cells (B$_{reg}$ cells) also secrete anti-inflammatory cytokines, including IL-10 and IL-35, which can suppress proinflammatory T cells. B$_{eff}$ cell, effector B cell; GM-CSF, granulocyte–macrophage colony-stimulating factor; LTα, lymphotoxin-α; TCR, T cell receptor; TNF, tumour necrosis factor.

B cell receptor
(BCR). A cell-surface immunoglobulin composed of two paired heavy (H) and light (L) chains. Each chain is generated by irreversible rearrangement and recombination of the B cell variable (V), diversity (D; heavy chain only) and junction (J) genes.

Germinal centre reaction
The formation of secondary lymphoid tissue, which is the site of B cell somatic hypermutation and isotype switching.

Immunoglobulin class switching
Also called 'isotype class switching' or 'class-switch recombination', this process refers to recombination of the immunoglobulin gene constant (C) region to allow generation of IgG, IgA or IgE isotypes.

Antibody isotypes
Antibodies are of five different isotypes: IgM, IgD, IgG, IgA and IgE. IgM and IgD are co-expressed by naive B cells, whereas the other isotypes are expressed by antigen-experienced B cells. Isotype is determined by the constant (C) region of the immunoglobulin gene, which encodes the antibody Fc region and binds to Fc receptors on various immune effector cell types.

rearrangement of heavy and light chain genes encoding the antibody's amino-terminal domains, whereas antibody isotype and effector functions are determined by the carboxy-terminal Fc domain (or constant region). Each of the five antibody isotypes (IgM, IgD, IgG, IgA and IgE) binds to a unique array of Fc receptors expressed on different innate immune cells. Binding of antibodies to their target antigen promotes Fc receptor-mediated target cell killing by white blood cells such as natural killer cells, macrophages and neutrophils through phagocytosis or cytotoxic granule release, processes known as antibody-dependent cellular phagocytosis and antibody-dependent cellular cytotoxicity, respectively (FIG. 1). IgG and IgM antibody isotypes can also activate the classical complement pathway, causing complement-dependent cytotoxicity (CDC).

B cells can internalize and digest native antigens, and then present degraded peptide fragments to antigen-specific $CD8^+$ and $CD4^+$ T cells in association with major histocompatibility complex (MHC) class I or class II molecules, thereby acting as antigen-presenting cells (APCs; FIG. 1). Although B cells are generally considered less efficient as APCs than are dendritic cells and other myeloid cells, antigen presentation by memory B cells is highly efficient when antigens recognized via the BCR are presented to T cells that recognize the same antigen[11–13]. B cells can also express co-stimulatory molecules, such as CD80, CD86 and CD40, which promote the activation of proinflammatory T cells. In addition to antibody secretion, B cells themselves produce a number of cytokines[14], including lymphotoxin-α, interleukin-6 (IL-6) and tumour necrosis factor (TNF), which promote the differentiation and activation of proinflammatory, interferon-γ (IFNγ)-secreting, type 1 T helper cells (T_H1 cells) or IL-17-secreting T helper cells (T_H17 cells) (FIG. 1). By contrast, some B cells produce anti-inflammatory cytokines, such as IL-10 (REFS[15,16]) and IL-35 (REF.[17]), and are referred to as B regulatory cells. Thus, B cells have the ability to either promote or dampen CNS inflammation.

The tremendous clinical success of B cell-depleting therapies in multiple sclerosis (MS) and other autoimmune CNS diseases has underscored the importance of B cells in their pathogenesis. In this Review, we illustrate B cell functions involved in the pathogenesis of autoimmune CNS disorders, and discuss evidence that supports potential contributions of B cells to neurodegenerative CNS diseases.

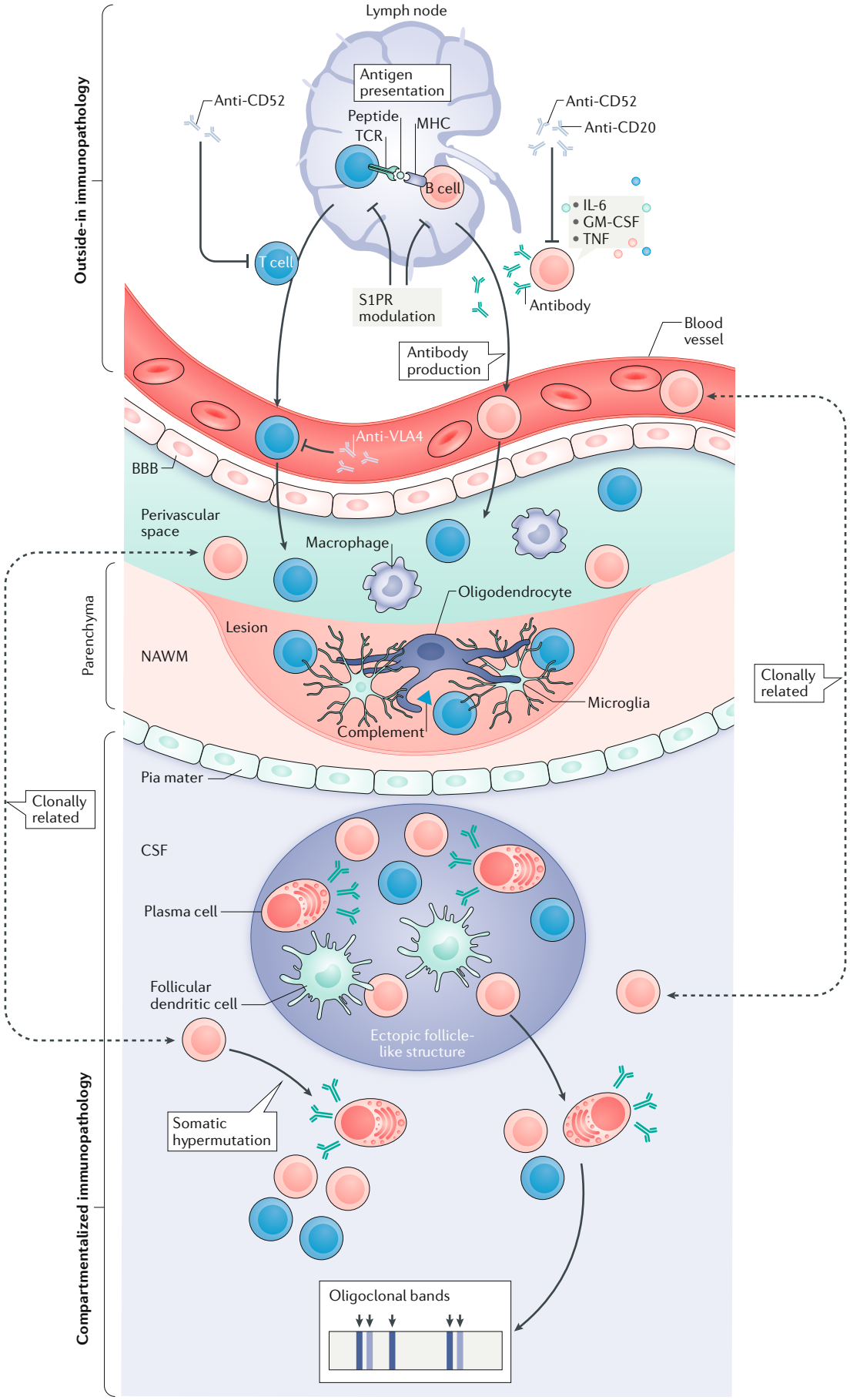
Multiple sclerosis

MS is a chronic inflammatory demyelinating condition of the CNS and is the most common neurological cause of disability in young adults, with a prevalence greater than 1 in 1,000[18,19]. The clinical course of MS differs, but approximately 90% of patients present with relapsing–remitting MS (RRMS), in which relapses — discrete self-limited episodes of neurological dysfunction — are followed by periods of remission. Approximately 50% of patients with RRMS eventually develop progressive disability independent of relapses[20], which is commonly referred to as secondary progressive MS (SPMS). The remaining 10% of patients present with an insidious course, in which neurological disability worsens from onset without discrete relapses, referred to as primary progressive MS (PPMS). To what extent disease progression in PPMS and SPMS involves shared or distinct pathophysiological mechanisms is currently unclear.

Pathophysiology. Although B cells are now known to be major contributors to MS pathogenesis, MS was traditionally viewed as a predominantly T cell-mediated autoimmune disease for several reasons. First, the MHC class II allele *HLA-DRB1*15:01* has been known for several decades to be the strongest genetic risk factor for MS[21]. MHC class II proteins are expressed on APCs and are required for antigen presentation to $CD4^+$ T cells. Second, T cells greatly outnumber B cells in the lymphocytic infiltrates associated with MS lesions[5]. Third, some evidence indicates a proinflammatory T cell imbalance in patients with MS[22,23]. Finally, a T cell-centred view of MS pathogenesis has also been driven by research conducted in animals with experimental autoimmune encephalomyelitis (EAE), a myelin-targeted CNS inflammatory condition that results in relapsing paralysis and demyelination[24]. In 1985, myelin-specific T cell clones were first shown to cause EAE[24,25], which also represented the initial observation that self-antigen-specific T cell clones could induce autoimmunity. In most but not all EAE models, myelin autoantigen-specific T cells, but not B cells or antibodies, are required for induction of disease[24,26,27]. However, EAE induced by one isoform of myelin oligodendrocyte glycoprotein (MOG) requires both MOG-specific T cells and MOG-specific B cells, reflecting a requirement for T cell activation via the APC function of B cells, and is referred to as B cell-dependent EAE[28].

The first indication that B cells might contribute to MS occurred decades ago with the identification of unique IgG fractions in the CSF[29] that represented antibodies produced by clonal B cell populations, which are referred to as oligoclonal bands. Oligoclonal bands are found in ~90% of all patients with MS[30] and are a diagnostic hallmark of the disease. Intrathecal B cells were later confirmed as the source of the antibodies that give rise to oligoclonal bands[31]. B cell numbers are generally increased in the CSF of patients with MS, in particular in those with contrast-enhanced lesions on MRI[32], which are indicative of acute inflammation and BBB breakdown. The levels of antigen-experienced, class-switched memory B cells and antibody-producing plasma cells are particularly elevated in the CSF (relative to their levels in blood) of patients with MS[32]. Studies of the CSF have therefore provided an important window into the B cell response in MS.

B cells can be detected in CNS lesions in early to late stages of MS, but are most abundant in active lesions of patients with RRMS compared with levels in inactive lesions and in patients with progressive MS (that is, SPMS or PPMS)[5,33]. In general, B cells are enriched in perivascular lesions and in the subarachnoid space in these individuals[5,34,35], but are sparsely present in the CNS parenchyma (FIG. 2). In 2004, ectopic lymphoid follicle-like structures containing $CD20^+$ B cells, $CD138^+$ plasma cells and follicular dendritic cells were identified in the leptomeninges of patients with SPMS[35–37], challenging


Lymph node
Antigen presentation
Peptide
MHC
TCR
B cell
Anti-CD52
T cell
Anti-CD52
Anti-CD20
IL-6
GM-CSF
TNF
Antibody
S1PR modulation
Antibody production
Blood vessel
Anti-VLA4
BBB
Perivascular space
Macrophage
Oligodendrocyte
Lesion
NAWM
Microglia
Complement
Parenchyma
Pia mater
Clonally related
Clonally related
CSF
Plasma cell
Follicular dendritic cell
Ectopic follicle-like structure
Somatic hypermutation
Oligoclonal bands
Outside-in immunopathology
Compartmentalized immunopathology

◀ Fig. 2 | **B cells in the immunopathogenesis of multiple sclerosis (MS).** B cells present antigen to T cells in peripheral secondary lymphoid tissue. Presentation of myelin-related proteins is associated with the MS risk allele *HLA-DRB1*15:01*. These T cells reciprocally activate B cells, leading to their secretion of proinflammatory cytokines, such as IL-6, granulocyte–macrophage colony-stimulating factor (GM–CSF) and tumour necrosis factor (TNF). Activated B cells and activated T cells travel to the central nervous system (CNS) in various ways, including across the blood–brain barrier (BBB). Once in the perivascular space, these activated B and T cells interact with macrophages, and can then cross the glia limitans to enter the CNS parenchyma. This infiltration of autoreactive immune cells from the periphery to the CNS can be conceptualized as 'outside-in' inflammation. Although T cells are abundant in the MS lesion parenchyma and perivascular space, most B cells are confined to the perivascular space. Microglia are the predominant immune cell at the leading edge of actively demyelinating lesions, which abuts normal-appearing white matter (NAWM). A subset of MS lesions (often referred to as pattern II) involve deposition of antibody and complement. Memory B cells, T cells and plasma cells enter the cerebrospinal fluid (CSF) through either the blood–CSF barrier or the blood–meningeal barrier. B cell aggregates are found in the pia mater overlying the cortex in all subtypes of MS. In secondary progressive MS, ectopic follicle-like lymphoid structures containing B cells, plasma cells, T cells and follicular dendritic cells are found along the meningeal pia mater. Antibody-producing memory B cells and plasma cells in the CSF of patients with MS give rise to oligoclonal bands. Persistence of lymphocytes in the CNS parenchyma, meninges and CSF can be conceptualized as 'compartmentalized' inflammation. B cells in the CSF of patients with MS are clonally related to B cells in the periphery and in the CNS parenchyma, which suggests that communication occurs between these compartments (although B cells in the CSF can undergo further somatic hypermutation). Disease-modifying therapies for MS (blocking arrows) mediate their effects largely through their actions on lymphocytes in the periphery. Anti-CD20 monoclonal antibodies predominantly deplete B cells, whereas anti-CD52 monoclonal antibodies deplete T cells and B cells. Sphingosine 1-phosphate receptor (S1PR) modulation prevents egress of T cells and B cells from lymphoid tissue, resulting in lymphopenia. Monoclonal antibodies directed against very late antigen 4 (VLA4) block the transit of B cells and T cells across the BBB.

the traditional T cell-driven view of MS pathology. Similar leptomeningeal follicle-like structures have also been demonstrated in B cell-dependent EAE[28,38]. These ectopic lymphoid tissues resemble those found in other organ-specific chronic inflammatory diseases, including the synovium in rheumatoid arthritis[39] and salivary glands in Sjögren syndrome[40]. Although ectopic follicle-like lymphoid structures have been described only in the CNS of patients with SPMS, meningeal aggregates of $CD20^+$ B cells and $CD3^+$ T cells can also be found in patients with RRMS or PPMS, and correlate with the degree of cortical demyelination[41,42]. The levels of $CD138^+$ plasma cells are also increased (particularly in the meninges) in patients with progressive MS[33]. These findings suggest a possible pathophysiological link between meningeal B cell inflammation and cortical pathology in all phenotypes of MS[43]. Several lines of evidence suggest that the CNS in patients with inflammatory diseases provides a unique environment that supports the long-term survival of B-lineage cells[44,45]. The level of B cell survival factors (such as TNF ligand superfamily member 13B, also known as BAFF or BLyS)[46,47] and chemoattractants such as stromal cell-derived factor 1 (also known as C-X-C motif chemokine ligand 12 (CXCL12)) and CXCL13 (REFS[46,48,49]) are increased in the inflamed CNS. Some data suggest that increased levels of CXCL13 in CSF correlate with a clinical response to B cell-depleting therapies[50].

The antigenic targets of B cells and pathogenic antibodies in patients with MS remain to be identified. Owing to the demyelinating nature of the disease, myelin is considered a putative autoantigen in MS. Despite extensive investigation, however, studies have yielded mixed results regarding whether patients with MS have increased levels of antibodies against myelin antigens (including MOG, myelin basic protein, proteolipid protein and myelin-derived lipids)[51–66] or other specific CNS antigens (such as inward rectifier-type potassium channel ($K_{ir}4.1$) family members, neurofascin and contactin-associated protein-like 2)[67–75]. In the past 5 years, several reports have indicated that expanded populations of plasma cells and plasmablasts from patients with MS target neurons, astrocytes and oligodendrocytes, although the precise antigens have not yet been identified[76–78]. Additionally, CSF antibody reactivity against measles, rubella and varicella–zoster viral antigens has long been noted[79,80]. The results of at least one study have suggested that oligoclonal band antibodies are not specific for CNS proteins but instead target ubiquitous self-antigens[81]. Collectively, these investigations suggest that the adaptive immune response in patients with MS is not directed at a single antigen or even a single CNS cell type. Rather, the humoral B cell response in patients with MS seems to be directed at a heterogeneous array of self-antigens and non-self antigens, which can differ greatly from one individual to another. The diversity of antigenic targets might be due to a combination of epitope spreading and secondary immune reactions to CNS cellular debris rather than a primary pathogenic response[82,83]. Furthermore, some data suggest that B cells secrete other products, besides antibodies, that are capable of killing oligodendrocytes and neurons[84,85].

