B Lineage Cells in the Inflammatory Central Nervous System Environment: Migration, Maintenance, Local Antibody Production, and Therapeutic Modulation

Edgar Meinl, MD,1,2 Markus Krumbholz, MD,1,2 and Reinhard Hohlfeld, MD1,2

B cells have long played an enigmatic role in the scenario of multiple sclerosis pathogenesis. This review summarizes recent progress in our understanding of B-cell trafficking, survival, and differentiation in the central nervous system (CNS). We propose four possible routes of intrathecal immunoglobulin-producing cells. The inflammatory CNS provides a unique, B-cell–friendly environment, in which B lineage cells, notably long-lived plasma cells, can survive for many years, perhaps even for a lifetime. These new findings offer a plausible explanation for the notorious persistence and stability of cerebrospinal fluid oligoclonal bands. Furthermore, we highlight similarities and differences of intrathecal immunoglobulin production in multiple sclerosis patients and patients with other CNS inflammatory conditions. Finally, we outline the possibly double-edged effects of B cells and immunoglobulin in the CNS and discuss various therapeutic strategies for targeting the B-cell response.

For decades, oligoclonal bands (OCBs) have been recognized to be a key immunopathological feature of multiple sclerosis (MS) and other neuroinflammatory diseases. Now, much additional evidence allows us to also assign an important role to B lymphocytes in the pathogenesis of MS (Table 1). (For a discussion of antigen-specific (auto) antibodies in MS, see reviews by Archelos and Hartung1 and Sospedra and Martin.2) In this article, we focus on recent findings on the mechanisms of migration, survival, proliferation, and differentiation of B cells in the central nervous system (CNS). We propose four possible origins of intrathecal immunoglobulin (Ig)-producing cells and consider properties of the inflamed CNS that create a milieu fostering the long-term survival of B cells and Ig-producing plasma cells.

Basics of B-Cell Biology Relating to Neuroinflammation

The first steps of B-cell maturation from hematopoietic stem cells to pro- and pre-B cells occur in the bone marrow (Fig 1). From there, naive immature B cells (surface IgM+/IgD−) migrate to secondary lymphatic organs (mainly the spleen) and develop into mature naïve B cells (surface IgMlow/IgDhigh). Various checkpoints have to be passed during the multiple steps of B-cell development. Different mechanisms (clonal deletion, receptor editing) are used to implement a certain level of B-cell tolerance (see Jacobi and Diamond3 for a recent review of this topic). When naïve B cells “see” their antigen in the secondary lymphoid tissue in an appropriate environment, which includes T cells and dendritic cells, they become activated and proliferate. Some of these antigen-activated B cells develop outside of lymph follicles to become short-lived plasmablasts; others further differentiate in germinal centers (GCs) (see Fig 1). GCs are specialized areas in lymph follicles where B cells undergo rounds of proliferation (as centroblasts) accompanied by somatic hypermutation. Somatic hypermutation is a unique mutation mechanism that is targeted to the variable regions of rearranged Ig gene segments. Combined with selection for B cells that produce high-affinity Igs, somatic hypermutation leads to affinity maturation of B cells in the GCs.4 This affinity maturation may continue after the GC reaction.5 B cells found in the CNS during inflammation typically have gone through somatic hy-
In the GC (mainly at the centrocyte stage), Ig class switching occurs, for example, from IgM to IgG. The centrocyte can develop into a memory B cell or into an antibody-secreting cell (ASC) (see Fig 1 and Table 2 for phenotype of these cells). ASCs include “plasmablasts,” an early, still proliferating stage of differentiation of an activated B cell, and “plasma cells,” which represent the nonproliferating end stage. Plasma cells can be short or long lived. During a primary response to an antigen, the generation of IgG-producing ASCs from naive B cells typically requires a GC reaction. Memory B cells have a much lower threshold for activation than naive B cells. Memory B cells rapidly differentiate into ASC after antigen recognition largely outside of GCs and in the presence of sufficient T-cell help, even independently of lymphoid organs. Virus-specific memory B cells can differentiate even in the absence of T-cell help to ASCs outside of GCs. The differentiation of memory B cells into ASCs also can occur independently of the antigen in a “bystander reaction.” This is enhanced by engagement of toll-like receptors on the B cells. ASCs translocate from secondary lymphatic organs into the CNS. Those plasmablasts that find appropriate survival conditions (see Fig 2) develop to long-lived plasma cells that cause oligoclonal bands.
The migration of lymphoid cells to secondary lymphoid tissue via the bloodstream to the bone marrow and also to inflamed tissues.\(^{12,18}\)

