Review Article

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Friend or foe? – B cells in stroke

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Abstract: Stroke is one of the leading causes of mortality and morbidity worldwide. Upon cerebral ischemia, an inflammatory reaction takes place in the brain. Infiltration of different immune cell subsets as well as activation of resident microglia cells have been shown to have both beneficial and detrimental effects on stroke outcome. For a long time, research in the field of adaptive immunity after stroke has mostly focused on T lymphocytes and only recently, several publications shed light on the importance of B lymphocytes in the acute and chronic phases of ischemic stroke. In this review, we will focus on the role of B cells in the ischemic brain and describe possible antibody-dependent and antibody-independent mechanisms in the development of post-stroke cognitive deficits.

Keywords: autoantibody; autoreactivity; ectopic lymphoid structure; cognitive decline; neuroinflammation

Zusammenfassung: Schlaganfall gehört nicht nur zu den häufigsten Todesursachen, sondern ist die wichtigste Ursache für lebenslange Behinderung weltweit. Unmittelbar nach einer zerebralen Ischämie kommt es zu einer lokalen entzündlichen Antwort, bei der neben den ortsständigen myeloiden Immunzellen früh aus der Peripherie in das ischämische Gehirn infiltrierende myeloide Zellen und später auch Lymphozyten eine Rolle spielen. Dabei werden neben schädlichen zunehmend auch für den Krankheitsverlauf positive Entzündungsreaktionen vermutet. Während bisher vor allem die Rolle von myeloiden Zellen und T-Lymphozyten im Vordergrund des Inte-

resses standen, sind mit der Entdeckung der verzögerten Einwanderung von B-Lymphozyten in der subakuten und chronischen Phase des ischämischen Schlaganfalls diese zunehmend in den Fokus gerückt. In dieser Übersichtsarbeit beschreiben wir mögliche antikörperabhängige und –unabhängige B-Zellfunktionen für den Langzeitverlauf nach Schlaganfall.

Schlüsselwörter: Autoantikörper; Autoreaktivität; ektope lymphoide Strukturen; kognitive Störung; Neuroinflammation

Immune mechanisms in stroke: does it matter?

According to the WHO, stroke is the second most common cause of mortality worldwide. In 2016 alone, 5.7 million people died after suffering from a stroke (WHO, Disease Burden and Mortality Estimates 2018). The clinical picture of acute traumatic or ischemic central nervous system (CNS) injury and stroke in particular is not only characterized by neurological deficits, but also by a high incidence of complications. Most prominent amongst these, is stroke-associated pneumonia (SAP) with a mortality of up to 37 % (Brommer et al., 2016; Chamorro et al., 2012; Hannawi et al., 2013; Meisel and Meisel, 2011). A key mechanism facilitating SAP is stroke-induced immune depression (Chamorro et al., 2012; Iadecola and Anrather, 2011a; Meisel et al., 2005; Westendorp et al., 2011). Lymphocytic apoptosis and dysfunction induced by an over-activation of the sympathetic nervous system (Prass et al., 2003) and anti-inflammatory effects on the innate immune system mediated by parasympathetic, cholinergic pathways (Engel et al., 2015) are involved in the pathogenesis of this temporary failure of host defense. Increased activity in the hypothalamus-pituitary axis results in release of corticosteroids further dampening immune responses (Chamorro et al., 2012; Meisel et al., 2005). The B cell compartment is equally affected by this lymphopenia. Especially splenic marginal zone (MZ) B cells are lost due to adrenergic over-activation. MZ B cells are innate-like immune cells rapidly producing immunoglobulin (Ig) M upon inflam-

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matory challenge. Their loss due to adrenergic over-activation after stroke therefore increases the susceptibility to bacterial infections (McCulloch et al., 2017).

Opposed to peripheral immune depression, cerebral ischemia also induces a cascade of inflammatory processes in the CNS, which may result in autoreactivity as we will discuss in this review focusing on B cell responses. The release of damage-associated molecular patterns and reactive oxygen species leads to the activation of sensors of the innate immune system, such as Toll-like receptors and subsequent production of inflammatory mediators (Chamorro et al., 2012; Iadecola and Anrather, 2011b). This results in microglia activation within hours after stroke and recruits peripheral immune cells to the affected brain region. Neutrophils accumulate shortly after the ischemic insult and monocytes follow in the first days after stroke (Anrather and Iadecola, 2016; Chamorro et al., 2012; Otxoa-de-Amezaga et al., 2018). Cells of the adaptive branch of the immune system, namely T and B lymphocytes, infiltrate in a delayed manner. Before entering the damaged brain area, T cells appear to be mainly primed in cervical lymph nodes by recognition of their cognate CNS antigens that are drained via lymphatic vessels or leak over the damaged blood brain barrier (Gelderblom et al., 2009; Kuntz et al., 2014; Laman and Weller, 2013). Several studies report presentation of CNS-specific antigens such as myelin oligodendrocyte glycoprotein (MOG), myelin basic protein (MBP), and N-methyl-D-aspartate (NMDA)-receptor components in antigen-presenting cells (APCs) residing in cervical lymph nodes of patients and experimental animals (Planas et al., 2012; van Zwam et al., 2009).