The advent of immune-repertoire sequencing of the BCR from different B cell populations has provided important insights into the clonal characteristics of B cells in the blood, CSF and CNS of patients with MS. Sequencing of IgG from MS lesions and CSF samples revealed clonally expanded antibodies with preferential use of certain variable heavy (V_H) chain genes[86–93], which strongly suggests antigen-driven clonal expansion. Indeed, clonally expanded B cells in the CSF of patients with MS show evidence of somatic hypermutation indicative of localized antigen-driven affinity maturation[87,89,94–96]. Parenchymal lesions, meninges, CSF, cervical lymph nodes and blood contain partially clonally related IgG molecules, implying that multidirectional B cell exchange occurs between these compartments[32,95,97–101]. Importantly, clonal B cells persist in the CSF of patients with MS and do not seem to be affected by immunomodulatory therapies[102].

Accumulating evidence has highlighted the importance of the antigen-presenting function of B cells for T cell activation in MS (FIG. 2). Peripheral, CSF and CNS B cells in patients with MS express increased levels of T cell co-stimulatory proteins and MHC class II molecules[103–105]. Polymorphisms that alter the expression of specific gene products associated with B cell maturation and antigen presentation are associated with the risk of MS in some, but not all, patients[106]. MHC class II-restricted antigen presentation by B cells is required for the induction of clinical symptoms and characteristic pathology in models of EAE that require both B cells and T cells[13,28,107–110]. Activated B cells can present myelin and other CNS antigens to inflammatory autoreactive

Somatic hypermutation
Insertion of point mutations into the immunoglobulin gene variable (V) region, which increases antibody diversity and allows the generation of antibodies with high affinity for antigen (affinity maturation).

T cells in MS and EAE[105,111–113]. In turn, T follicular helper cells, which promote B cell proliferation and differentiation, isotype switching and antibody production in geminal centres (FIG. 1), have a key role in MS pathogenesis[114–116]. Thus, bidirectional B cell–T cell communication is crucial in both homeostasis and disease.

Treatment. The remarkable efficacy of therapies that target CD20 in patients with MS has confirmed that B cells are critical to MS pathogenesis. Treatment with anti-CD20 monoclonal antibodies, such as rituximab and ocrelizumab, results in the near-complete ablation of $CD20^+$ B cells in the blood, CSF[117] and CNS perivascular space[118] (FIG. 2), despite limited penetration of this agent across the BBB. Memory ($CD27^+$) and naive ($CD27^-$) B cells are efficiently depleted following anti-CD20 monoclonal antibody therapy[119,120]. Reconstitution occurs ontologically (FIG. 1), initially shifting towards a primarily naive ($CD27^-$) B cell phenotype[120–122]. Plasmablasts and plasma cells, the cells that produce antibodies, do not generally express CD20 (FIG. 1) and are thus not directly depleted by anti-CD20 monoclonal antibodies.

Importantly, the clinical benefit of anti-CD20 B cell depletion in MS frequently precedes reductions in total IgM and IgG levels, demonstrating that the initial therapeutic effect of anti-CD20 treatment in MS is not due to a reduction in global humoral immunity[122,123]. In patients with MS, memory B cells produce elevated amounts of proinflammatory cytokines, including IL-6, granulocyte–macrophage colony-stimulating factor and TNF, and produce decreased amounts of anti-inflammatory cytokines, such as IL-10 (REFS[121,124–127]). The IL-6 produced by B cells promotes differentiation of proinflammatory T_H17 cells[28,125], whereas the granulocyte–macrophage colony-stimulating factor they produce stimulates production of proinflammatory cytokines (IL-6 and IL-12) by myeloid cells[126]. By contrast, the IL-10 produced by IgA-secreting plasma cells might have a protective role in MS[16]. Following cessation of anti-CD20 therapy, the reconstituting B cells exhibit reduced production of proinflammatory cytokines and increased production of IL-10 (REFS[125,126]), consistent with an increased proportion of naive B cells. Studies in animal models also suggest that the immunoregulatory effects of anti-CD20 treatment are partly associated with changes in T regulatory cells and monocytes[128]. The importance of maintaining a balance between proinflammatory memory B cells and B regulatory cells in MS pathogenesis is highlighted by the failed clinical trials of atacicept, a recombinant fusion protein that blocks several B cell maturation and survival factors such as BAFF and TNF ligand superfamily member 13 (also known as APRIL)[129]. The atacicept trials in patients with MS were halted owing to an increase in relapses[130,131], which were associated with increases in the levels of memory B cells[132] and reductions in the levels of IL-10-producing B cells[133].

The results of clinical trials have taught us much about MS pathophysiology. The most effective disease-modifying therapies for MS involve ablation[122,134] or blocking the trafficking[135–138] of B cells and T cells in the periphery, which results in a substantial reduction in new CNS lesion formation and associated clinical relapses. This observation indicates that MS relapses are mediated by episodes of BBB breakdown with recruitment of peripheral lymphocytes and macrophages into the CNS, a process we refer to herein as 'outside-in' immunopathology (FIG. 2). In comparison, disease-modifying therapies for MS (including anti-CD20 therapies) have a much more modest effect on the progressive phase of the disease[139,140]. This lack of efficacy is thought to be at least partly due to sequestration (that is, compartmentalization) of some pathogenic immune responses behind an intact BBB. Although B cell and T cell numbers are reduced in the CSF of rituximab-treated patients[117], the concentrations of rituximab in CSF are approximately 1,000-fold lower than in blood[141]. In addition, oligoclonal bands in the CSF of patients with MS are not affected by treatment with anti-CD20 monoclonal antibodies[117,142]. Aggregates of B cells in the leptomeninges of patients with progressive MS are linked to subpial cortical pathology[37], and this represents another CNS-confined compartment that is difficult to target with current therapies (FIG. 2). In B cell-dependent models of EAE, intrathecal administration of anti-CD20 monoclonal antibodies partially reduced levels of B cells in the meninges and CNS parenchyma, although this reduction did not correlate with clinical improvement[143]. Attempts have been made to target B cells in poorly accessible CNS compartments by intrathecal rituximab administration in patients with progressive MS; however, this treatment resulted in only partial and transient reductions of the levels of B cells in the CSF[144–146] and had an unclear effect on the clinical course[145]. The ability to manipulate immune responses sequestered behind the BBB therefore remains an ongoing therapeutic challenge in CNS inflammatory diseases characterized by a compartmentalized pathophysiology. By contrast, systemic administration of B cell-depleting therapies can achieve sustained disease suppression in antibody-mediated CNS disorders that are mediated predominantly by immune reactions originating outside the CNS, such as in neuromyelitis optica (NMO) spectrum disorder (NMOSD).

Neuromyelitis optica spectrum disorder

NMOSD is a rare inflammatory demyelinating disorder that predominantly affects the spinal cord, optic nerves and brainstem, and less frequently affects the brain[147]. Soon after the first reports were published in the late nineteenth century[148,149], NMOSD was considered a clinical variant of MS, the most common CNS inflammatory demyelinating disease[150]. In 2004, most patients with NMOSD were found to have elevated serum levels of IgG1 antibodies, a T cell-dependent antibody subclass, and it was found that these antibodies bound to structures adjacent to the CNS microvasculature and pia mater[151,152]. Subsequently, aquaporin 4 (AQP4), a membrane-bound water channel expressed abundantly on astrocyte end-feet, was identified as the target antigen of these antibodies (also called NMO-IgG). Accordingly, NMOSD was recognized to be primarily a humoral autoimmune disease, and was redefined as a disease entity distinct from MS[152,153].

Although NMOSD can mimic the clinical presentation of MS, NMOSD differs from MS in its epidemiology

and pathogenesis. NMOSD has an estimated prevalence of 0.1–4.4 cases per 100,000 individuals[147], more than 30-fold fewer than MS, and therefore has been designated as an orphan disease. About 85% of anti-AQP4-seropositive patients with NMOSD are female[154], compared with the 3:1 female–male ratio in MS. Unlike patients with RRMS, who typically experience mild relapses with good recovery, patients with NMOSD have an increased frequency and severity of relapses with incomplete recovery and an increased likelihood of death[147]. A secondary progressive phase, which occurs commonly in MS, is rare in NMOSD.

Pathophysiology. NMOSD exhibits a primarily outside-in immunopathology (FIG. 3). Anti-AQP4 IgG1 antibodies are present in the serum of 70–90% of patients with NMOSD[155,156] and titres are up to 1,000-fold higher in blood than in CSF[157]. CSF and peripheral B cell V_H sequences are aligned with one another[158], and CSF oligoclonal bands are present in only 15–30% of patients with NMOSD[147]. Anti-AQP4 IgG-producing B cells seem to arise from naive autoreactive B cells owing to defects in central and peripheral tolerance but require somatic hypermutation for AQP4 binding[159].

NMOSD and MS have distinct histopathological features[160]. Antibody and complement deposition in association with astrocyte loss is a key feature of NMOSD lesions. Unlike MS lesions, those associated with NMOSD are characterized by an abundance of neutrophils and eosinophils, with few lymphocytes[161,162] (FIG. 3). Numbers of neutrophils, which are not detected in normal CSF, are elevated in the CSF of patients with NMOSD and are associated with elevated levels of IL-17, a neutrophil-attracting proinflammatory cytokine[163]. In addition, levels of T_H17 cells are increased in the peripheral blood of patients with NMOSD[164], and AQP4-specific T cells in such patients exhibit T_H17 cell polarization[165], which suggests that NMOSD is a T_H17 cell-associated disease. This idea is further supported by the fact that IFNβ therapy, a common therapy for MS, increases relapse rates in patients with NMOSD[166,167] possibly by increasing levels of IL-17 (REF.[168]). The levels of a number of other proinflammatory cytokines are elevated in the CSF in patients with NMOSD[169], including IL-6, the level of which is elevated in the CSF during disease exacerbations[170,171]. IL-6 promotes the development and maintenance of T_H17 cells[172] and stimulates plasma cell development and antibody production[173,174]. These data provided the rationale for clinical trials of anti-IL-6 receptor monoclonal antibodies, such as satralizumab and tocilizumab, which have been shown to reduce relapse rates in patients with NMOSD[175].

The pathogenicity of anti-AQP4 antibodies (which are predominantly IgG1, a T cell-dependent isotype) has been demonstrated both in vitro and in vivo. Anti-AQP4 IgG causes CDC in transfected cells[176–179], and intracerebral injection of AQP4-specific IgG along with complement in rodents causes demyelination resembling the lesions associated with NMOSD[178]. Peripheral administration of anti-AQP4 IgG together with either pathogenic T cells[180] or human complement promotes the development of NMOSD-like CNS lesions in rodents[178]. Moreover, high-dose systemic administration of anti-AQP4 IgG can directly induce CNS pathology, although this effect is enhanced in the presence of T cells[181]. AQP4-specific IgG also promotes antibody-dependent cellular cytotoxicity[182]. Most data, however, indicate that the presence of anti-AQP4 antibodies is not pathogenic in the absence of CNS inflammation.

Although AQP4 is most strongly expressed in the CNS, it is also present in epithelial cells in the kidney (collecting duct), stomach (parietal cells), airways, salivary glands and skeletal muscle[183]. Despite rare reports of myositis in patients with NMOSD, peripheral organ damage does not typically occur, which raises the question of why AQP4-specific IgG selectively targets the CNS. As described for CNS tissue injury by AQP4-specific antibodies, cell-mediated inflammation could be a prerequisite for peripheral organ damage by AQP4-specific antibodies[180,184]. Another compelling explanation for CNS organ selectivity is the high expression of complement inhibitory proteins in peripheral tissues[185], which protects AQP4-expressing cells in the periphery from CDC[183]. Lastly, the unique organization of AQP4 into orthogonal arrays of particles in astrocytes seems to influence anti-AQP4 IgG binding and CDC[186].

To date, the triggers for NMOSD remain elusive, although environmental factors such as gut bacteria have been suggested to play a crucial part[187–189]. One study reported an increased abundance of *Clostridium perfringens* in patients with NMOSD[187]. The ATP-binding cassette transporter of *C. perfringens* shares sequence homology with AQP4 and is able to stimulate AQP4-specific $CD4^+$ T cells from patients with NMOSD, which suggests that molecular mimicry might contribute to the pathogenesis of NMOSD[165,187,189] (FIG. 3).

Treatment. Owing to the high morbidity associated with NMOSD exacerbations, immunosuppressive therapy is typically started soon after the first attack[147,190,191]. Several immunomodulatory agents used in patients with MS, including IFNβ[166,167], natalizumab[192] and fingolimod[193], can precipitate exacerbations of NMOSD, highlighting the distinct immunopathological features of these two diseases. The importance of complement in NMOSD lesion development served as the foundation for development of the complement inhibitor eculizumab, which showed remarkable efficacy in clinical trials[194,195] and became the first approved medication for NMOSD. B cell depletion using anti-CD20 (REFS[196,197]) and anti-CD19 (REF.[198]) monoclonal antibody therapies is very effective in NMOSD. However, despite the pathogenic role of AQP4-specific autoantibodies in NMOSD, therapeutic responses following B cell-depleting therapy do not necessarily correlate with reductions in peripheral antibody titres[197,199,200], indicating that factors in addition to anti-AQP4 IgG are required for mediating NMOSD pathophysiology[201] (FIG. 3).

MOG antibody-associated disorder

We now recognize that the clinical presentation and prognosis of AQP4-seronegative and AQP4-seropositive patients with NMO frequently differ[202–204]. Anti-MOG antibodies are rarely detected in patients