Ig production, for example, against a certain pathogen (or an autoantigen), can be maintained by three nonmutually exclusive ways (Table 3). First, chronic antigen activation induces continuous differentiation of memory B cells into ASC and Ig production.\(^{14}\) Second, human memory B lymphocytes proliferate and differentiate into ASCs in response to polyclonal stimuli, such as bystander T-cell help. An ongoing polyclonal activation of memory B cells was suggested as a means to maintain serological memory for a human lifetime.\(^{16}\) Third, Ig production is provided by long-term plasma cells residing in the bone marrow and possibly at sites of chronic inflammation.\(^{12}\) The ability of plasma cells to survive for many years is an important feature of the humoral immune response. These long-lived plasma cells produce Igs in the absence of antigen and DNA synthesis.\(^{12}\) The survival of plasma cells depends on the environment. A synergistic effect of cytokines and adhesion-dependent signals mediates plasma cell survival.\(^{4,12,19}\) CXCL12/SDF-1, interleukin-6 (IL-6), tumor necrosis factor-\(\alpha\) (TNF-\(\alpha\)), ligation of CD44,\(^{19}\) engagement of \(\alpha_\beta_1\) integrin,\(^a\) and the B-cell–activating factor of the TNF family (BAFF)/APRIL receptor BCMA\(^b\) mediate plasma cell survival. Many of these mediators are found in the inflamed CNS (Fig 2; see also later in this article).

The migration of lymphoid cells to secondary lymphoid tissue is largely regulated by certain chemokines (CXCL12/SDF-1, CXCL13/BCA-1, CCL19/MIP3B, and CCL21/SLC). These chemokines are frequently called homeostatic or lymphoid chemokines, because they are essential for the development and maintenance of lymphoid tissue. They are distinguished from inflammatory chemokines, which direct immune cells to sites of inflammation. Recent evidence indicates that these homeostatic chemokines participate in the regulation of neuroinflammation\(^{21–25}\) (see later for details).

The migration of ASCs is mediated via chemokines and adhesion molecules in an isotype-specific way. This ensures that IgG-positive ASCs migrate to the sites of inflammation, IgA-positive ASCs to mucosal surfaces, and both to the bone marrow.\(^{26}\) The ASCs that emigrate from secondary lymphatic tissue have lost their responsiveness to most of the homeostatic chemokines, but retain the chemokine receptors CXCR4 and CXCR3.\(^{27}\)

**B Lineage Cells in the Central Nervous System**

Low numbers of B lymphocytes enter all parts of the normal human brain.\(^{28}\) B cells and plasma cells have long been considered a numerically minor component of MS lesions (Fig 3).\(^{29,30}\) The relative proportion of Ig-producing cells, however, is significantly increased in late chronic MS lesions.\(^{30}\) The ratio of T cells/Ig-containing cells was 190:1 in early MS lesions, it was

---

**Table 2. Features of B Lineage Cells Potentially Involved in Inflammatory Central Nervous System Diseases**

<table>
<thead>
<tr>
<th>Mature Naive B Cell</th>
<th>Memory B Cell</th>
<th>Plasmablast</th>
<th>Plasma Cell</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surface markers allowing subset differentiation</td>
<td>+</td>
<td>+</td>
<td>+/−</td>
</tr>
<tr>
<td>CD19</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>CD20 (from pre-B cell stage on)</td>
<td>+</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>CD27</td>
<td>−</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>CD138</td>
<td>−</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>Adhesion molecule</td>
<td>α_β_1 integrin(^a)</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Functions</td>
<td>Ig secretion</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td></td>
<td>Surface Ig</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Proliferative capacity</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Antigen presentation</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Survival mediated via BAFF(^b)</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

\(^a\)B lineage cells have many additional adhesion molecules, which are involved in tissue-specific recruitment.\(^5,26\) \(^b\)α_β_1 is singled out due to its potential relevance for multiple sclerosis therapy.

**Table 3. Three Principles (Not Mutually Exclusive) of Persistent Immunoglobulin Production against Pathogens or Autoantigens**

- Continuous activation of memory B cells by antigen (Ag) and generation of short-lived plasmablasts\(^{14}\)
- Persistence and immunoglobulin secretion of long-lived plasma cells in the bone marrow and at sites of inflammation\(^{72}\)
- Bystander activation of memory B cells in the absence of Ag and generation of short-lived plasmablasts\(^{16}\)
Rearranged Ig genes were examined in the cerebrospinal fluid (CSF) cells of patients with MS, subacute sclerosing panencephalitis, and focal encephalitis. Likewise, Ig rearrangement was analyzed in brain specimens of patients with MS, subacute sclerosing panencephalitis, and focal encephalitis. These studies consistently detected somatic hypermutation of the Ig genes, indicating that these B lineage cells were expanded by antigen and had undergone a GC reaction. Dominant clonotypes indicating local B-cell proliferation were also observed in the CSF of patients with clinically isolated syndrome and early after onset of MS. Single-cell analysis of CD19+ and CD138+ cells in the CSF showed clonal expansion in both populations. The significance of sequence overlap between these B lineage cell populations remains to be determined.

The B-cell composition of CSF cells differs from that of blood cells. B cells can hardly be detected in the normal CSF. In MS and other inflammatory neurological diseases, the mean percentage of B cells among CSF cells was about 5%. The interindividual variability is great: 1 to 17%. The B-cell percentage in CSF is generally lower than in blood mononuclear cells and is not linked to B-cell number and percentage in blood. The highest numbers of B cells in the CSF were observed in patients with neuroborreliosis. In contrast with B cells in blood, most B cells in the CSF have a memory phenotype (CD27+), A B-cell population with the phenotype of centroblasts (CD19+, CD38high, CD77+,
Ki67$^+$, Bcl-2$^-$) was found in the CSF of MS and OIND patients. Such centroblasts are typically found in GCs in lymphatic tissue, but not in blood. The most frequent ASCs in the CSF were identified as plasmablasts (CD19$^+$CD138$^+$) or plasma cells (CD19$^-$CD138$^-$). In one study, the kinetics of plasmablasts were analyzed in the CSF of OIND and MS patients. Although the plasmablasts rapidly disappeared in OIND patients after the antigen was cleared, they persisted in MS patients. This could indicate a continuous antigen-driven activation in the MS patients. The number of plasmablasts in the CSF correlated with the amount of intrathecal Ig production and with inflammatory parenchymal disease activity as measured by magnetic resonance imaging.

**Survival Factors for B Cells in the Central Nervous System**

One crucial survival factor for B lineage cells is BAFF. BAFF is important for the maturation and survival of B cells, as well as ASCs. It binds to three receptors: BCMA, TACI (Transmembrane activator and CAML interactor), and BAFF receptor (BAFF-R). Two of these receptors, BCMA and TACI, are also targeted by the BAFF-related factor APRIL. BCMA is essential for the long-term survival of plasma cells. The level of constitutive BAFF produced by stromal cells in lymphatic tissue determines the size of the peripheral B-cell pool, whereas inducible BAFF produced at sites of inflammation supports local survival of B lymphocytes and can be associated with the development of autoimmunity. In the CNS, BAFF is constitutively present and produced by astrocytes. In active MS lesions, BAFF expression reaches the same levels as in lymphatic tissue, where its critical role in fostering B cells is performed. Infiltrating cells expressing the BAFF-R are located in close vicinity to BAFF-producing astrocytes in MS lesions. BAFF production in the CNS also has implications for the pathogenesis of primary CNS lymphomas, which are almost exclusively of B-cell origin. These lymphomas contain high levels of BAFF, and their cells abundantly express BAFF-receptors. Local production of BAFF

| Overall frequency: 1-17%; not linked to B-cell number and percentage in blood; usually lower frequency than in blood; great interindividual variability; highest number in neuroborreliosis |
| Memory phenotype: CD19$^+$CD27$^+$ (80% in cerebrospinal fluid [CSF], 40% in blood) |
| Occurrence of centroblasts (B-cell differentiation of secondary lymphatic tissues): CD19$^+$, CD38$^{high}$, CD77$^+$, Ki67$^+$, Bcl-2$^-$; these cells are usually absent from blood |
| Chemokine receptors: almost all B cells express CXCR5 (as in blood); memory B cells expressing CCR1, CCR2, and CCR4 are enriched; CXCR3- and CCR5-positive B cells are enriched in CSF compared with blood, and CCR7 as in blood |
by astrocytes in the CNS might promote B-cell survival in MS and primary CNS lymphomas.