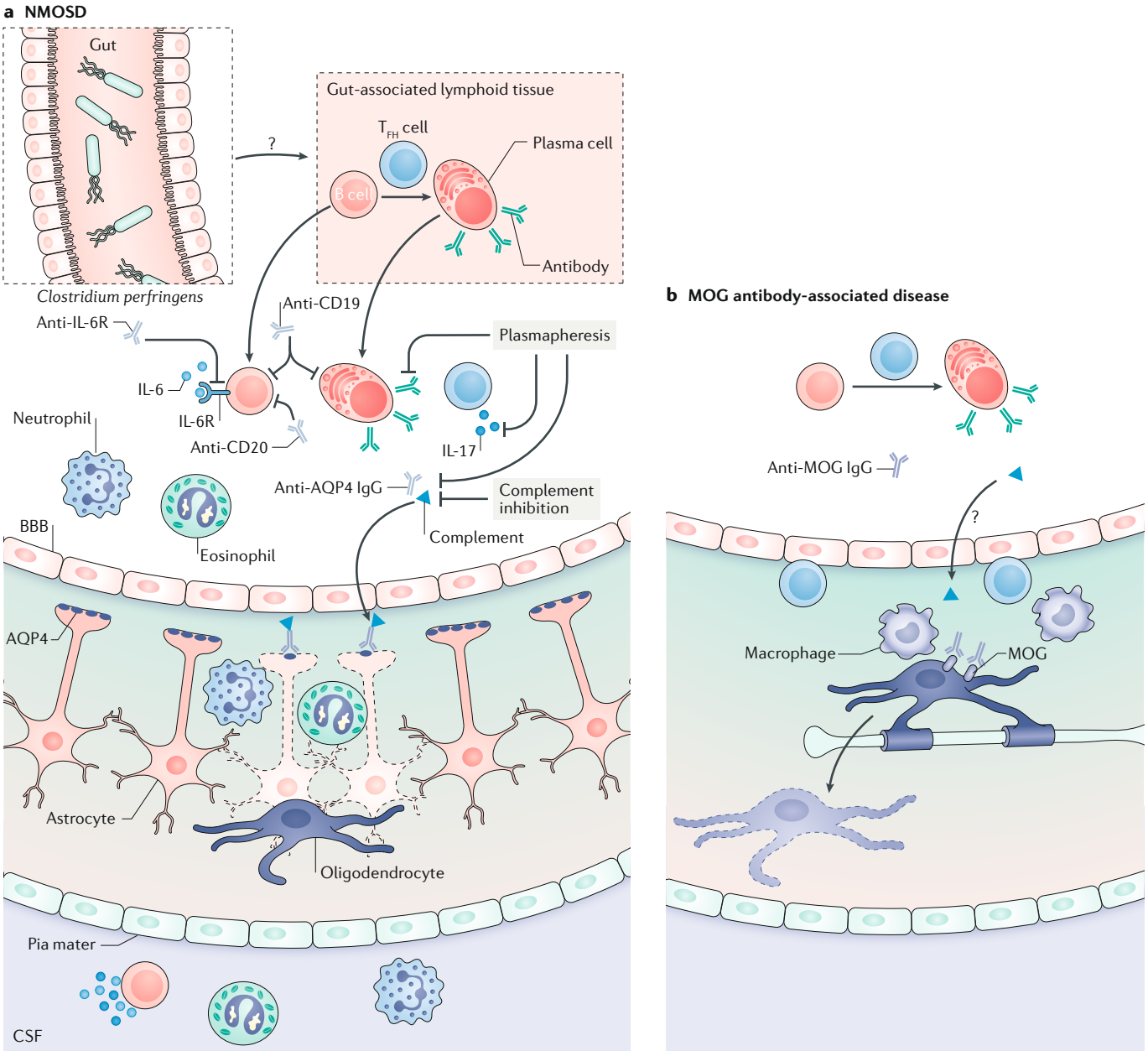


Fig. 3 | **B cell-mediated pathogenesis of neuromyelitis optica spectrum disorder (NMOSD) and myelin oligodendrocyte glycoprotein (MOG) antibody-associated disease. a** | In the lymph nodes of patients with NMOSD, aquaporin 4 (AQP4)-specific B cells differentiate into anti-AQP4 antibody-secreting plasma cells generated through interactions with proinflammatory CD4$^+$ T cells, such as T follicular helper cells (T_{FH} cells), which are also specific for AQP4. The gut microbiota, such as an overabundance of *Clostridium perfringens*, might influence the development of NMOSD, possibly through molecular mimicry of AQP4-specific T cells. The levels of proinflammatory IL-6 and IL-17 are increased in the periphery and cerebrospinal fluid (CSF). IL-6 is also important for plasma cell development. Anti-AQP4 IgG antibodies, along with complement, eosinophils and neutrophils, cross the blood–brain barrier (BBB), where they bind to AQP4 (denoted by blue symbols) on astrocyte end-foot processes. This inflammatory response causes an AQP4-mediated astrocytopathy that leads to secondary demyelination and neurological impairment. Plasmapheresis, which is sometimes used to treat short-term relapse in patients with NMOSD, helps to clear soluble proteins, including IgG, proinflammatory cytokines and complement, from the blood. Several disease-modifying therapies for NMOSD target B cells in the periphery (blocking arrows). Anti-CD20 monoclonal antibodies deplete most B cells, including memory B cells (but not plasma cells). Anti-CD19 monoclonal antibodies also deplete anti-AQP4 IgG-producing plasmablasts. Anti-IL-6 receptor (anti-IL-6R) monoclonal antibodies block the proinflammatory effects of IL-6, including IL-6-stimulated antibody production by plasma cells. Complement can also be blocked through anti-complement monoclonal antibodies, such as eculizumab. **b** | In MOG antibody-associated spectrum disorder (MOGSD), MOG-specific T_{FH} cells promote differentiation of MOG-specific B cells into anti-MOG antibody-secreting plasma cells outside the central nervous system (CNS). Upon CNS inflammation, thought to be caused by proinflammatory MOG-specific T cells and macrophages, anti-MOG antibodies enter the CNS and bind to MOG, where they cause oligodendrocyte damage and demyelination. However, it is not yet known whether complement participates in the pathogenesis of MOGSD. Steroids and plasmapheresis are used for the treatment of MOGSD but it is not clear whether B cell depletion is as effective in MOGSD as it is in NMOSD.

with MS[205–208] but have been identified in up to 50% of patients with AQP4-seronegative NMOSD[66,209–217] and in 40–47% of paediatric patients with acute demyelinating encephalomyelitis[205,218,219]. Indeed, more diseases are associated with anti-MOG antibodies than with anti-AQP4 antibodies. Besides causing opticospinal disease resembling NMOSD, anti-MOG antibodies have been identified in association with atypical presentations of optic neuritis[220], cortical encephalitis and seizures[221–223], a leukodystrophy-like presentation in children[224] and meningitis with intracranial hypertension[225]. Currently, no consensus has been reached with regard to the nomenclature of diseases associated with anti-MOG antibodies. Accordingly, given the diversity of clinical phenotypes, we introduce the term 'MOG spectrum disorder' (MOGSD) to refer to this group of diseases.

Pathophysiology. MOG is expressed exclusively within the CNS and is located on the outer lamella of the myelin sheath[226]. MOG is a well-known autoantigen in EAE[227–229]. Histological analysis of CNS tissue samples from a limited number of anti-MOG-seropositive patients with encephalitis identified numerous myelin-filled macrophages in areas of demyelination, with deposition of IgG and activated complement[230,231]. The composition of these lesions more closely resembles the most common MS lesion type (pattern II) than it does the lesions found in AQP4-seropositive patients with NMOSD[232]. These pathological findings are consistent with observations that anti-MOG antibodies are typically of the IgG1 isotype[205], which can activate complement and promote CDC. In animal models, the presence of anti-MOG IgG alone is insufficient to elicit CNS inflammation and demyelination[233]. Despite the presence of complement in CNS lesions of anti-MOG-seropositive patients, patient-derived anti-MOG antibodies demonstrate a limited ability to initiate complement-mediated demyelination either in vitro[179,218,234] or in vivo in animal models[235,236]. Pathogenicity of anti-MOG IgG in animal models has been demonstrated primarily when antibody transfer is accompanied by CNS inflammation induced by myelin-specific T cells[28,236]. These data highlight the importance of the cellular and humoral arms of the adaptive immune system in MOG antibody-associated CNS autoimmunity. The heterogeneity of MOGSD clinical phenotypes might reflect, in part, differences in the relative contribution of MOG-specific antibodies, complement and T cells.

Despite the increasing number of conditions associated with anti-MOG antibodies, the immune triggers remain largely unknown. Disease onset or relapse is often preceded by infections or vaccination[237,238], suggesting the existence of peripheral immune triggers. Only a minority of anti-MOG-seropositive patients have detectable antibodies in CSF[215,239], and most have a normal IgG index and no oligoclonal bands, indicating that MOGSD has an outside-in pathophysiology similar to that of anti-AQP4 NMOSD. Although MOG antibody-positive patients respond to steroids and plasmapheresis, it is not clear that B cell depletion is as effective as in NMOSD[238].

Table 1 | **Overview of autoantibody targets in autoimmune encephalitis syndromes**

Autoantibody target	Clinical presentation	Refs
N-Methyl-D-aspartate receptor (specifically the NR1 subunit)	Psychosis, seizures, memory deficits, autonomic dysfunction	243–245
Leucine-rich glioma-inactivated protein 1 (LGI1)	Memory deficits, confusion, seizures	310,311
Contactin-associated protein-like 2 (CASPR2)	Cognitive changes, cerebellar symptoms, autonomic dysfunction, insomnia, neuropathic pain, weight loss	311
AMPA receptor (specifically glutamate receptors 1 and 2)	Memory deficits, confusion, seizures	312
GABA receptors (specifically types A or B)	Memory deficits, confusion, seizures	313
IgLON family member 5 (IGLON5)	Sleep disorder, bulbar symptoms, cognitive impairment	314
Dipeptidyl peptidase-like protein 6 (DPPX)	Gastrointestinal sympoms, hyperexcitability (agitation, tremor, seizures, myoclonus), cognitive dysfunction, memory deficits	315
Glycine receptor	Progressive encephalomyelitis, rigidity and myoclonus	316,317
Glutamic acid decarboxylase	Progressive encephalomyelitis, rigidity and myoclonus	318
Metabotropic glutamate receptor 5 (MGLUR5)	Movement disorder, sleep dysfunction, seizures	319

Anti-*N*-methyl-D-aspartate receptor encephalitis

The autoimmune encephalitides constitute a group of inflammatory brain diseases characterized by prominent neuropsychiatric symptoms associated with antibodies that target neuronal proteins[240]. Antibodies to more than ten CNS targets have been identified for encephalitides of various phenotypes (TABLE 1). The annual incidence of all types of antibody-mediated encephalitis is approximately 5–8 cases per 100,000 (REF.[240]). As for acute demyelinating encephalomyelitis, CNS viral infections are well-known causes of encephalitis[241]. In many patients, however, the cause is unknown[241,242].

In 2007, Dalmau and colleagues first described an encephalitis syndrome characterized by memory deficits, psychiatric symptoms and decreased consciousness that occurred in young women with ovarian teratomas and was associated with antibodies targeting the NR1 subunit of *N*-methyl-D-aspartate receptors (NMDARs)[243–245], a subclass of neuronal excitatory glutamate receptors. The prevalence of autoimmune encephalitis is now recognized to be similar to that of infectious encephalitis; anti-NMDAR encephalitis, which affects predominantly children and young adults, is among the most common forms[242].

Autoimmune encephalitis syndromes mediated by autoantibodies that target cell-surface CNS antigens are associated with humoral immunity, such as anti-NMDAR encephalitis. By contrast, cytotoxic T cells, which recognize processed antigens, have a prominent role in autoimmune encephalitis syndromes associated with immune responses to intracellular antigens, such as anti-Hu encephalitis[240].

Pathophysiology. Two reported clinical conditions can lead to anti-NMDAR encephalitis. More than half of patients with anti-NMDAR encephalitis have a history of malignancy, most often young women with ovarian

teratoma, which contains neuronal tissue that expresses NMDARs[245]. Evidence indicates that this ectopic NMDAR expression serves as the stimulus for NMDAR-specific peripheral B cell and T cell responses (FIG. 4). A smaller proportion of anti-NMDAR encephalitis cases occur following encephalitis caused by the neurotropic virus herpes simplex virus 1 (HSV-1)[246–248]. Virus-induced neuronal damage and the associated

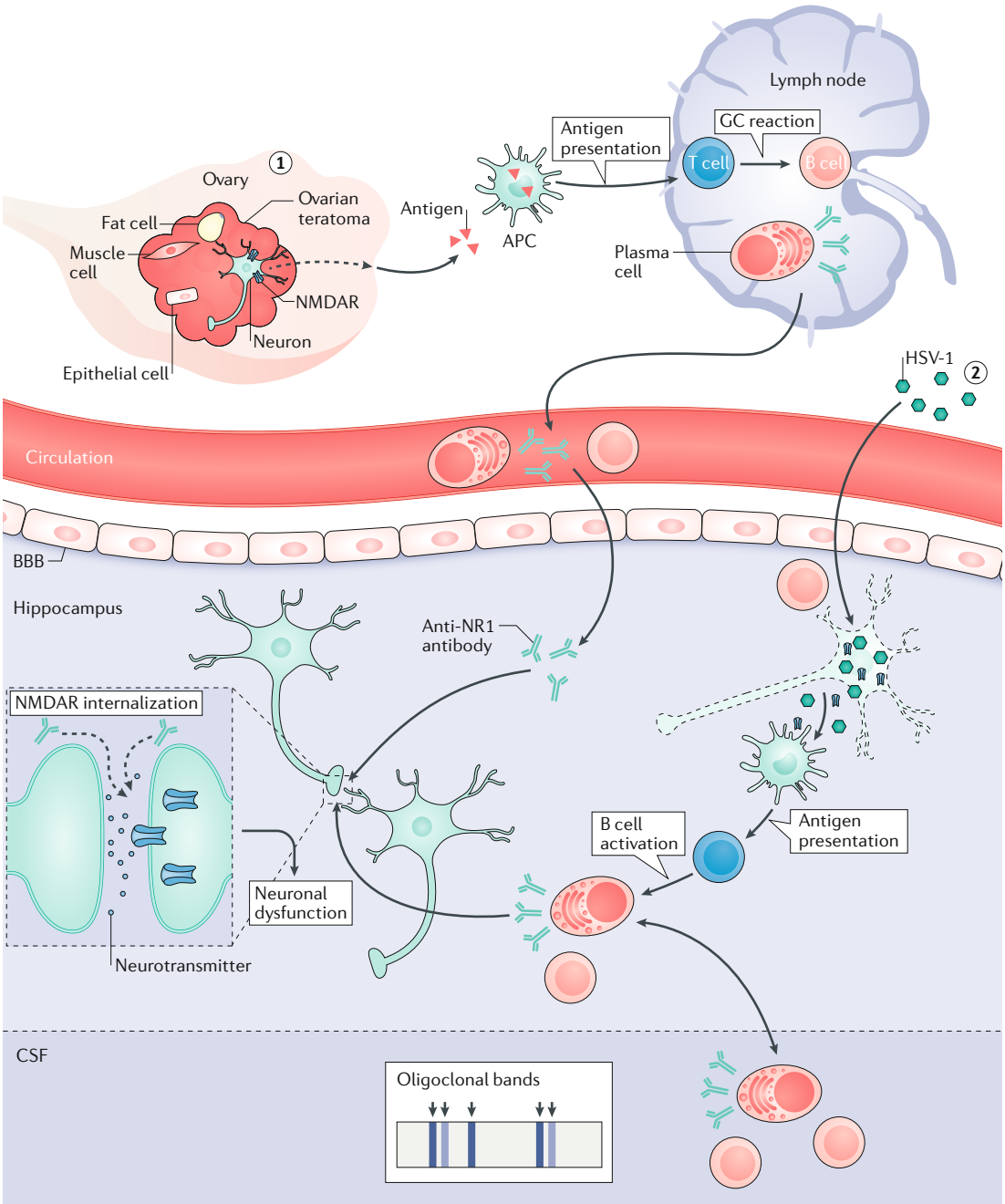


Fig. 4 | **Anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis.** This autoantibody-mediated encephalitis syndrome is caused either by a peripheral tumour (most commonly ovarian teratoma) that ectopically expresses NMDARs (1) or by neuronal injury secondary to herpes simplex virus 1 (HSV-1) encephalitis (2). Tumour cells are taken up by antigen-presenting cells (APCs), which activate NMDAR-specific B cells and T cells in local draining lymph nodes. In addition, lymphocytes and APCs might directly infiltrate peripheral tumours, leading to local antigen-specific immune responses within the teratoma (not shown). Anti-NMDAR-specific B cells and antibodies then travel to the central nervous system (CNS). Alternatively, the neuronal injury caused by HSV-1 encephalitis can release both viral and neuronal antigens, including NMDARs. As a result of epitope spreading, uptake of these antigens by local APCs leads to activation of NMDAR-specific B cells and T cells in the CNS. The presence of autoantibodies directed against NMDARs in the CNS leads to internalization of NMDARs and neuronal dysfunction (central part). In both scenarios, NMDAR-specific B cells and plasma cells are enriched in the CNS. Titres of anti-NMDAR antibodies are typically higher in the cerebrospinal fluid (CSF) than in plasma, and oligoclonal bands are frequently present, suggesting that the autoimmune process is largely compartmentalized within the CNS. BBB, blood–brain barrier; GC, germinal centre.

CNS tissue inflammation presumably causes release of NMDARs, which trigger NMDAR-specific T cell and B cell immune responses within the CNS.

Compelling clinical and laboratory evidence supports the pathogenicity of anti-NMDAR antibodies in patients with anti-NMDAR encephalitis. High titres of anti-NR1 antibodies in CSF are generally correlated with worse clinical outcomes in affected patients[249]. However, neuronal and synaptic loss do not occur to a clinically significant extent in anti-NMDAR encephalitis, and no evidence indicates the presence of either CDC or antibody-dependent cellular cytotoxicity[250,251]. Rather, the pathogenicity of anti-NR1 antibodies seems to result from crosslinking of surface NMDARs, leading to their reversible internalization and subsequent neuronal hypofunction[240,252]. Anti-NR1 antibodies localize to the synapses and cause a reversible decrease in NMDAR density in rodent antibody transfer models[245,252–256]. Intraventricular injection of anti-NMDAR IgG from patients with anti-NMDAR encephalitis produces memory deficits, anhedonia and depression-like behaviours in mice[255,257].

Numerous B cells and plasma cells are found, along with T cells, in perivascular and interstitial spaces in the CNS of patients with anti-NMDAR encephalitis[240,256,258], although lymphocyte levels are generally low in CNS parenchymal lesions[250,251]. Unlike in NMOSD, in which anti-AQP4 antibody levels are higher in serum than in the CSF, anti-NMDAR antibodies are more reliably detected in the CSF than in serum[245,249]. Clonally expanded NMDAR-specific plasma cells have also been detected in the CSF of patients with anti-NMDAR encephalitis[256], and B cells in the CSF of these individuals can produce anti-NR1 antibodies[254]. Furthermore, CSF oligoclonal bands are also frequently detected in individuals with anti-NMDAR encephalitis[245,258]. Plasmapheresis is often ineffective in individuals with anti-NMDAR encephalitis[259], in contrast to patients with disorders such as NMOSD and myasthenia gravis, in which antibody production occurs in the periphery. Although malignancy-associated NMDAR-specific immunity is similarly triggered peripherally, these findings collectively highlight an NMDAR-specific B cell response that becomes compartmentalized in the CNS in both tumour-associated and virus-associated anti-NMDAR encephalitis (FIG. 4).