Nerve growth factor and CXCL12 play critical roles in the development of the nervous system, are constitutively present in the adult CNS, and contribute to B lineage cell maintenance in the CNS. Nerve growth factor, the prototype of the family of neurotrophins, functions in addition as a survival factor for memory B cells.\(^{43}\) CXCL12 is essential for normal cerebellar development\(^{44}\) and is also an important survival factor for long-lived plasma cells.\(^{4,12,19}\) It is constitutively displayed on endothelial cells in the adult human CNS\(^{22}\) and upregulated in both active and inactive MS lesions.\(^{22}\)

The inflamed CNS provides a number of mediators needed for the maintenance of long-lived plasma cells (see Fig 2). CXCL12 is elevated in MS lesions\(^{22}\) and synergizes with IL-6, TNF-\(\alpha\), ligation of CD44, engagement of \(\alpha_\beta_1\) integrin, and the BAFF/APRIL receptor BCMA (see Fig 2; see also earlier)\(^{4,12,19}\). In addition to the typical inflammatory mediators TNF-\(\alpha\)\(^{45}\) and IL-6,\(^{46}\) CXCL12,\(^{22}\) BAFF,\(^{41}\) the CD44 ligand hyaluronan,\(^{47}\) and the \(\alpha_\beta_1\) ligand vascular cell adhesion molecule-1 (VCAM-1)\(^{48}\) were also abundantly detected in MS lesions. This suggests that the inflamed CNS provides the essentials to support survival of long-lived plasma cells (see Fig 2). This is most likely the basis for persistence of OCB in the CSF of MS patients (see later).

### B-Cell-Attracting Chemokines in the Normal and Inflamed Central Nervous System

Although considerable progress has been made in understanding the migration of T cells and monocytes into sites of inflammation including the CNS,\(^{49}\) almost nothing was known until recently about the regulation of B-cell trafficking to the inflamed CNS.\(^{50}\) The latest research has suggested that homeostatic chemokines (CXCL12, CXCL13)\(^{22-24}\) which are essential for maintaining immune organs, regulate B-cell traffic to the inflamed CNS.

An important chemokine that directs the migration of B cells before they differentiate to ASCs is CXCL13. Virtually all B cells in the blood and CSF express the receptor to this chemokine.\(^{22,51}\) CXCL13 is induced in active MS lesions, but not in inactive ones.\(^{22}\) It was initially thought to be restricted to stroma cells in the G\(Cs\), but recently various groups have reported that it is also produced by monocytes, macrophages, and dendritic cells.\(^{22,52}\) Myeloid cell–derived CXCL13 was linked to the recruitment of autoantibody-producing B cells in an animal model of systemic lupus erythematosus.\(^{53}\) Immunostaining showed CXCL13 in infiltrating cells, presumably macrophages, in active MS lesions,\(^{22}\) in lymphoid follicles in the meninges,\(^{24}\) in blood vessels in chronic active lesions,\(^{25}\) and in the endothelium in primary CNS lymphoma.\(^{54}\) The level of CXCL13 in the CSF of MS patients correlated strongly with the intrathecal Ig production, the number of B cells, plasmablasts, and interestingly, also T cells.\(^{22}\) The linkage between the CXCL13 level and T-cell number might be because once activated, virtually all T cells transiently express the receptor CXCR5.\(^{55}\) Currently, however, little is known about the effects of CXCL13 on activated T cells. High levels of CXCL13, even exceeding those in MS, were observed in the CSF of patients with acute neuroborreliosis\(^{25}\) and also in patients with severe meningoencephalitis.\(^{22}\)