Neurodegenerative diseases

Understanding how the immune system participates in the pathogenesis of neurodegenerative diseases, including Parkinson disease (PD), Alzheimer disease (AD), amyotrophic lateral sclerosis, frontotemporal dementia and some leukodystrophies, has attracted substantial interest. Here we focus on PD and AD, two of the most common CNS neurodegenerative diseases, each of which is associated with characteristic CNS pathology. Although not associated with inflammation in the CSF[260,261], activation of the innate immune system, in particular microglia, is strongly implicated in the pathogenesis of both PD and AD[262,263]. Whether the adaptive immune system contributes to these disorders is an area of active research. Here we review evidence supporting the potential roles of B cells and humoral responses in PD and AD.

Parkinson disease. PD is the second most common neurodegenerative disorder (after AD), and is characterized by movement abnormalities, often accompanied by cognitive impairment. The pathological hallmark of PD is intracellular aggregations of α-synuclein termed 'Lewy bodies', which result in neuronal toxicity.

Indirect evidence supports the involvement of adaptive immunity in PD. Specific HLA variants (*HLA-DRA* and *HLA-DRB1*) are associated with PD[264,265], and α-synuclein-specific T cells might be involved in the pathogenesis of PD[266]. By contrast, β-synuclein-reactive T cells have been linked to grey matter pathology in a rat model of MS[267]. The levels of activated T cells are also increased in the CSF of patients with PD[268], and T cells are detectable in the midbrains of these patients[269]. A potential role for B cells in PD is also emerging. Although B cells have not been detected in the brains of patients with PD[269], deposits of IgG are found on dopaminergic neurons in these patients, and Lewy bodies themselves are coated with IgG[270], which suggests that dopaminergic neurons might be targeted by these immunoglobulins (FIG. 5). Some data suggest that levels of anti-α-synuclein antibodies are increased in the blood[271–274] and CSF[275,276] of patients with PD. Antibodies that target nitrated α-synuclein are elicited following injection of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (a toxin that targets dopaminergic neurons) into mice[277], although no pathogenic role has been identified for such antibodies. Bulk IgG obtained from patients with PD caused selective dopaminergic neuron loss in passive transfer experiments compared with IgG from control individuals, although the precise specificities of the transferred IgG antibodies were not defined[278]. B cell levels might be reduced in patients with PD[279,280], which could be linked to alterations in the expression of B cell-related genes[272,281]. Expression of *LRRK2* (encoding dardarin, also known as leucine-rich repeat serine/threonine-protein kinase 2), a gene linked to familial PD, is increased in B cells in patients with PD[282] and is associated with altered B cell function in mice[283]. Despite increasing evidence of a potential role for B cells in PD, it is unclear whether the observed changes in adaptive immunity are causal or are secondary to the CNS injury associated with its pathogenesis. Early clinical trials are under way to determine whether treatment with anti-α-synuclein monoclonal antibodies benefits patients with PD[284].

Alzheimer disease. AD is the most common type of dementia and presents with progressive memory loss and cognitive impairment that ultimately proves fatal. AD is characterized by extracellular amyloid-β (Aβ) plaques, intracellular neurofibrillary tangles containing hyperphosphorylated tau and neuronal loss in the CNS grey matter. A prominent role for the innate immune system in AD has been recognized: areas of AD plaques contain an increased number of activated microglia containing intracellular Aβ[262]. By contrast, limited evidence supports a pathogenetic role of the adaptive immune system, including B cells, in AD. Certain HLA alleles, including *HLA-DRB1*15:01*, are associated with an elevated risk of developing AD[285]. Reductions in the levels of peripheral B cell subsets have been detected in some patients with

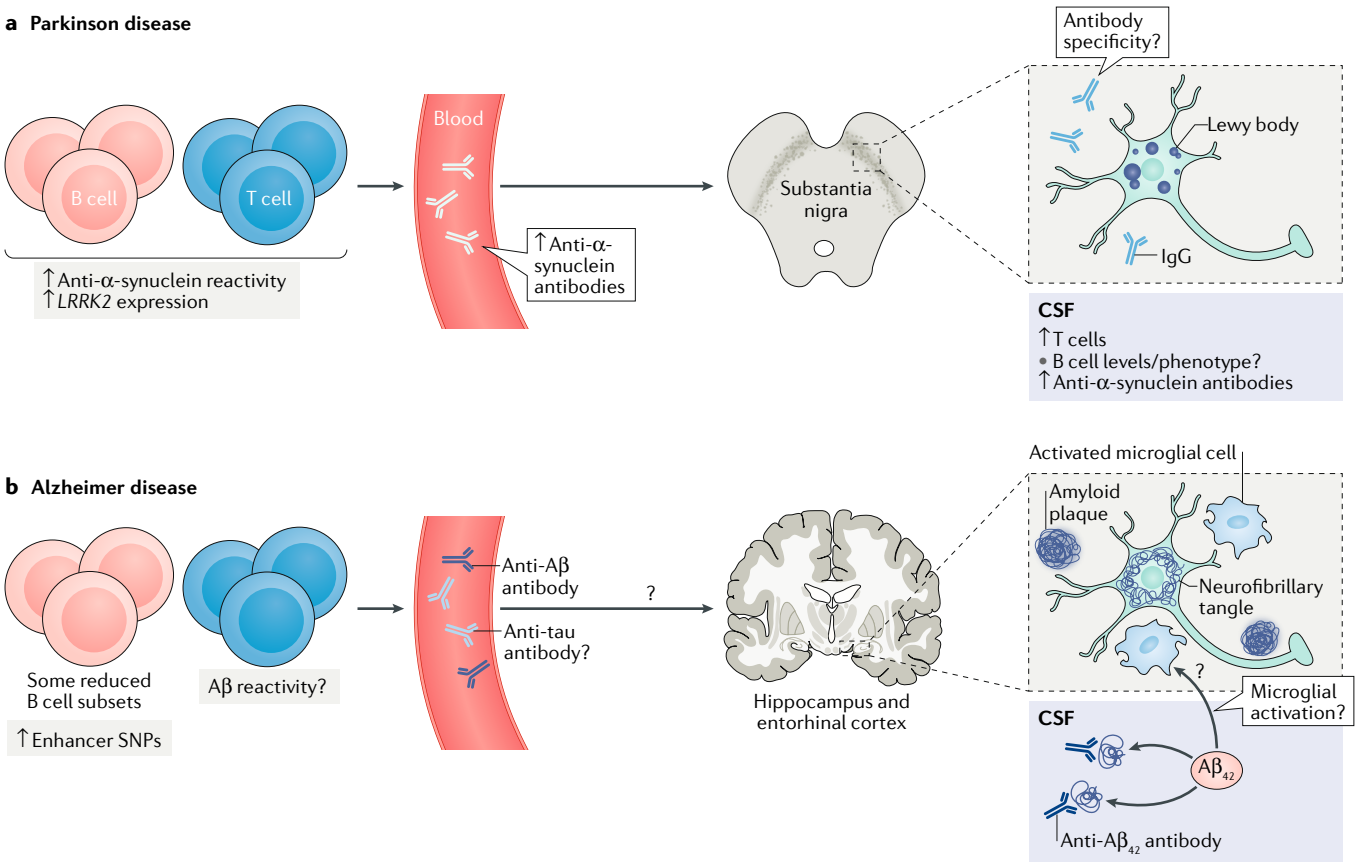


Fig. 5 | **Potential roles for B cells in neurodegenerative disorders. a** | B cell levels can be reduced in patients with Parkinson disease (PD) despite increased numbers of α-synuclein-specific T cells and B cells in the blood. Expression of the *LRRK2* gene, which is linked to familial PD, is increased in both T cells and B cells of patients with PD. Anti-α-synuclein antibodies are present in the blood and cerebrospinal fluid (CSF) of patients with PD, but it is unclear whether these are identical to the antibodies that bind to neurons in the substantia nigra and Lewy bodies in these individuals. Although the levels of T cells are also increased in the CSF of patients with PD, whether B cells or antibodies in the CSF of these individuals possess any unique features is unclear. **b** | Some patients with Alzheimer disease (AD) have reductions in the levels of specific B cell subsets, which might be linked to B cell genetic abnormalities. A role for amyloid-β (Aβ)-specific T cells in AD is hypothesized but remains unexplored. Anti-Aβ and anti-tau antibodies are present in the blood in many individuals, but it is unclear whether their levels are increased in patients with AD. Aβ-specific antibodies can also be present in the CSF, but similarly it is unclear whether their levels are increased in patients with AD. The levels of antibodies directed against $Aβ_{42}$, the most neurotoxic species of Aβ, are also increased in the CSF of patients with AD, and this might explain the reduction in CSF levels of soluble (free) $Aβ_{42}$ observed in these individuals. Anti-Aβ antibodies might promote microglial activation in patients with AD, but this hypothesis remains unconfirmed. SNPs, single-nucleotide polymorphisms.

AD[286–288] and might be linked to genetic changes in these cells[289]. In addition, conflicting reports describe either pathogenic[280] or protective[281] effects of B cells in mouse models of AD. The increasing evidence that infections with herpesviruses and other pathogens might be associated with AD is also worthy of note, and these associations could be an additional link to the adaptive immune system[290].

Antibodies directed against Aβ or tau can be used to visualize their target antigens in AD brain tissue[291,292], although little evidence suggests that these antibodies can cross the BBB in vivo. Reports of whether levels of antibodies against $Aβ_{42}$ (the most aggregation-prone and neurotoxic species of Aβ) in either serum or CSF differ between patients with AD and healthy control individuals have been very inconsistent[286,293–296]. These inconsistencies might be related to increased binding of anti-Aβ antibodies to $Aβ_{42}$ in patients with AD, which would lead to reductions in the levels of both free antibody and unbound antigen[297] (FIG. 5). Such a phenomenon could account for the observed reduction in the levels of soluble $Aβ_{42}$ in the CSF of patients with AD, which supports a potential therapeutic benefit of anti-Aβ antibody therapy. Indeed, intracerebral administration of anti-Aβ antibodies in AD-prone animals led to clearance of Aβ plaques, which was at least in part due to effects on microglia[298]. The presence of anti-Aβ antibodies in healthy individuals was the basis for clinical trials of intravenous immunoglobulin (IVIG)[299], a mixture of polyclonal antibodies from numerous donors, in patients with AD. Similarly to the results of studies involving purified anti-Aβ monoclonal antibody, injection of IVIG into the CNS in animal models of AD led to Aβ clearance and microglial activation[300]. Although IVIG treatment did not slow cognitive decline due to AD in human phase III clinical trials, treated individuals

showed a reduction in serum $A\beta_{42}$ levels compared with placebo-treated patients[301].

Additional immune-based strategies have been attempted to clear toxic forms of Aβ in patients with AD. One clinical trial of Aβ immunization (that is, vaccination) was halted owing to the development of T cell-associated meningoencephalitis in a subset of patients with AD[302,303]. The patients who developed this treatment-related complication demonstrated T cell immunity against Aβ, which was more common in patients carrying the *HLA-DRB1*15:01* allele[304].

Unfortunately, clinical trials of Aβ plaque clearance strategies using anti-Aβ monoclonal antibodies in patients with mild-to-moderate AD have not clearly led to clinical improvements[305–307]. These studies might have failed because in these participants the disease process was too advanced for them to benefit from plaque clearance, or alternatively these failures might represent insufficient understanding of the pathophysiological and therapeutic relevance of the humoral response in AD. Collectively, the evidence for a prominent role of B cells in AD pathogenesis remains unsubstantiated and warrants further research.

Conclusions

Appreciation for the contribution of B cells to CNS inflammatory diseases and their potential role in CNS neurodegenerative diseases has grown markedly. The role of B cell responses differs considerably between different CNS disorders. B cells can have a primary role in the initiation of CNS inflammation, such as in antibody-mediated disorders like NMOSD and tumour-associated NMDAR encephalitis. In other diseases, antigen release following an initial CNS injury leads to an antibody response that develops into CNS autoimmunity (that is, by epitope spreading), as occurs in HSV-associated NMDAR encephalitis. Finally, unique populations of antibodies are present in the CSF of patients with MS, and the available evidence suggests that antibody reactivity in these patients is directed against a diverse array of CNS autoantigens[61,76,78] and non-specific cellular debris[81,82]. Thus, the antibody response in MS is complex and could comprise a combination of pathogenic and non-pathogenic specificities.

We have compared MS and antibody-mediated neurological disorders in terms of either peripheral autoimmune effectors that originate outside the CNS (outside-in immunopathology) or autoimmune reactions confined to the CNS itself (compartmentalized immunopathology). However, we emphasize that these two paradigms are not mutually exclusive and both processes might occur at the same time or consecutively. Nonetheless, it is beneficial to keep these distinctions in mind as they are likely to have clinical and therapeutic relevance. For instance, although relapses in patients with NMOSD can cause sustained severe neurological injury, there is no evidence that these individuals develop a progressive neurologic decline independent of attacks, consistent with an outside-in-driven process. True remission of NMOSD might therefore be possible with use of peripheral immune-targeted therapies. By contrast, the compartmentalized CNS immune response occurring in patients with MS continues to be a major therapeutic challenge, as it is believed to drive cortical pathology and progressive disability[41,42].

In the inflammatory CNS disorders in which B cells clearly have a pathogenic role, determining the causes of failure of immune tolerance is paramount for establishing appropriate treatment. For example, in individuals with NMDAR encephalitis, peripheral tolerance can be broken by ectopic CNS antigen expression in an ovarian teratoma. In such patients, treatment is directed at prompt removal of the tumour, which is adequate to extinguish the autoimmune process in some individuals. NMDAR encephalitis can also occur following HSV encephalitis, probably as a result of epitope spreading, which leads to the generation of populations of autoreactive B cells distinct from those that respond to viral antigen. In these patients, even after clearance of the viral antigen, further immunosuppressive therapy might be required to treat the secondary autoimmune response.

The uncertain relevance of autoantibodies in PD and AD highlights the need for caution in interpreting their potential contributions to disease. Autoantibodies can be generated as a secondary response to cellular injury[83] and might not contribute to pathogenesis. Changes in the peripheral B cell compartment in these neurodegenerative disorders could be related to genetic factors, but their biological relevance is currently unclear. Several criteria must be fulfilled to establish a pathogenetic contribution of B cells to these conditions. First, it is important to define which B cells are related to the disease process. Sequencing of antibodies and B cells in multiple tissues, such as brain, CSF and blood, could be needed to identify disease-relevant clonotypes and detect disease-specific compartmentalization. Second, the antigen specificity of those B cell clonotypes must be determined. Screening for reactivity to prototypic disease-specific markers (such as Aβ, phosphorylated tau and α-synuclein) as well as unbiased antigen discovery approaches[308] should be informative. Third, B cell phenotyping and antibody transfer studies in relevant animal models can be instrumental in confirming the pathogenicity of candidate B cells and their corresponding antibodies. Further defining the roles of B cells using these approaches is expected to facilitate the development of novel therapies for these neurodegenerative conditions.

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1. Engelhardt, B., Vajkoczy, P. & Weller, R. O. The movers and shapers in immune privilege of the CNS. *Nat. Immunol.* **18**, 123–131 (2017).
2. Louveau, A. et al. Understanding the functions and relationships of the glymphatic system and meningeal lymphatics. *J. Clin. Invest.* **127**, 3210–3219 (2017).
3. Anthony, I. C., Crawford, D. H. & Bell, J. E. B lymphocytes in the normal brain: contrasts with HIV-associated lymphoid infiltrates and lymphomas. *Brain* **126**, 1058–1067 (2003).
4. Kowarik, M. C. et al. Immune cell subtyping in the cerebrospinal fluid of patients with neurological diseases. *J. Neurol.* **261**, 130–143 (2014).
5. Machado-Santos, J. et al. The compartmentalized inflammatory response in the multiple sclerosis brain is composed of tissue-resident $CD8^+$ T lymphocytes and B cells. *Brain* **141**, 2066–2082 (2018).
This study provides in-depth immunohistochemical characterization of different lymphocyte subsets within MS lesions and in other neurological conditions.
6. Louveau, A. et al. Structural and functional features of central nervous system lymphatic vessels. *Nature* **523**, 337–341 (2015).

7. Prinz, M. & Priller, J. The role of peripheral immune cells in the CNS in steady state and disease. *Nat. Neurosci.* **20**, 136–144 (2017).
8. Seifert, M. & Küppers, R. Human memory B cells. *Leukemia* **30**, 2283–2292 (2016).
9. Thaler, F. S. et al. Abundant glutamic acid decarboxylase (GAD)-reactive B cells in GAD-antibody-associated neurological disorders. *Ann. Neurol.* **85**, 448–454 (2019).
10. Halliley, J. L. et al. Long-lived plasma cells are contained within the $CD19^{-}CD38^{hi}CD138^{+}$ subset in human bone marrow. *Immunity* **43**, 132–145 (2015).
11. Lanzavecchia, A. Antigen-specific interaction between T and B cells. *Nature* **314**, 537–539 (1985).
12. Constant, S., Schweitzer, N., West, J., Ranney, P. & Bottomly, K. B lymphocytes can be competent antigen-presenting cells for priming $CD4^{+}$ T cells to protein antigens in vivo. *J. Immunol.* **155**, 3734–3741 (1995).
13. Weber, M. S. et al. B-cell activation influences T-cell polarization and outcome of anti-CD20 B-cell depletion in central nervous system autoimmunity. *Ann. Neurol.* **68**, 369–383 (2010).
14. Harris, D. P. et al. Reciprocal regulation of polarized cytokine production by effector B and T cells. *Nat. Immunol.* **1**, 475–482 (2000).
15. Fillatreau, S., Sweenie, C. H., McGeachy, M. J., Gray, D. & Anderton, S. M. B cells regulate autoimmunity by provision of IL-10. *Nat. Immunol.* **3**, 944–950 (2002).
16. Rojas, O. L. et al. Recirculating intestinal IgA-producing cells regulate neuroinflammation via IL-10. *Cell* **176**, 610–624 (2019).
17. Shen, P. et al. IL-35-producing B cells are critical regulators of immunity during autoimmune and infectious diseases. *Nature* **507**, 366–370 (2014).
18. Evans, C. et al. Incidence and prevalence of multiple sclerosis in the Americas: a systematic review. *Neuroepidemiology* **40**, 195–210 (2013).
19. Wallin, M. T. et al. The prevalence of MS in the United States. *Neurology* **92**, e1029–e1040 (2019).
20. Tremlett, H. & Devonshire, V. Natural history of secondary-progressive multiple sclerosis. *Mult. Scler.* **14**, 314–324 (2008).
21. The International Multiple Sclerosis Genetics Consortium & The Wellcome Trust Case Control Consortium 2. Genetic risk and a primary role for cell-mediated immune mechanisms in multiple sclerosis. *Nature* **476**, 214–219 (2011).
22. Kebir, H. et al. Human T_H17 lymphocytes promote blood–brain barrier disruption and central nervous system inflammation. *Nat. Med.* **13**, 1173–1175 (2007).
23. Cao, Y. et al. Functional inflammatory profiles distinguish myelin-reactive T cells from patients with multiple sclerosis. *Sci. Transl. Med.* **7**, 287ra74 (2015).
24. Zamvil, S. et al. T-cell clones specific for myelin basic protein induce chronic relapsing paralysis and demyelination. *Nature* **317**, 355–358 (1985).
25. Zamvil, S. S. et al. Encephalitogenic T cell clones specific for myelin basic protein. An unusual bias in antigen recognition. *J. Exp. Med.* **162**, 2107–2124 (1985).
26. Wolf, S. D., Dittel, B. N., Hardardottir, F. & Janeway, J. C. A. Experimental autoimmune encephalomyelitis induction in genetically B cell-deficient mice. *J. Exp. Med.* **184**, 2271–2278 (1996).
This study demonstrates that B cells are not required in myelin-induced EAE.
27. Hjelmström, P., Juedes, A. E., Fjell, J. & Ruddle, N. H. Cutting edge: B cell-deficient mice develop experimental allergic encephalomyelitis with demyelination after myelin oligodendrocyte glycoprotein sensitization. *J. Immunol.* **161**, 4480–4483 (1998).
28. Molnarfi, N. et al. MHC class II-dependent B cell APC function is required for induction of CNS autoimmunity independent of myelin-specific antibodies. *J. Exp. Med.* **210**, 2921–2937 (2013).
This study demonstrates that the antigen-presenting capacity of myelin-specific B cells is required for the induction of B cell-dependent EAE.
29. Yahr, B. M. D., Goldensohn, S. S. & Kabat, E. A. Further studies on the gamma globulin content of cerebrospinal fluid in multiple sclerosis and other neurological diseases. *Ann. N. Y. Acad. Sci.* **68**, 613–624 (1954).
30. Dobson, R., Ramagopalan, S., Davis, A. & Giovannoni, G. Cerebrospinal fluid oligoclonal bands in multiple sclerosis and clinically isolated syndromes: a meta-analysis of prevalence, prognosis and effect of latitude. *J. Neurol. Neurosurg. Psychiatry* **84**, 909–914 (2013).
31. Obermeier, B. et al. Matching of oligoclonal immunoglobulin transcriptomes and proteomes of cerebrospinal fluid in multiple sclerosis. *Nat. Med.* **14**, 688–693 (2008).
This study confirms that CSF-infiltrating B cells are the source of antibodies in the oligoclonal bands detected in patients with MS.
32. Eggers, E. L. et al. Clonal relationships of CSF B cells in treatment-naive multiple sclerosis patients. *JCI Insight* **2**, 1–16 (2017).
33. Frischer, J. M. et al. The relation between inflammation and neurodegeneration in multiple sclerosis brains. *Brain* **132**, 1175–1189 (2009).
34. Lucchinetti, C. F. et al. Heterogenity of multiple sclerosis lesions: implication for the pathogenesis of demyelination. *Ann. Neurol.* **47**, 707–717 (2000).
35. Serafini, B., Rosicarelli, B., Magliozzi, R., Stigliano, E. & Aloisi, F. Detection of ectopic B-cell follicles with germinal centers in the meninges of patients with secondary progressive multiple sclerosis. *Brain Pathol.* **14**, 164–174 (2004).
This is the first study to report B cell aggregates in lymphoid-like follicles in the meninges of patients with SPMS.
36. Magliozzi, R. et al. Meningeal B-cell follicles in secondary progressive multiple sclerosis associate with early onset of disease and severe cortical pathology. *Brain* **130**, 1089–1104 (2007).
37. Howell, O. W. et al. Meningeal inflammation is widespread and linked to cortical pathology in multiple sclerosis. *Brain* **134**, 2755–2771 (2011).
38. Lehmann-Horn, K., Wang, S., Sagan, S. A., Zamvil, S. S. & von Büdingen, H.-C. B cell repertoire expansion occurs in meningeal ectopic lymphoid tissue. *JCI Insight* **1**, e87234 (2016).
39. Humby, F. et al. Ectopic lymphoid structures support ongoing production of class-switched autoantibodies in rheumatoid synovium. *PLOS Med.* **6**, 0059–0075 (2009).
40. Stott, D. I., Hiepe, F., Hummel, M., Steinhauser, G. & Berek, C. Antigen-driven clonal proliferation of B-cells within the target tissues of an autoimmune disease. *J. Clin. Invest.* **102**, 938–946 (1998).
41. Lucchinetti, C. F. C. et al. Inflammatory cortical demyelination in early multiple sclerosis. *N. Engl. J. Med.* **365**, 2188–2197 (2011).
42. Choi, S. R. et al. Meningeal inflammation plays a role in the pathology of primary progressive multiple sclerosis. *Brain* **135**, 2925–2937 (2012).
43. Schirmer, L. et al. Neuronal vulnerability and multilineage diversity in multiple sclerosis. *Nature* **573**, 75–82 (2019).
44. Meinl, E., Krumbholz, M. & Hohlfeld, R. B lineage cells in the inflammatory central nervous system environment: migration, maintenance, local antibody production, and therapeutic modulation. *Ann. Neurol.* **59**, 880–892 (2006).
45. Meinl, E., Krumbholz, M., Derfuss, T., Junker, A. & Hohlfeld, R. Compartmentalization of inflammation in the CNS: a major mechanism driving progressive multiple sclerosis. *J. Neurol. Sci.* **274**, 42–44 (2008).
46. Magliozzi, R., Columba-Cabezas, S., Serafini, B. & Aloisi, F. Intracerebral expression of CXCL13 and BAFF is accompanied by formation of lymphoid follicle-like structures in the meninges of mice with relapsing experimental autoimmune encephalomyelitis. *J. Neuroimmunol.* **148**, 11–23 (2004).
This study demonstrates that B cell growth factors are produced in the CNS of patients with MS.
47. Krumbholz, M. et al. BAFF is produced by astrocytes and up-regulated in multiple sclerosis lesions and primary central nervous system lymphoma. *J. Exp. Med.* **201**, 195–200 (2005).
48. Krumbholz, M. et al. Chemokines in multiple sclerosis: CXCL12 and CXCL13 up-regulation is differentially linked to CNS immune cell recruitment. *Brain* **129**, 200–211 (2006).
49. Kowarik, M. C. et al. CXCL13 is the major determinant for B cell recruitment to the CSF during neuroinflammation. *J. Neuroinflammation* **9**, 93 (2012).
50. Alvarez, E. et al. Predicting optimal response to B-cell depletion with rituximab in multiple sclerosis using CXCL13 index, magnetic resonance imaging and clinical measures. *Mult. Scler. J. Exp. Transl. Clin.* **1**, 205521731562380 (2015).
51. Xiao, B. G., Linington, C. & Link, H. Antibodies to myelin-oligodendrocyte glycoprotein in cerebrospinal fluid from patients with multiple sclerosis and controls. *J. Neuroimmunol.* **31**, 91–96 (1991).
52. Warren, K. G., Catz, I., Johnson, E. & Mielke, B. Anti-myelin basic protein and anti-proteolipid protein specific forms of multiple sclerosis. *Ann. Neurol.* **35**, 280–289 (1994).
53. Genain, C. P., Cannella, B., Hauser, S. L. & Raine, C. S. Identification of autoantibodies associated with myelin damage in multiple sclerosis. *Nat. Med.* **5**, 170–175 (1999).
54. O'Connor, K. C. et al. Antibodies from inflamed central nervous system tissue recognize myelin oligodendrocyte glycoprotein. *J. Immunol.* **175**, 1974–1982 (2005).
This study demonstrates that anti-MOG antibodies are present in the blood of a subset of patients with acute demyelinating encephalomyelitis.
55. Quintana, F. J. et al. Antigen microarrays identify CNS-produced autoantibodies in RRMS. *Neurology* **78**, 532–539 (2012).
56. Villar et al. Intrathecal synthesis of oligoclonal IgM against myelin lipids. *J. Clin. Invest.* **115**, 187–194 (2005).
57. Berger, T. et al. Antimyelin antibodies as a predictor of clinically definite multiple sclerosis after a first demyelinating event. *N. Engl. J. Med.* **349**, 139–145 (2003).
58. Lalive, P. H. et al. Antibodies to native myelin oligodendrocyte glycoprotein are serologic markers of early inflammation in multiple sclerosis. *Proc. Natl Acad. Sci. USA* **103**, 2280–2285 (2006).
59. Zhou, D. et al. Identification of a pathogenic antibody response to native myelin oligodendrocyte glycoprotein in multiple sclerosis. *Proc. Natl Acad. Sci. USA* **103**, 19057–19062 (2006).
60. Quintana, F. J. et al. Antigen microarrays identify unique serum autoantibody signatures in clinical and pathologic subtypes of multiple sclerosis. *Proc. Natl Acad. Sci. USA* **105**, 18889–18894 (2008).
This study suggests that a diverse array of antibodies against multiple CNS autoantigens are found in distinct subtypes of MS.
61. Owens, G. P. et al. Antibodies produced by clonally expanded plasma cells in multiple sclerosis cerebrospinal fluid. *Ann. Neurol.* **65**, 639–649 (2009).
62. Haase, C. G. et al. The fine specificity of the myelin oligodendrocyte glycoprotein autoantibody response in patients with multiple sclerosis and normal healthy controls. *J. Neuroimmunol.* **114**, 220–225 (2001).
63. Kuhle, J. et al. Lack of association between antimyelin antibodies and progression to multiple sclerosis. *N. Engl. J. Med.* **356**, 371–378 (2007).
64. Pelayo, R. et al. Antimyelin antibodies with no progression to multiple sclerosis. *N. Engl. J. Med.* **356**, 426–428 (2007).
65. O'Connor, K. C. et al. Self-antigen tetramers discriminate between myelin autoantibodies to native or denatured protein. *Nat. Med.* **13**, 211–217 (2007).
66. Ketelslegers, I. A. et al. Anti-MOG antibodies plead against MS diagnosis in an acquired demyelinating syndromes cohort. *Mult. Scler.* **21**, 1513–1520 (2015).
67. Srivastava, R. et al. Potassium channel KIR4.1 as an immune target in multiple sclerosis. *N. Engl. J. Med.* **367**, 115–123 (2012).
68. Kraus, V. et al. Potassium channel KIR4.1-specific antibodies in children with acquired demyelinating CNS disease. *Neurology* **82**, 470–473 (2014).
69. Schirmer, L. et al. Differential loss of KIR4.1 immunoreactivity in multiple sclerosis lesions. *Ann. Neurol.* **75**, 810–828 (2014).
70. Brickshawana, A. et al. Investigation of the KIR4.1 potassium channel as a putative antigen in patients with multiple sclerosis: a comparative study. *Lancet Neurol.* **13**, 795–806 (2014).
71. Nerrant, E. et al. Lack of confirmation of anti-inward rectifying potassium channel 4.1 antibodies as reliable markers of multiple sclerosis. *Mult. Scler.* **20**, 1699–1703 (2014).
72. Pröbstel, A. K. et al. Multiple sclerosis and antibodies against KIR4.1. *N. Engl. J. Med.* **374**, 1496–1498 (2016).
73. Chastre, A., Hafler, D. A. & O'Connor, K. C. Evaluation of KIR4.1 as an immune target in multiple sclerosis. *N. Engl. J. Med.* **374**, 1495–1496 (2016).
74. Mathey, E. K. et al. Neurofascin as a novel target for autoantibody-mediated axonal injury. *J. Exp. Med.* **204**, 2363–2372 (2007).
75. Derfuss, T. et al. Contactin-2/TAG-1-directed autoimmunity is identified in multiple sclerosis patients and mediates gray matter pathology in animals. *Proc. Natl Acad. Sci. USA* **106**, 8302–8307 (2009).
76. Blauth, K. et al. Antibodies produced by clonally expanded plasma cells in multiple sclerosis cerebrospinal fluid cause demyelination of spinal cord explants. *Acta Neuropathol.* **130**, 765–781 (2015).