CXCL13 synergizes with CXCL12 in directing B cells to lymph follicles.\(^{56}\) CXCL12 is constitutively displayed on blood vessels in the normal adult brain\(^{22}\) and is upregulated in both active and inactive MS lesions.\(^{22}\) In MS lesions, CXCL12 was detected on blood vessels.\(^{22,23}\)

In addition to these homeostatic chemokines, inflammatory chemokines also participate in directing B-cell migration. A prime example is CXCL10/IP10, which has been known for a couple of years to be a prominent chemokine in MS lesions.\(^{57,58}\) Its receptor, CXCR3, which is induced in memory B cells, remains highly expressed during plasma cell development.\(^{59}\) The CSF concentration of CXCL10 positively correlates with leukocyte count and intrathecal Ig production.\(^{60}\) CSF B cells show an upregulated expression of CCR1, CCR2, and CCR4,\(^{23}\) and the corresponding ligands (CCL2/MCP-1 and CCL3/MIP1\(\alpha\)) are high in MS lesions.\(^{57,58}\) In vitro, B cells migrate more rapidly through the blood–brain barrier than T cells from the same individual\(^{61}\); CCL2 and interestingly also \(\alpha_\beta_1\) integrin promoted B-cell migration in this system.\(^{61}\) Plasmablasts express CXCR4 and CXCR3 and migrate toward CXCL12 and CXCL10,\(^{62}\) both of which are upregulated in MS lesions.\(^{52,57}\)

In summary, current evidence indicates that CXCL10 and CXCL12 contribute to migration and maintenance of ASCs (see Fig 2), whereas CXCL10, CXCL12, CXCL13, CCL2, and CCL3 attract B cells to the CNS.

### Four Possible Pathways to Immunoglobulin Production in the Central Nervous System

We propose four different tracks by which Ig-secreting cells could arrive in the inflamed CNS (see Fig 1). The chemokine pattern in the CNS of MS patients suggests that both ASCs and B cells migrate to the CNS.

First, Ig-secreting cells, which have differentiated in peripheral lymphoid organs, might enter the inflamed CNS by means of plasmablasts, which appear in the blood 6 days after antigen response.\(^{62}\) Their migration is directed via CXCR4 and CXCR3,\(^{4}\) and ligands of both (CXCL12, CXCL10) are upregulated in MS le-
Second, memory B cells might differentiate into ASCs in the inflamed CNS. CSF analyses consistently have shown that the overwhelming majority of B cells in the CSF (in contrast with the blood) are memory B cells. The observations of somatic hypermutation of B cells in CSF and CNS also point to the presence of memory B cells in the CNS. Memory B cells are restimulated to proliferate and to differentiate into ASCs in the presence of T-cell help, largely outside of GCs. The T-cell–dependent differentiation of memory B cells into ASCs does not even require lymphoid organs. For example, a CNS infection is rapidly accompanied by an intrathecal Ig production against the causative agent; this is presumably based on a local antigen-driven differentiation of memory B cells into ASCs in the inflammatory environment. Sequence analysis of rearranged Ig genes in CSF B cells indicated that antigen-driven B-cell clonal expansion occurs in patients with monosymptomatic optic neuritis, in patients with clinically isolated syndrome, and in MS patients early after disease onset. This indicates that antigen-driven B-cell activation inside of the CNS is an early event in the pathogenesis of MS. Animal experiments have shown that antigen present in the CNS is delivered to cervical lymph nodes. There it stimulates B-cell differentiation and initiates intrathecal Ig production, provided the antigen is retained in the CNS. This can be explained by migration of memory B cells from the cervical lymph nodes to the CNS, where they undergo a local antigen-driven differentiation into ASCs.