77. Rivas, J. R. et al. Peripheral VH4$^+$ plasmablasts demonstrate autoreactive B cell expansion toward brain antigens in early multiple sclerosis patients. *Acta Neuropathol.* **133**, 43–60 (2017).
78. Liu, Y. et al. Myelin-specific multiple sclerosis antibodies cause complement-dependent oligodendrocyte loss and demyelination. *Acta Neuropathol. Commun.* **5**, 25 (2017).
79. Reiber, H., Ungefehr, S. & Jacobi, C. The intrathecal, polyspecific and oligoclonal immune response in multiple sclerosis. *Mult. Scler.* **4**, 111–117 (1998).
80. Jarius, S. et al. The MRZ reaction as a highly specific marker of multiple sclerosis: re-evaluation and structured review of the literature. *J. Neurol.* **264**, 453–466 (2017).
81. Brändle, S. M. et al. Distinct oligoclonal band antibodies in multiple sclerosis recognize ubiquitous self-proteins. *Proc. Natl Acad. Sci. USA* **113**, 7864–7869 (2016).
This study demonstrates that at least some antibodies in CSF oligoclonal bands bind to ubiquitous self-antigens.
82. Winger, R. C. & Zamvil, S. S. Antibodies in multiple sclerosis oligoclonal bands target debris. *Proc. Natl Acad. Sci. USA* **113**, 7696–7698 (2016).
83. Grabar, P. 'Self' and 'not-self' in immunology. *Lancet* **1**, 1320–1322 (1974).
84. Lisak, R. P. et al. Secretory products of multiple sclerosis B cells are cytotoxic to oligodendroglia in vitro. *J. Neuroimmunol.* **246**, 85–95 (2012).
85. Lisak, R. P. et al. B cells from patients with multiple sclerosis induce cell death via apoptosis in neurons in vitro. *J. Neuroimmunol.* **309**, 88–99 (2017).
86. Owens, G. P. et al. Restricted use of V(H)4 germline segments in an acute multiple sclerosis brain. *Ann. Neurol.* **43**, 236–243 (1998).
87. Qin, Y. et al. Clonal expansion and somatic mutation of V(H) genes of B cells from cerebrospinal fluid in multiple sclerosis. *J. Clin. Invest.* **102**, 1045–1050 (1998).
88. Baranzini, S. et al. B cell repertoire diversity and clonal expansion in multiple sclerosis brain lesions. *J. Immunol.* **163**, 5133–5144 (1999).
89. Colombo, M. et al. Accumulation of clonally related B lymphocytes in the cerebrospinal fluid of multiple sclerosis patients. *J. Immunol.* **164**, 2782–2789 (2000).
90. Owens, G. P. et al. Single-cell repertoire analysis demonstrates that clonal expansion is a prominent feature of the B cell response in multiple sclerosis cerebrospinal fluid. *J. Immunol.* **171**, 2725–2733 (2003).
91. Colombo, M. et al. Maintenance of B lymphocyte-related clones in the cerebrospinal fluid of multiple sclerosis patients. *Eur. J. Immunol.* **33**, 3433–3438 (2003).
92. Ritchie, A. M. et al. Comparative analysis of the CD19$^+$ and CD138$^+$ cell antibody repertoires in the cerebrospinal fluid of patients with multiple sclerosis. *J. Immunol.* **173**, 649–656 (2004).
93. Owens, G. P. et al. VH4 gene segments dominate the intrathecal humoral immune response in multiple sclerosis. *J. Immunol.* **179**, 6343–6351 (2007).
94. Harp, C. et al. Cerebrospinal fluid B cells from multiple sclerosis patients are subject to normal germinal center selection. *J. Neuroimmunol.* **183**, 189–199 (2007).
95. Bankoti, J. et al. In multiple sclerosis, oligoclonal bands connect to peripheral B-cell responses. *Ann. Neurol.* **75**, 266–276 (2014).
96. Beltrán, E. et al. Intrathecal somatic hypermutation of IgM in multiple sclerosis and neuroinflammation. *Brain* **137**, 2703–2714 (2014).
97. Lovato, L. et al. Related B cell clones populate the meninges and parenchyma of patients with multiple sclerosis. *Brain* **134**, 534–541 (2011).
98. Obermeier, B. et al. Related B cell clones that populate the CSF and CNS of patients with multiple sclerosis produce CSF immunoglobulin. *J. Neuroimmunol.* **233**, 245–248 (2011).
This study identifies clonally related but distinct B cell clonotypes in the CSF and blood of patients with MS, suggesting that bidirectional exchange occurs between these compartments.
99. von Büdingen, H.-C. et al. B cell exchange across the blood–brain barrier in multiple sclerosis. *J. Clin. Invest.* **122**, 24–28 (2012).
100. Palanichamy, A. et al. Immunoglobulin class-switched B cells form an active immune axis between CNS and periphery in multiple sclerosis. *Sci. Transl. Med.* **6**, 248ra106 (2014).
101. Stern, J. N. H. et al. B cells populating the multiple sclerosis brain mature in the draining cervical lymph nodes. *Sci. Transl. Med.* **6**, 248ra107 (2014).
102. Greenfield, A. L. et al. Longitudinally persistent cerebrospinal fluid B cells can resist treatment in multiple sclerosis. *JCI Insight* **4**, 126599 (2019).
103. Genç, K., Dona, D. L. & Reder, A. T. Increased CD80$^+$ B cells in active multiple sclerosis and reversal by interferon β-1b therapy. *J. Clin. Invest.* **99**, 2664–2671 (1997).
104. Comabella, M. et al. MRI phenotypes with high neurodegeneration are associated with peripheral blood B-cell changes. *Hum. Mol. Genet.* **25**, 308–316 (2016).
105. Fraussen, J. et al. B cells of multiple sclerosis patients induce autoreactive proinflammatory T cell responses. *Clin. Immunol.* **173**, 1–9 (2016).
106. Madireddy, L. et al. A systems biology approach uncovers cell-specific gene regulatory effects of genetic associations in multiple sclerosis. *Nat. Commun.* **10**, 2236 (2019).
107. Bettelli, E., Baeten, D., Jäger, A., Sobel, R. A. & Kuchroo, V. K. Myelin oligodendrocyte glycoprotein-specific T and B cells cooperate to induce a Devic-like disease in mice. *J. Clin. Invest.* **116**, 2393–2402 (2006).
This study demonstrates that mice genetically engineered to express T cells and B cells both targeting MOG develop a spontaneous demyelinating syndrome resembling anti-MOG opticospinal disease.
108. Krishnamoorthy, G., Lassmann, H., Wekerle, H. & Holz, A. Spontaneous opticospinal encephalomyelitis in a double-transgenic mouse model of autoimmune T cell/B cell cooperation. *J. Clin. Invest.* **116**, 2385–2392 (2006).
109. Parker Harp, C. R. et al. B cell antigen presentation is sufficient to drive neuroinflammation in an animal model of multiple sclerosis. *J. Immunol.* **194**, 5077–5084 (2015).
110. Parker Harp, C. R. et al. B cells are capable of independently eliciting rapid reactivation of encephalitogenic CD4 T cells in a murine model of multiple sclerosis. *PLOS ONE* **13**, 1–20 (2018).
111. Harp, C. T. et al. Memory B cells from a subset of treatment-naive relapsing–remitting multiple sclerosis patients elicit CD4$^+$ T-cell proliferation and IFN-γ production in response to myelin basic protein and myelin oligodendrocyte glycoprotein. *Eur. J. Immunol.* **40**, 2942–2956 (2010).
112. Häusler, D. et al. Functional characterization of reappearing B cells after anti-CD20 treatment of CNS autoimmune disease. *Proc. Natl Acad. Sci. USA* **115**, 9773–9778 (2018).
113. Jelcic, I. et al. Memory B cells activate brain-homing, autoreactive CD4$^+$ T cells in multiple sclerosis. *Cell* **175**, 85–100 (2018).
114. Craft, J. E. Follicular helper T cells in immunity and systemic autoimmunity. *Nat. Rev. Rheumatol.* **8**, 337–347 (2012).
115. Crotty, S. T follicular helper cell differentiation, function, and roles in disease. *Immunity* **41**, 529–542 (2014).
116. Fan, X. et al. Circulating CCR7$^+$ICOS$^+$ memory T follicular helper cells in patients with multiple sclerosis. *PLOS ONE* **10**, 1–14 (2015).
117. Cross, A. H., Stark, J. L., Lauber, J., Ramsbottom, M. J. & Lyons, J. A. Rituximab reduces B cells and T cells in cerebrospinal fluid of multiple sclerosis patients. *J. Neuroimmunol.* **180**, 63–70 (2006).
118. Martin, M. et al. Depletion of B lymphocytes from cerebral perivascular spaces by rituximab. *Arch. Neurol.* **66**, 1016–1021 (2009).
119. Roll, P., Palanichamy, A., Kneitz, C., Dorner, T. & Tony, H. P. Regeneration of B cell subsets after transient B cell depletion using anti-CD20 antibodies in rheumatoid arthritis. *Arthritis Rheum.* **54**, 2377–2386 (2006).
120. Palanichamy, A. et al. Rituximab efficiently depletes increased CD20-expressing T cells in multiple sclerosis patients. *J. Immunol.* **193**, 580–586 (2014).
121. Duddy, M. et al. Distinct effector cytokine profiles of memory and naive human B cell subsets and implication in multiple sclerosis. *J. Immunol.* **178**, 6092–6099 (2007).
122. Hauser, S. et al. B-cell depletion with rituximab in relapsing–remitting multiple sclerosis. *N. Engl. J. Med.* **358**, 676–688 (2008).
This phase II clinical trial demonstrates that B cell depletion has a robust therapeutic effect in patients with RRMS.
123. Hauser, S. L. et al. Ocrelizumab versus interferon β1a in relapsing multiple sclerosis. *N. Engl. J. Med.* **376**, 221–234 (2017).
124. Bar-Or, A. et al. Abnormal B-cell cytokine responses a trigger of T-cell-mediated disease in MS? *Ann. Neurol.* **67**, 452–461 (2010).
This study reveals that anti-CD20 antibody treatment in MS reduces proinflammatory B cell and T cell levels in peripheral blood.
125. Barr, T. A. et al. B cell depletion therapy ameliorates autoimmune disease through ablation of IL-6-producing B cells. *J. Exp. Med.* **209**, 1001–1010 (2012).
126. Li, R. et al. Proinflammatory GM-CSF–producing B cells in multiple sclerosis and B cell depletion therapy. *Sci. Transl. Med.* **7**, 310ra166 (2015).
127. Guerrier, T. et al. Proinflammatory B-cell profile in the early phases of MS predicts an active disease. *Neurol. Neuroimmunol. NeuroInflamm.* **5**, 1–7 (2018).
128. Lehmann-Horn, K. et al. Anti-CD20 B-cell depletion enhances monocyte reactivity in neuroimmunological disorders. *J. Neuroinflamm.* **8**, 146 (2011).
129. Mackay, F. & Browning, J. L. BAFF: a fundamental survival factor for B cells. *Nat. Rev. Immunol.* **2**, 465–475 (2002).
130. Kappos, L. et al. Atacicept in multiple sclerosis (ATAMS): a randomised, placebo-controlled, double-blind, phase 2 trial. *Lancet Neurol.* **13**, 353–363 (2014).
131. Sergott, R. C. et al. ATON: results from a phase II randomized trial of the B-cell-targeting agent atacicept in patients with optic neuritis. *J. Neurol. Sci.* **351**, 174–178 (2015).
132. Tak, P. P. et al. Atacicept in patients with rheumatoid arthritis: results of a multicenter, phase Ib, double-blind, placebo-controlled, dose-escalating, single- and repeated-dose study. *Arthritis Rheum.* **58**, 61–72 (2008).
133. Yang, M., Sun, L., Wang, S. & Ko, K. Cutting edge: novel function of B cell-activating factor in the induction of IL-10-producing regulatory B cells. *J. Immunol.* **184**, 3321–3325 (2010).
134. The CAMMS223 Trial Investigators. Alemtuzumab versus interferon β1a in early multiple sclerosis. *N. Engl. J. Med.* **359**, 1786–1801 (2008).
135. Polman, C. H. et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. *N. Engl. J. Med.* **354**, 899–910 (2006).
136. Rudick, R. A. et al. Natalizumab plus interferon β1a for relapsing multiple sclerosis. *N. Engl. J. Med.* **354**, 911 (2006).
137. Cohen, J. a et al. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. *N. Engl. J. Med.* **362**, 402–415 (2010).
138. Kappos, L. et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. *N. Engl. J. Med.* **362**, 387–401 (2010).
139. Hawker, K. et al. Rituximab in patients with primary progressive multiple sclerosis: results of a randomized double-blind placebo-controlled multicenter trial. *Ann. Neurol.* **66**, 460–471 (2009).
This pivotal clinical trial demonstrates that B cell depletion is beneficial in patients with PPMS — the first clinical trial of a therapy for progressive MS to achieve its primary end point.
140. Montalban, X. et al. Ocrelizumab versus placebo in primary progressive multiple sclerosis. *N. Engl. J. Med.* **376**, 209–220 (2017).
141. Petereit, H. F. & Rubbert-Roth, A. Rituximab levels in cerebrospinal fluid of patients with neurological autoimmune disorders. *Mult. Scler.* **15**, 189–192 (2009).
142. von Büdingen, H. C. et al. Onset of secondary progressive MS after long-term rituximab therapy — a case report. *Ann. Clin. Transl. Neurol.* **4**, 46–52 (2016).
143. Lehmann-Horn, K. et al. Intrathecal anti-CD20 efficiently depletes meningeal B cells in CNS autoimmunity. *Ann. Clin. Transl. Neurol.* **1**, 490–496 (2014).
144. Svenningsson, A. et al. Rapid depletion of B lymphocytes by ultra-low-dose rituximab delivered intrathecally. *Neurol. Neuroimmunol. Neuroinflamm.* **2**, e79 (2015).
145. Komori, M. et al. Insufficient disease inhibition by intrathecal rituximab in progressive multiple sclerosis. *Ann. Clin. Transl. Neurol.* **3**, 166–179 (2016).
146. Topping, J. et al. The effects of intrathecal rituximab on biomarkers in multiple sclerosis. *Mult. Scler. Relat. Disord.* **6**, 49–53 (2016).
147. Wingerchuk, D. M., Lennon, V. A., Lucchinetti, C. F., Pittock, S. J. & Weinshenker, B. G. The spectrum of neuromyelitis optica. *Lancet Neurol.* **6**, 805–815 (2007).
148. Devic, E. Myélite aiguë dorso-lombaire avec névrite optique. Autopsie [French]. In *Congrès Français de Médecine (Prem. Session; Lyon, 1894; procès-verbaux, mémoires et discussions; publiés par*

M. le Dr L. Bard) 434–443 (Asselin et Houzeau & Lyon, Louis Savy, 1895).
149. Jarius, S., Wuthenow, A. B. & Wildemann, B. The first Japanese report on neuromyelitis optica rediscovered: acute bilateral blindness, tetraparesis and respiratory insufficiency in a 35-year-old man (1891). *J. Neurol. Sci.* **395**, 121–125 (2018).
150. Wingerchuk, D. M., Hogancamp, W. F., O'Brien, P. C. & Weinshenker, B. G. The clinical course of neuromyelitis optica (Devic's syndrome). *Neurology* **53**, 1107–1107 (1999).
151. Lennon, V. A. et al. A serum autoantibody marker of neuromyelitis optica. *Lancet* **364**, 2106–2112 (2004). **This study demonstrates that an astrocyte-specific autoantibody (NMO-IgG) is found uniquely in NMO**.
152. Lennon, V. A., Kryzer, T. J., Pittock, S. J., Verkman, A. S. & Hinson, S. R. IgG marker of optic-spinal multiple sclerosis binds to the aquaporin-4 water channel. *J. Exp. Med.* **202**, 473–477 (2005).
153. Wingerchuk, D. M. et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. *Neurology* **85**, 177–189 (2015).
154. Pandit, L. et al. Demographic and clinical features of neuromyelitis optica: a review. *Mult. Scler.* **21**, 845–853 (2015).
155. Flanagan, E. P. et al. Epidemiology of aquaporin-4 autoimmunity and neuromyelitis optica spectrum. *Ann. Neurol.* **79**, 775–783 (2016).
156. Miyamoto, K. et al. Nationwide epidemiological study of neuromyelitis optica in Japan. *J. Neurol. Neurosurg. Psychiatry* **89**, 667–668 (2018).
157. Majed, M., Fryer, J. P., McKeon, A., Lennon, V. A. & Pittock, S. J. Clinical utility of testing for AQP4-IgG in CSF: guidance for physicians. *Neurol. Neuroimmunol. NeuroInflamm.* **3**, 1–6 (2016).
158. Kowarik, M. C. et al. CNS aquaporin-4-specific B cells connect with multiple B-cell compartments in neuromyelitis optica spectrum disorder. *Ann. Clin. Transl. Neurol.* **4**, 369–380 (2017).
159. Cotzomi, E. et al. Early B cell tolerance defects in neuromyelitis optica favour anti-AQP4 autoantibody production. *Brain* **142**, 1598–1615 (2019). **Results from this study indicate that defects in central and peripheral tolerance lead to the expansion of AQP4-specific B cells in NMO**.
160. Misu, T. et al. Loss of aquaporin 4 in lesions of neuromyelitis optica: distinction from multiple sclerosis. *Brain* **130**, 1224–1234 (2007).
161. Lucchinetti, C. F. C. et al. A role for humoral mechanisms in the pathogenesis of Devic's neuromyelitis optica. *Brain* **125**, 1450–1461 (2002). **This study reveals that NMO lesions have unique pathological characteristics, including the presence of activated complement, neutrophils and eosinophils**.
162. Matsuoka, T. et al. Heterogeneity of aquaporin-4 autoimmunity and spinal cord lesions in multiple sclerosis in Japanese. *Brain* **130**, 1206–1223 (2007).
163. Matsushita, T. et al. Characteristic cerebrospinal fluid cytokine/chemokine profiles in neuromyelitis optica, relapsing remitting or primary progressive multiple sclerosis. *PLOS ONE* **8**, 2–9 (2013).
164. Herges, K. et al. Protective effect of an elastase inhibitor in a neuromyelitis optica-like disease driven by a peptide of myelin oligodendroglial glycoprotein. *Mult. Scler.* **18**, 398–408 (2012).
165. Varrin-Doyer, M. et al. Aquaporin 4-specific T cells in neuromyelitis optica exhibit a TH17 bias and recognize *Clostridium* ABC transporter. *Ann. Neurol.* **72**, 53–64 (2012).
166. Shimizu, J. et al. IFNβ-1b may severely exacerbate Japanese optic-spinal MS in neuromyelitis optica spectrum. *Neurology* **75**, 1423–1427 (2010).
167. Kim, S. H., Kim, W., Li, X. F., Jung, I. J. & Kim, H. J. Does interferon β treatment exacerbate neuromyelitis optica spectrum disorder? *Mult. Scler.* **18**, 1480–1483 (2012).
168. Axtell, R. C. et al. T helper type 1 and 17 cells determine efficacy of interferon-β in multiple sclerosis and experimental encephalomyelitis. *Nat. Med.* **16**, 406–412 (2010).
169. Kaneko, K. et al. CSF cytokine profile in MOG-IgG$^+$ neurological disease is similar to AQP4-IgG$^+$ NMOSD but distinct from MS: a cross-sectional study and potential therapeutic implications. *J. Neurol. Neurosurg. Psychiatry* **89**, 927–936 (2018).
170. Chihara, N. et al. Interleukin 6 signaling promotes anti-aquaporin 4 autoantibody production from plasmablasts in neuromyelitis optica. *Proc. Natl Acad. Sci. USA* **108**, 3701–3706 (2011).
171. Uzawa, A. et al. Cerebrospinal fluid interleukin-6 and glial fibrillary acidic protein levels are increased during initial neuromyelitis optica attacks. *Clin. Chim. Acta* **421**, 181–183 (2013).
172. Korn, T. et al. IL-6 controls Th17 immunity in vivo by inhibiting the conversion of conventional T cells into Foxp3$^+$ regulatory T cells. *Proc. Natl Acad. Sci. USA* **105**, 18460–18465 (2008).
173. Nutt, S. L., Hodgkin, P. D., Tarlinton, D. M. & Corcoran, L. M. The generation of antibody-secreting plasma cells. *Nat. Rev. Immunol.* **15**, 160–171 (2015).
174. Murakami, M., Kamimura, D. & Hirano, T. Pleiotropy and specificity: insights from the interleukin 6 family of cytokines. *Immunity* **50**, 812–831 (2019).
175. Ringelstein, M. et al. Long-term therapy with interleukin 6 receptor blockade in highly active neuromyelitis optica spectrum disorder. *JAMA Neurol.* **72**, 756–763 (2015).
176. Hinson, S. R. et al. Pathogenic potential of IgG binding to water channel extracellular domain in neuromyelitis optica. *Neurology* **69**, 2221–2231 (2007).
177. Ratelade, J., Bennett, J. L. & Verkman, A. S. Evidence against cellular internalization in vivo of NMO-IgG, aquaporin-4, and excitatory amino acid transporter 2 in neuromyelitis optica. *J. Biol. Chem.* **286**, 45156–45164 (2011).
178. Saadoun, S. et al. Intra-cerebral injection of neuromyelitis optica immunoglobulin G and human complement produces neuromyelitis optica lesions in mice. *Brain* **133**, 349–361 (2010).
179. Mader, S. et al. Complement activating antibodies to myelin oligodendrocyte glycoprotein in neuromyelitis optica and related disorders. *J. Neuroinflammation* **8**, 1–14 (2011).
180. Bradl, M. et al. Neuromyelitis optica: pathogenicity of patient immunoglobulin in vivo. *Ann. Neurol.* **66**, 630–643 (2009). **This study demonstrates the pathogenicity of polyclonal AQP4-specific antibodies derived from patients with NMO in an animal model of T cell-dependent demyelination**.
181. Hillebrand, S. et al. Circulating AQP4-specific auto-antibodies alone can induce neuromyelitis optica spectrum disorder in the rat. *Acta Neuropathol.* **137**, 467–485 (2019).
182. Ratelade, J. et al. Neuromyelitis optica IgG and natural killer cells produce NMO lesions in mice without myelin loss. *Acta Neuropathol.* **123**, 861–872 (2012).
183. Papadopoulos, M. C. & Verkman, A. S. Aquaporin 4 and neuromyelitis optica. *Lancet Neurol.* **11**, 535–544 (2012).
184. Bennett, J. L. et al. Intrathecal pathogenic anti-aquaporin-4 antibodies in early neuromyelitis optica. *Ann. Neurol.* **66**, 617–629 (2009). **This study demonstrates that recombinant AQP4-specific antibodies derived from patients with NMO were pathogenic in an animal model of T cell-dependent demyelination**.
185. Yao, X. & Verkman, A. S. Complement regulator CD59 prevents peripheral organ injury in rats made seropositive for neuromyelitis optica immunoglobulin G. *Acta Neuropathol. Commun.* **5**, 57 (2017).
186. Soltys, J. et al. Membrane assembly of aquaporin-4 autoantibodies regulates classical complement activation in neuromyelitis optica. *J. Clin. Invest.* **129**, 2000–2013 (2019).
187. Cree, B. A. C., Spencer, C. M., Varrin-Doyer, M., Baranzini, S. E. & Zamvil, S. S. Gut microbiome analysis in neuromyelitis optica reveals overabundance of *Clostridium perfringens*. *Ann. Neurol.* **80**, 443–447 (2016).
188. Gong, J. et al. Lack of short-chain fatty acids and overgrowth of opportunistic pathogens define dysbiosis of neuromyelitis optica spectrum disorders: a Chinese pilot study. *Mult. Scler.* **25**, 1316–1325 (2018).
189. Zamvil, S. S., Spencer, C. M., Baranzini, S. E. & Cree, B. A. C. The gut microbiome in neuromyelitis optica. *Neurotherapeutics* **15**, 92–101 (2018).
190. Kitley, J. et al. Prognostic factors and disease course in aquaporin-4 antibody-positive patients with neuromyelitis optica spectrum disorder from the United Kingdom and Japan. *Brain* **135**, 1834–1849 (2012).
191. Papadopoulos, M. C., Bennett, J. L. & Verkman, A. S. Treatment of neuromyelitis optica: State-of-the-art and emerging therapies. *Nat. Rev. Neurol.* **10**, 493–506 (2014).
192. Kleiter, I., Hellwig, K., Berthele, A. & Al, E. Failure of natalizumab to prevent relapses in neuromyelitis optica. *Arch. Neurol.* **69**, 239–245 (2012).
193. Min, J. H., Kim, B. J. & Lee, K. H. Development of extensive brain lesions following fingolimod (FTY720) treatment in a patient with neuromyelitis optica spectrum disorder. *Mult. Scler.* **18**, 113–115 (2012).
194. Pittock, S. J. et al. Eculizumab in AQP4-IgG-positive relapsing neuromyelitis optica spectrum disorders: an open-label pilot study. *Lancet Neurol.* **12**, 554–562 (2013). **This clinical trial demonstrates that a monoclonal antibody against complement terminal pathway components is highly effective in preventing relapse of NMO**.
195. Pittock, S. J. et al. Eculizumab in aquaporin-4–positive neuromyelitis optica spectrum disorder. *N. Engl. J. Med.* **381**, 614–625 (2019).
196. Jacob, A. et al. Treatment of neuromyelitis optica with rituximab: retrospective analysis of 25 patients. *Arch. Neurol.* **65**, 1443–1448 (2008).
197. Kim, S., Huh, S., Lee, S., Joung, A. & Kim, H. A 5-year follow-up of rituximab treatment in patients with neuromyelitis optica spectrum disorder. *JAMA Neurol.* **70**, 1110–1117 (2013).
198. Cree, B. et al. A double-masked, placebo-controlled study with open-label period to evaluate the efficacy and safety of inebilizumab in adult subjects with neuromyelitis optica spectrum disorders — top line efficacy and safety results (Plen02.001). *Neurology* **92**, Plen02.001 (2019).
199. Jarius, S. et al. Antibody to aquaporin-4 in the long-term course of neuromyelitis optica. *Brain* **131**, 3072–3080 (2008).
200. Pellkofer, H. L. et al. Long-term follow-up of patients with neuromyelitis optica after repeated therapy with rituximab. *Neurology* **76**, 1310–1315 (2011). **This study demonstrates that anti-AQP4 antibody production is derived from naive and memory B cells rather than plasmablasts and plasma cells**.
201. Wilson, R. et al. Condition-dependent generation of aquaporin-4 antibodies from circulating B cells in neuromyelitis optica. *Brain* **141**, 1063–1074 (2018).
202. Jarius, S. et al. Contrasting disease patterns in seropositive and seronegative neuromyelitis optica: a multicentre study of 175 patients. *J. Neuroinflamm.* **9**, 1–17 (2012).
203. Zamvil, S. S. & Slavin, A. J. Does MOG Ig-positive AQP4-seronegative opticospinal inflammatory disease justify a diagnosis of NMO spectrum disorder? *Neurol. Neuroimmunol. NeuroInflamm.* **2**, 1–7 (2015).
204. Reindl, M. & Waters, P. Myelin oligodendrocyte glycoprotein antibodies in neurological disease. *Nat. Rev. Neurol.* **15**, 89–102 (2019).
205. Pröbstel, A. K. et al. Antibodies to MOG are transient in childhood acute disseminated encephalomyelitis. *Neurology* **77**, 580–588 (2011).
206. Hennes, E. M. et al. Prognostic relevance of MOG antibodies in children with an acquired demyelinating syndrome. *Neurology* **89**, 900–908 (2017).
207. Spadaro, M. et al. Autoantibodies to MOG in a distinct subgroup of adult multiple sclerosis. *Neurol. Neuroimmunol. Neuroinflamm.* **3**, e257 (2016).
208. Pauli, F. Di & Berger, T. Myelin oligodendrocyte glycoprotein antibody-associated disorders: toward a new spectrum of inflammatory demyelinating CNS disorders? *Front. Immunol.* **9**, 1–12 (2018). **This study identifies anti-MOG antibodies in a subset of AQP4-seronegative patients with NMOSD**.
209. Kitley, J. et al. Myelin-oligodendrocyte glycoprotein antibodies in adults with a neuromyelitis optica phenotype. *Neurology* **79**, 1273–1277 (2012).
210. Kitley, J. et al. Neuromyelitis optica spectrum disorders with aquaporin-4 and myelin-oligodendrocyte glycoprotein antibodies a comparative study. *JAMA Neurol.* **71**, 276–283 (2014).
211. Sato, D. K. et al. Distinction between MOG antibody-positive and AQP4 antibody-positive NMO spectrum disorders. *Neurology* **82**, 474–481 (2014).
212. Ramanathan, S. et al. Antibodies to myelin oligodendrocyte glycoprotein in bilateral and recurrent optic neuritis. *Neurol. Neuroimmunol. NeuroInflamm.* **1**, 1–12 (2014).
213. Pröbstel, A. K. et al. Anti-MOG antibodies are present in a subgroup of patients with a neuromyelitis optica phenotype. *J. Neuroinflamm.* **12**, 1–7 (2015).
214. Martinez-Hernandez, E. et al. Antibodies to aquaporin 4, myelin-oligodendrocyte glycoprotein, and the glycine receptor α1 subunit in patients with isolated optic neuritis. *JAMA Neurol.* **72**, 187–193 (2015).
215. Höftberger, R. et al. Antibodies to MOG and AQP4 in adults with neuromyelitis optica and suspected limited forms of the disease. *Mult. Scler.* **21**, 866–874 (2015).
216. Hacohen, Y. et al. Myelin oligodendrocyte glycoprotein antibodies are associated with a non-MS course in children. *Neurol. Neuroimmunol. Neuroinflamm.* **2**, e81 (2015).