Third, ASCs might originate from lymphoid follicles in the meninges, which have been observed in 30 to 40% of MS patients with secondary chronic progressive MS and long-standing disease. Follicle-like structures, however, were not observed in the inflamed parenchyma and not in relapsing-remitting MS. These structures in the meninges contained proliferating B cells, T cells, plasma cells, and a network of CXCL13-producing cells. Lymphoid follicles occur in many tissues during chronic inflammation with a variable frequency depending on the inflamed tissue and the particular disease. This so-called lymphoid neogenesis occurs with a different degree of differentiation and similarity to secondary lymphoid organs, ranging from lymphoid aggregates to secondary B-cell follicles with GCs surrounded by distinct T-cell areas that contain high endothelial venules. Such high endothelial venules, which allow continuous transmigration of lymphocytes, were not detected around lymphoid follicles in the meninges. It is unclear whether memory or naive B cells differentiate into ASCs in the lymphoid follicles in the meninges. The enrichment of the CSF for memory B cells might argue for an involvement of this population. The concept of B-cell differentiation in follicle-like structures in the CNS also is supported by flow cytometry analysis, which detected B-cell differentiation stages in the CSF of patients with MS and OIND.

Fourth, memory B cells in the CNS might differentiate locally into ASCs in a bystander reaction. Such antigen-independent bystander reactions require T-cell help and are enhanced by toll-like receptor engagement on the B cells. Studies of infectious CNS diseases have shown that most intrathecally produced Ig is directed against the causative agent. Therefore, the antigen-independent bystander activation in the CNS can presumably explain only a small part of the total Ig production in the inflamed CNS.

Notably, Ig production in the CNS compartment can be both antigen-driven and antigen-independent. ASCs, which arrive in the brain via tracks 1 or 4, secrete antibodies independently of antigen recognition. In contrast, those arriving via tracks 2 or 3 secrete antibodies in an antigen-dependent way. A subset of plasmablasts might further develop to plasma cells, and some of them might persist as long-lived plasma cells in the inflamed CNS. The survival of plasma cells is not an autonomous feature of these cells, but the environment and the inflamed CNS provide a milieu that supports them (see Fig 2; see also earlier). Long-lived plasma cells produce IgG independently of antigen.

**Features of Intrathecally Produced IgG**

The intrathecal Ig production with the formation of OCBs is a key feature of MS, as well as other neuroinflammatory diseases (Table 6). The amount of IgG produced per day in the CNS of MS patients has been quantified by two methods. The concordant results show that the average production of IgG in the CNS of MS patients was 29mg/day (range, 0–207mg/day).

The OCBs in the CSF of MS patients remain for many years, although changes of the banding pattern have been observed longitudinally in some patients. The tendency of the OCBs to persist suggests that the CNS provides a long-term survival niche for plasma cells (see Fig 2). The changes of the banding pattern might indicate that the plasma cells compete for the limited survival niches. It is not known whether the presumed, long-lived plasma cells that cause the persisting OCBs in MS originate from tracks 1, 2, 3, or 4 (see Fig 1). The view that the OCBs are derived from long-lived plasma cells also is supported by the observation that OCBs persist after irradiation; plasma cells are insensitive to irradiation. OCBs were reported to persist for at least 1 year after autologous irradiation.
Table 5. Effects of B Cells and Immunoglobulin in Central Nervous System Inflammation

<table>
<thead>
<tr>
<th>Tissue-Destructive</th>
<th>Tissue-Protective and Antiinflammatory</th>
</tr>
</thead>
<tbody>
<tr>
<td>B cells Production of proinflammatory cytokines such as IL-6, IL-12, and lymphotixin</td>
<td>Production of antiinflammatory cytokines such as IL-10 and TGF-β</td>
</tr>
<tr>
<td>Antigen presentation</td>
<td>Neuroprotection via release of neurotrophic factors such as nerve growth factor, brain-derived neurotrophic factor, and neurturin.</td>
</tr>
<tr>
<td>Ig Ig to CNS autoantigens may induce complement activation, perturbation of oligodendrocyte physiology, proteolysis of myelin basic protein, Stimulation of macrophages/microglia via activating Fc receptors</td>
<td>Ig to myelin may facilitate remyelination and axonal regeneration.</td>
</tr>
<tr>
<td>Downmodulation of inflammation via binding to inhibitory Fc receptors</td>
<td>Downmodulation of inflammation.</td>
</tr>
</tbody>
</table>

*Transforming growth factor-β (TGF-β) might perform opposing roles in neuroinflammation (see B-Cell–Directed Therapies section). IL = interleukin; Ig = immunoglobulin; CNS = central nervous system.

stem cell transplantation in four longitudinally followed patients. There is typically a strong intrathecal Ig response to the causative pathogen in infectious CNS diseases, and the OCBs in the CSF recognize the infectious agent. Infectious agent-specific ASCs predominate, and therefore have the best chances to occupy the proposed limiting niches for long-term plasma cells in the inflamed CNS.

One important difference between the intrathecal Ig production of MS patients and OIND patients has been known for many years (Table 6). Whereas MS patients typically display an intrathecal immune response against many different common pathogens such as measles virus, rubella virus, and varicella-zoster virus, as well as Chlamydia pneumoniae and human herpesvirus type 6, OIND patients do not. This polyclonal antipathogen Ig does not correspond to the major OCBs in the CSF and is considered a bystander reaction (measles-rubella-zoster reaction), which can be detected in about 90% of MS patients. The reason for this polyclonal Ig response in MS is unclear; it probably does not simply reflect a consequence of long-lasting disease, because it is typically present at the beginning of MS and is even used as a diagnostic criterion in some clinics. This measles-rubella-zoster reaction occurred in only 1 of 17 patients with human T-cell lymphotrophic virus type I–associated myelopathy and in 2 of 27 neuroborreliosis patients. The polyclonal intrathecal Ig response in MS may indicate an enhanced B-cell–promoting environment long before the clinical disease starts, and may also reflect the individual’s history of infections.

Effects of B Cells on the Central Nervous System

B cells and Iggs in the CNS milieu can have tissue-destroying and tissue-repairing effects (see Table 5). B cells are extremely potent antigen presenters for antigens that bind to their surface Iggs; they selectively internalize their antigen and present this to T cells at concentrations 103- to 104-fold lower than required for presentation by nonspecific B cells or monocytes. The ability of B cells to promote immunopathological disease in the absence of Ig secretion has been shown in a rodent model of systemic lupus erythematosus. They can produce a wide array of cytokines, for example, mediators with immunosuppressive activity, such as IL-10 and transforming growth factor-β (TGF-β); cytokines that regulate inflammation and T-cell polarization, such as IL-4, interferon-γ, and IL-12; and lymphoid tissue–organizing cytokines, such as TNF-α and lymphotixin. IL-10 production by B cells downregulates CNS inflammation in an experimental autoimmune encephalomyelitis model. TGF-β, which also is produced by B cells, might have opposing effects in the CNS. On the one hand, TGF-β is a well-known inhibitor of inflammatory mediators; on the other hand, TGF-β might promote CNS inflammation, because (1) transgenic expression of TGF-β in the CNS enhanced experimental encephalomyelitis, and (2) TGF-β promotes the generation of IL-17–producing T cells, which are considered to have a dominant role in provoking chronic autoimmune inflammation of the CNS. B cells can also produce neurotrophic factors such as nerve growth factor, brain-derived neurotrophic factor, and neurturin, and thus could help to promote CNS integrity, which recognize the conformationally intact target in a subset of patients.

Myelin-specific Iggs could induce tissue degeneration via complement activation, activation of microglia/macrophages via activating Fc receptors, perturbation of oligodendrocyte physiology, and as recently suggested, also via a proteolytic activity on myelin basic protein. In addition to the MS subtype II, Ig-mediated pathology is probably involved in the Devic’s subtype of MS. Antibodies that recognize aquaporin-4 have been reported for this subset.

In contrast, Iggs might also have an inhibitory effect...
on inflammation by binding to inhibitory Fc receptors.\textsuperscript{106} Oligodendrocyte-specific Igs might promote remyelination.\textsuperscript{107} Igs reactive against the myelin protein Nogo were found in the serum and CSF of MS patients.\textsuperscript{108} Anti-Nogo antibodies are well-established promoters of axonal regeneration.\textsuperscript{109}