217. Jurynczyk, M. et al. Clinical presentation and prognosis in MOG-antibody disease: a UK study. *Brain* **140**, 3128–3138 (2017).
218. Brilot, F. et al. Antibodies to native myelin oligodendrocyte glycoprotein in children with inflammatory demyelinating central nervous system disease. *Ann. Neurol.* **66**, 833–842 (2009).
219. Selter, R. C. et al. Antibody responses to EBV and native MOG in pediatric inflammatory demyelinating CNS diseases. *Neurology* **74**, 1711–1715 (2010).
220. Chalmoukou, K. et al. Anti-MOG antibodies are frequently associated with steroid-sensitive recurrent optic neuritis. *Neurol. Neuroimmunol. Neuroinflamm.* **2**, e131 (2015).
221. Ogawa, R. et al. MOG antibody-positive, benign, unilateral, cerebral cortical encephalitis with epilepsy. *Neurol. Neuroimmunol. Neuroinflamm.* **4**, e322 (2017).
222. Fujimori, J. et al. Bilateral frontal cortex encephalitis and paraparesis in a patient with anti-MOG antibodies. *J. Neurol. Neurosurg. Psychiatry* **88**, 534–536 (2017).
223. Hamid, S. H. M. et al. Seizures and encephalitis in myelin oligodendrocyte glycoprotein igg disease vs aquaporin 4 igg disease. *JAMA Neurol.* **75**, 65–71 (2018).
224. Hacohen, Y. et al. 'Leukodystrophy-like' phenotype in children with myelin oligodendrocyte glycoprotein antibody-associated disease. *Dev. Med. Child Neurol.* **60**, 417–423 (2018).
225. Narayan, R. N., Wang, C., Sguigna, P., Husari, K. & Greenberg, B. Atypical Anti-MOG syndrome with aseptic meningoencephalitis and pseudotumor cerebri-like presentations. *Mult. Scler. Relat. Disord.* **27**, 30–33 (2019).
226. Brunner, C., Lassmann, H., Waehneldt, T. V., Matthieu, J. M. & Linington, C. Differential ultrastructural localization of myelin basic protein, myelin/oligodendroglial glycoprotein, and 2′,3′-cyclic nucleotide 3′-phosphodiesterase in the CNS of adult rats. *J. Neurochem.* **52**, 296–304 (1989).
227. Lebar, R., Lubetzki, C., Vincent, C., Lombrail, P. & Boutry, J. M. The M2 autoantigen of central nervous system myelin, a glycoprotein present in oligodendrocyte membrane. *Clin. Exp. Immunol.* **66**, 423–434 (1986).
228. Schluesener, H. J., Sobel, R. A., Linington, C. & Weiner, H. L. A monoclonal antibody against a myelin oligodendrocyte glycoprotein induces relapses and demyelination in central nervous system autoimmune disease. *J. Immunol.* **139**, 4016–4021 (1987).
229. Genain, C. P. et al. Antibody facilitation of multiple sclerosis like lesions in a nonhuman primate. *J. Clin. Invest.* **96**, 2966–2974 (1995).
This study demonstrates that anti-MOG antibodies can elicit MS-like lesions in a marmoset model of demyelination.
230. Spadaro, M. et al. Histopathology and clinical course of MOG-antibody-associated encephalomyelitis. *Ann. Clin. Transl. Neurol.* **2**, 295–301 (2015).
231. Di Pauli, F. et al. Fulminant demyelinating encephalomyelitis. *Neurol. Neuroimmunol. Neuroinflamm.* **2**, e175 (2015).
232. Weber, M. S., Derfuss, T., Metz, I. & Brück, W. Defining distinct features of anti-MOG antibody associated central nervous system demyelination. *Ther. Adv. Neurol. Disord.* **11**, 1–15 (2018).
233. Litzenburger, T. et al. B lymphocytes producing demyelinating autoantibodies: development and function in gene-targeted transgenic mice. *J. Exp. Med.* **188**, 169–180 (1998).
234. Peschl, P. et al. Human antibodies against the myelin oligodendrocyte glycoprotein can cause complement-dependent demyelination. *J. Neuroinflamm.* **14**, 208 (2017).
235. Saadoun, S. et al. Neuromyelitis optica MOG-IgG causes reversible lesions in mouse brain. *Acta Neuropathol. Commun.* **2**, 35 (2014).
236. Spadaro, M. et al. Pathogenicity of human antibodies against myelin oligodendrocyte glycoprotein. *Ann. Neurol.* **84**, 315–328 (2018).
237. Ramanathan, S., Dale, R. C. & Brilot, F. Anti-MOG antibody: the history, clinical phenotype, and pathogenicity of a serum biomarker for demyelination. *Autoimmun. Rev.* **15**, 307–324 (2016).
238. Jarius, S. et al. MOG-IgG in NMO and related disorders: a multicenter study of 50 patients. Part 2: epidemiology, clinical presentation, radiological and laboratory features, treatment responses, and long-term outcome. *J. Neuroinflamm.* **13**, 280 (2016).
239. Jarius, S. et al. MOG-IgG in NMO and related disorders: a multicenter study of 50 patients. Part 1: frequency, syndrome specificity, influence of disease activity, long-term course, association with AQP4-IgG, and origin. *J. Neuroinflamm.* **13**, 279 (2016).
240. Dalmau, J. & Graus, F. Antibody-mediated encephalitis. *N. Engl. J. Med.* **378**, 840–851 (2018).
241. Granerod, J. et al. Causes of encephalitis and differences in their clinical presentations in England: a multicentre, population-based prospective study. *Lancet Infect. Dis.* **10**, 835–844 (2010).
242. Dubey, D. et al. Autoimmune encephalitis epidemiology and a comparison to infectious encephalitis. *Ann. Neurol.* **83**, 166–177 (2018).
243. Vitaliani, R. et al. Paraneoplastic encephalitis, psychiatric symptoms, and hypoventilation in ovarian teratoma. *Ann. Neurol.* **58**, 594–604 (2005).
This is the first report to identify the antigenic target in anti-NMDAR encephalitis and its association with ovarian teratoma.
244. Dalmau, J. et al. Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. *Ann. Neurol.* **61**, 25–36 (2007).
245. Dalmau, J. et al. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. *Lancet Neurol.* **7**, 1091–1098 (2008).
246. Prüss, H. et al. N-methyl-D-aspartate receptor antibodies in herpes simplex encephalitis. *Ann. Neurol.* **72**, 902–911 (2012).
This study reveals that more than 25% of patients with HSV-1 encephalitis subsequently develop anti-NMDAR encephalitis.
247. Armangue, T. et al. Frequency, symptoms, risk factors, and outcomes of autoimmune encephalitis after herpes simplex encephalitis: a prospective observational study and retrospective analysis. *Lancet Neurol.* **17**, 760–772 (2018).
248. Hara, M. et al. Clinical and pathogenic significance of IgG, IgA, and IgM antibodies against the NMDA receptor. *Neurology* **90**, e1386–e1394 (2018).
249. Gresa-Arribas, N. et al. Antibody titres at diagnosis and during follow-up of anti-NMDA receptor encephalitis: a retrospective study. *Lancet Neurol.* **13**, 167–177 (2014).
250. Tüzün, E. et al. Evidence for antibody-mediated pathogenesis in anti-NMDAR encephalitis associated with ovarian teratoma. *Acta Neuropathol.* **118**, 737 (2009).
251. Bien, C. G. et al. Immunopathology of autoantibody-associated encephalitides: clues for pathogenesis. *Brain* **135**, 1622–1638 (2012).
252. Hughes, E. G. et al. Cellular and synaptic mechanisms of anti-NMDA receptor encephalitis. *J. Neurosci.* **30**, 5866–5875 (2010).
253. Mikasova, L. et al. Disrupted surface cross-talk between NMDA and ephrin-B2 receptors in anti-NMDA encephalitis. *Brain* **135**, 1606–1621 (2012).
254. Kreye, J. et al. Human cerebrospinal fluid monoclonal N-methyl-D-aspartate receptor autoantibodies are sufficient for encephalitis pathogenesis. *Brain* **139**, 2641–2652 (2016).
255. Planagumà, J. et al. Human N-methyl D-aspartate receptor antibodies alter memory and behaviour in mice. *Brain* **138**, 94–109 (2015).
256. Malviya, M. et al. NMDAR encephalitis: passive transfer from man to mouse by a recombinant antibody. *Ann. Clin. Transl. Neurol.* **4**, 768–783 (2017).
257. Planagumà, J. et al. Ephrin-B2 prevents N-methyl-D-aspartate receptor antibody effects on memory and neuroplasticity. *Ann. Neurol.* **80**, 388–400 (2016).
258. Martinez-Hernandez, E. et al. Analysis of complement and plasma cells in the brain of patients with anti-NMDAR encephalitis. *Neurology* **77**, 589–593 (2011).
259. Titulaer, M. J. et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. *Lancet Neurol.* **12**, 157–165 (2013).
260. Haussermann, P., Kuhn, W., Przuntek, H. & Muller, T. Integrity of the blood–cerebrospinal fluid barrier in early Parkinson's disease. *Neurosci. Lett.* **300**, 182–184 (2001).
261. Jesse, S. et al. Summary of cerebrospinal fluid routine parameters in neurodegenerative diseases. *J. Neurol.* **258**, 1034–1041 (2011).
262. Heppner, F. L., Ransohoff, R. M. & Becher, B. Immune attack: the role of inflammation in Alzheimer disease. *Nat. Rev. Neurosci.* **16**, 358–372 (2015).
263. Hickman, S., Izzy, S., Sen, P., Morsett, L. & El Khoury, J. Microglia in neurodegeneration. *Nat. Neurosci.* **21**, 1359–1369 (2018).
264. Hamza, T. H. et al. Common genetic variation in the HLA region is associated with late-onset sporadic Parkinson's disease. *Nat. Genet.* **42**, 781 (2010).
265. Hollenbach, J. A. et al. A specific amino acid motif of HLA-DRB1 mediates risk and interacts with smoking history in Parkinson's disease. *Proc. Natl Acad. Sci. USA* **116**, 7419–7424 (2019).
266. Sulzer, D. et al. T cells from patients with Parkinson's disease recognize α-synuclein peptides. *Nature* **546**, 656–661 (2017).
267. Lodygin, D. et al. β-Synuclein-reactive T cells induce autoimmune CNS grey matter degeneration. *Nature* **566**, 503–508 (2019).
268. Schröder, J. B. et al. Immune cell activation in the cerebrospinal fluid of patients with Parkinson's disease. *Front. Neurol.* **9**, 1–7 (2018).
269. Brochard, V. et al. Infiltration of $CD4^+$ lymphocytes into the brain contributes to neurodegeneration in a mouse model of Parkinson disease. *J. Clin. Invest.* **119**, 182–192 (2009).
This study identifies the presence of IgG on substantia nigra neurons and Lewy bodies in patients with PD, which correlated with microglial activation.
270. Orr, C. F., Rowe, D. B., Mizuno, Y., Mori, H. & Halliday, G. M. A possible role for humoral immunity in the pathogenesis of Parkinson's disease. *Brain* **128**, 2665–2674 (2005).
271. Papachroni, K. K. et al. Autoantibodies to α-synuclein in inherited Parkinson's disease. *J. Neurochem.* **101**, 749–756 (2007).
272. Gruden, M. A. et al. Immunoprotection against toxic biomarkers is retained during Parkinson's disease progression. *J. Neuroimmunol.* **233**, 221–227 (2011).
273. Shalash, A. et al. Elevated serum α-synuclein autoantibodies in patients with Parkinson's disease relative to Alzheimer's disease and controls. *Front. Neurol.* **8**, 720 (2017).
274. Besong-Agbo, D. et al. Naturally occurring α-synuclein autoantibody levels are lower in patients with Parkinson disease. *Neurology* **80**, 169–175 (2013).
275. Horvath, I., Iashchishyn, I. A., Forsgren, L. & Morozova-Roche, L. A. Immunochemical detection of α-synuclein autoantibodies in Parkinson's disease: correlation between plasma and cerebrospinal fluid levels. *ACS Chem. Neurosci.* **8**, 1170–1176 (2017).
276. Akhtar, R. S. et al. Measurements of auto-antibodies to α-synuclein in the serum and cerebral spinal fluids of patients with Parkinson's disease. *J. Neurochem.* **145**, 489–503 (2018).
277. Benner, E. J. et al. Nitrated α-synuclein immunity accelerates degeneration of nigral dopaminergic neurons. *PLOS One* **3**, e1376 (2008).
This study demonstrates that transfer of polyclonal IgG from patients with PD can lead to loss of midbrain dopaminergic neurons in a rat model.
278. Chen, S. et al. Experimental destruction of substantia nigra initiated by Parkinson disease immunoglobulins. *Arch. Neurol.* **55**, 1075–1080 (1998).
279. Bas, J. et al. Lymphocyte populations in Parkinson's disease and in rat models of parkinsonism. *J. Neuroimmunol.* **113**, 146–152 (2001).
280. Stevens, C. H. et al. Reduced T helper and B lymphocytes in Parkinson's disease. *J. Neuroimmunol.* **252**, 95–99 (2012).
281. Kobo, H. et al. Down-regulation of B cell-related genes in peripheral blood leukocytes of Parkinson's disease patients with and without GBA mutations. *Mol. Genet. Metab.* **117**, 179–185 (2016).
282. Cook, D. A. et al. LRRK2 levels in immune cells are increased in Parkinson's disease. *NPJ Parkinsons Dis.* **3**, 11 (2017).
283. Kubo, M. et al. Leucine-rich repeat kinase 2 is a regulator of B cell function, affecting homeostasis, BCR signaling, IgA production, and TI antigen responses. *J. Neuroimmunol.* **292**, 1–8 (2016).
284. Jankovic, J. et al. Safety and tolerability of multiple ascending doses of PRX002/RG7935, an anti–α-synuclein monoclonal antibody, in patients with Parkinson disease: a randomized clinical trial. *JAMA Neurol.* **75**, 1206–1214 (2018).
285. Steele, N. Z. R. et al. Fine-mapping of the human leukocyte antigen locus as a risk factor for Alzheimer disease: a case–control study. *PLOS Med.* **14**, 1–25 (2017).
This study suggests that the frequency of B cells producing antibodies against $A\beta_{42}$ was increased in patients with AD.
286. Söllvander, S. et al. Increased number of plasma B cells producing autoantibodies against $A\beta_{42}$ protofibrils in Alzheimer's disease. *J. Alzheimer's Dis.* **48**, 63–72 (2015).
287. Bulati, M. et al. Double negative ($IgG^+IgD^-CD27^-$) B cells are increased in a cohort of moderate–severe Alzheimer's disease patients and show a pro-

inflammatory trafficking receptor phenotype. *J. Alzheimers Dis.* **44**, 1241–1251 (2015).
288. Busse, M. et al. Alterations in the peripheral immune system in dementia. *J. Alzheimers Dis.* **58**, 1303–1313 (2017).
289. Jiang, Q. et al. Alzheimer's disease variants with the genome-wide significance are significantly enriched in immune pathways and active in immune cells. *Mol. Neurobiol.* **54**, 594–600 (2017).
290. Readhead, B. et al. Multiscale analysis of independent Alzheimer's cohorts finds disruption of molecular, genetic, and clinical networks by human herpesvirus. *Neuron* **99**, 64–82 (2018).
291. Gaskin, F., Finley, J., Fang, Q., Xu, S. & Fu, S. M. Human antibodies reactive with β-amyloid protein in Alzheimer's disease. *J. Exp. Med.* **177**, 1181–1186 (1993).
292. Pascual, G. et al. Immunological memory to hyperphosphorylated tau in asymptomatic individuals. *Acta Neuropathol.* **133**, 767–783 (2017).
293. Du, Y. et al. Reduced levels of amyloid β-peptide antibody in Alzheimer disease. *Neurology* **57**, 801–805 (2001).
294. Hyman, B. T. et al. Autoantibodies to amyloid-β and Alzheimer's disease. *Ann. Neurol.* **49**, 808–810 (2001).
295. Weksler, M. E. et al. Patients with Alzheimer disease have lower levels of serum anti-amyloid peptide antibodies than healthy elderly individuals. *Exp. Gerontol.* **37**, 943–948 (2002).
296. Piazza, F. et al. Anti–amyloid β autoantibodies in cerebral amyloid angiopathy–related inflammation: implications for amyloid-modifying therapies. *Ann. Neurol.* **73**, 449–458 (2013).
297. Maftei, M. et al. Increased levels of antigen-bound β-amyloid autoantibodies in serum and cerebrospinal fluid of Alzheimer's disease patients. *PLOS ONE* **8**, e68996 (2013).
298. Wilcock, D. M. et al. Intracranially administered anti-Aβ antibodies reduce β-amyloid deposition by mechanisms both independent of and associated with microglial activation. *J. Neurosci.* **23**, 3745–3751 (2003).
299. Relkin, N. Clinical trials of intravenous immunoglobulin for Alzheimer's disease. *J. Clin. Immunol.* **34**, 74–79 (2014).
300. Sudduth, T. L., Greenstein, A. & Wilcock, D. M. Intracranial injection of Gammagard, a human IVIg, modulates the inflammatory response of the brain and lowers Aβ in APP/PS1 mice along a different time course than anti-Aβ antibodies. *J. Neurosci.* **33**, 9684–9692 (2013).
301. Relkin, N. R. et al. A phase 3 trial of IV immunoglobulin for Alzheimer disease. *Neurology* **88**, 1768–1775 (2017).
302. Gilman, S. et al. Clinical effects of Aβ immunization (AN1792) in patients with AD in an interrupted trial. *Neurology* **64**, 1553–1562 (2005).
303. Ferrer, I., Rovira, M. B., Guerra, M. L. S., Rey, M. J. & Costa-Jussá, F. Neuropathology and pathogenesis of encephalitis following amyloid β immunization in Alzheimer's disease. *Brain Pathol.* **14**, 11–20 (2004).
304. Zota, V. et al. HLA-DR alleles in amyloid peptide autoimmunity: a highly immunogenic role for the *DRB1*1501* allele. *J. Immunol.* **183**, 3522–3530 (2009).
305. Salloway, S. et al. Two phase 3 trials of bapineuzumab in mild-to-moderate Alzheimer's disease. *N. Engl. J. Med.* **370**, 322–333 (2014).
306. Doody, R. S. et al. Phase 3 trials of solanezumab for mild-to-moderate Alzheimer's disease. *N. Engl. J. Med.* **370**, 311–321 (2014).
307. Honig, L. S. et al. Trial of solanezumab for mild dementia due to Alzheimer's disease. *N. Engl. J. Med.* **378**, 321–330 (2018).
308. Larman, H. B. et al. Autoantigen discovery with a synthetic human peptidome. *Nat. Biotechnol.* **29**, 535 (2011).
309. Jenks, S. A. et al. Distinct effector B cells induced by unregulated Toll-like receptor 7 contribute to pathogenic responses in systemic lupus erythematosus. *Immunity* **49**, 725–739 (2018).
310. Lai, M. et al. Investigation of LGI1 as the antigen in limbic encephalitis previously attributed to potassium channels: a case series. *Lancet Neurol.* **9**, 776–785 (2010).
311. Irani, S. R. et al. Antibodies to Kv1 potassium channel-complex proteins leucine-rich, glioma inactivated 1 protein and contactin-associated protein-2 in limbic encephalitis, Morvan's syndrome and acquired neuromyotonia. *Brain* **133**, 2734–2748 (2010). **This study identifies anti-LRG1 and anti-CASPR2 antibodies in a heterogeneous group of patients with limbic encephalitis and peripheral nerve hyperexcitability**.
312. Lai, M. et al. AMPA receptor antibodies in limbic encephalitis alter synaptic receptor location. *Ann. Neurol.* **65**, 424–434 (2009).
313. Lancaster, E. et al. Antibodies to the GABAB receptor in limbic encephalitis with seizures: case series and characterisation of the antigen. *Lancet Neurol.* **9**, 67–76 (2010).
314. Sabater, L. et al. A novel non-rapid-eye movement and rapid-eye-movement parasomnia with sleep breathing disorder associated with antibodies to IgLON5: a case series, characterisation of the antigen, and post-mortem study. *Lancet Neurol.* **13**, 575–586 (2014).
315. Boronat, A. et al. Encephalitis and antibodies to dipeptidyl-peptidase-like protein-6, a subunit of Kv4.2 potassium channels. *Ann. Neurol.* **73**, 120–128 (2013).
316. Hutchinson, M. et al. Progressive encephalomyelitis, rigidity, and myoclonus: a novel glycine receptor antibody. *Neurology* **71**, 1291 LP–1292 LP (2008).
317. McKeon, A. et al. Glycine receptor autoimmune spectrum with stiff-man syndrome phenotype. *JAMA Neurol.* **70**, 44–50 (2013).
318. Solimena, M. et al. Autoantibodies to glutamic acid decarboxylase in a patient with stiff-man syndrome, epilepsy, and type i diabetes mellitus. *N. Engl. J. Med.* **318**, 1012–1020 (1988).
319. Lancaster, E. et al. Antibodies to metabotropic glutamate receptor 5 in the Ophelia syndrome. *Neurology* **77**, 1698–1701 (2011).

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Competing interests
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