### B-Cell–Directed Therapies

Currently approved immunomodulatory treatments for MS (glatiramer acetate, interferon-\(\beta\)/\(\gamma\), mitoxantrone) do not selectively target B cells, although they affect B cells in different ways. Recently, however, there has been much interest in exploring B-cell–selective therapies for MS treatment. The most notable example is the anti-CD20 monoclonal antibody (MAb) rituximab.\textsuperscript{110} Human CD20 expression is evident at the pre-B-cell stage, but is lost during terminal differentiation into ASCs. Rituximab induces a rapid, long-lasting (up to 6–9 months), almost complete depletion of circulating B cells. Plasmablasts express hardly any CD20.\textsuperscript{72} Nevertheless, they disappear after treatment with this anti-CD20 MAb. Their disappearance is easily explained by their short life span (a few days) and the depletion of those B cells that cause plasmablasts. A case report on anti-CD20 treatment described the clinical improvement, reduction of magnetic resonance imaging activity, and depletion of B cells in both the blood and CSF of an MS patient.\textsuperscript{111} Although there is compelling evidence that (auto)reactive Ig contributes to tissue destruction at least in a subset of MS patients,\textsuperscript{101} it is unclear whether pathogenic antibodies in this subset of patients derive from short-lived or long-lived plasma cells.\textsuperscript{72} Other therapeutic strategies should be used to target plasma cells, for example, transcription factors such as PRDM1/BLIMP1 or XBP1 required for the maintenance of plasma cells,\textsuperscript{4} the BAFF/APRIL receptor BCMA, which is needed for plasma cell survival,\textsuperscript{20} or antithymocyte globulin.\textsuperscript{116}

Another strategy to inhibit B-cell activity is to target BAFF function, for example, by soluble BAFF-receptors or with an anti-BAFF MAb. Such therapeutic approaches must take the complexity of the BAFF/APRIL system into consideration; BAFF binds to three different receptors, two of which are shared by the BAFF-related APRIL.\textsuperscript{39} Clinical trials targeting BAFF in rheumatic diseases are forthcoming. No information about BAFF inhibition in human inflammatory CNS diseases currently is available.

### Table 6. Intrathecal Immunoglobulin Production in Multiple Sclerosis and Other Inflammatory Neurological Diseases

<table>
<thead>
<tr>
<th>CSF Feature</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ig production in the CNS\textsuperscript{66}</td>
<td>Yes</td>
</tr>
<tr>
<td>Oligoclonal Ig in CSF\textsuperscript{66,69,70}</td>
<td>Yes</td>
</tr>
<tr>
<td>Polyspecific Ig production in the CNS against different agents, eg, measles virus, rubella virus, varicella-zoster virus\textsuperscript{74,75,77-81}</td>
<td>Nearly always</td>
</tr>
<tr>
<td>Antigen specificity of oligoclonal Ig in the CSF\textsuperscript{66}</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

CSF = cerebrospinal fluid; MS = multiple sclerosis; Ig = immunoglobulin; CNS = central nervous system.
only modulate T-cell migration, but also affect the B-cell compartment, because anti-α4β1 inhibits B-cell migration in vitro across the blood–brain barrier.61 It participates in activation of human memory B cells,118 and is used by long-lived plasma cells to remain in their survival niche4 (see Fig 2).

Conclusions and Outlook

B cells have long (re)taken center stage within the scenario of MS pathogenesis. Antibodies directed at specific target antigens such as MOG and aquaporin-4 have been proposed as prognostic and diagnostic biomarkers, respectively, but these findings are preliminary and need confirmation. Much progress has been made recently to improve our understanding of B-cell trafficking and survival. It appears that the inflammatory CNS provides a unique, B-cell–friendly environment in which B lineage cells, notably long-lived plasma cells, can survive for many years, perhaps even for a lifetime. Not only do these new findings offer a plausible explanation for the notorious persistence and stability of CSF OCBs, but they also allow us to take a fresh look at B-cell–directed therapies. Several molecules involved in B-cell trafficking and survival are considered attractive targets for immune intervention. These avenues currently are being explored in therapeutic trials.

This work was supported by the Deutsche Forschungsgemeinschaft (SFB 571), the Gemeinnützige Hertie-Foundation, the Deutsche Multiple Sklerose Gesellschaft, and the Verein zur Therapieforschung für MS-Kranke. The Institute for Clinical Neuroimmunology is supported by the Hermann and Lilly Schilling Foundation.

We are grateful to J. Benson for valuable help in editing, R. Schorner for his assistance with the figures, and Dr T. Winkler for helpful comments. We thank Prof H. Lassmann for providing Figure 3.

References