Unpublished data from our group indicate that T cell infiltration into the ischemic brain is antigen-specific. By adoptive cell transfer of either naïve, MOG-specific or ovalbumin-specific T cells into immunodeficient mice before middle cerebral artery occlusion (MCAO), we found that only MOG-specific T cells accumulated in the ischemic region of the brain (Klehmet et al. unpublished data). Once in the brain, both detrimental and protective features have been attributed to infiltrating T lymphocytes (Chamorro et al., 2012; Gelderblom et al., 2009; Kleinschnitz et al., 2013; Liesz et al., 2009; Shichita et al., 2009). Stroke outcome depends on the immune cell composition in the CNS after stroke, as mice with a pro-inflammatory immune response show more severe dysfunction after stroke, compared to mice prone to anti-inflammatory responses (Kim et al., 2014). Recently, it has been shown, that anti-inflammatory immune phenotypes and protection from stroke can be promoted by hypoxic preconditioning and subsequent upregulation of chemokine ligand 2 (CCL2) (Monson et al., 2014; Stowe et al., 2012).

Studies from our group demonstrate that blocking peripheral immunodepression after stroke increases inflammatory T cell responses in the brain (Romer et al., 2015). This finding suggests that CNS inflammation is not an isolated process and might well be influenced by the ongoing immune challenges in the periphery. For instance, SAP increases the infiltration of CNS antigen-specific T cells into the brain. In contrast, prevention of SAP decreases the recruitment of inflammatory macrophages and T lymphocytes to the ischemic brain, but increases the influx of regulatory T lymphocytes, resulting in a significantly better neurological outcome. These findings are in line with human stroke studies showing increased autoreactive CNS antigen-specific immune responses in the blood of patients with post-stroke infections compared to stroke patients without bacterial infections. Since increased levels of autoreactivity correlate with poorer stroke outcome, preventing bacterial post-stroke infections is a crucial aim in post-stroke care (Becker et al., 2011).

In experimental models, preventive antibiotic treatment succeeds in reducing the bacterial burden after stroke and effectively averts post-stroke infections, thus also improving the neurological outcome. However, two large randomized controlled phase III clinical trials failed to reduce bacterial pneumonia in stroke patients (Meisel and Smith, 2015). These findings warrant research into further treatment strategies to improve long-term outcome after stroke. One possible approach is to modulate immune responses by a pharmacological intervention in order to reverse stroke-induced immune depression in the periphery. However, temporal dampening of the immune system might be an adaptive mechanism to limit autoreactive CNS antigen-specific immune responses in the brain. Hence, any immune intervention after CNS injury must consider both, peripheral and central consequences. Another approach is to hinder peripheral immune cells from infiltrating into the brain after cerebral ischemia, restricting local inflammation and autoreactivity and therefore improving neurological function. Complete deficiency of T and B lymphocytes led to reduction of lesion size and inflammation in a mouse model (Hum et al., 2007), indicating that these cells contribute to secondary brain injury after stroke.

Most research in the field of stroke immunology has focused on innate immune cells or T lymphocytes, rather than B cells in the past. Nevertheless, it has been known for years that stroke patients can develop oligoclonal bands in their cerebrospinal fluid (CSF), which is an indication of local antibody production, and thus the presence of B lymphocytes, in the ischemic brain (Prüss et al., 2012; Tsementzis et al., 1986). Increasing evidence establishes the concept of B cells playing a pivotal role in CNS auto-

reactive processes (Ransohoff et al., 2015). Here we will review recent developments in investigating the role of B cells for stroke in comparison with findings in multiple sclerosis (MS) and spinal cord injury (SCI).

B cells in the ischemic brain

First experiments analyzing the effect of B cells on experimental stroke were carried out in $\mu\text{MT}^{-/-}$ mice. Due to a mutation in the μ chain of the B cell receptor, these mice do not develop mature B lymphocytes (Kitamura et al., 1991). When subjected to MCAO, they develop significantly larger lesions and suffer from higher mortality. Flow cytometric enumeration of infiltrating immune cells 48 hours after reperfusion demonstrated higher numbers of neutrophils, T cells, microglia and infiltrating macrophages in the ischemic hemisphere of the $\mu\text{MT}^{-/-}$ mice (Ren et al., 2011a). Intraperitoneal or intrastriatal transfer of B lymphocytes into $\mu\text{MT}^{-/-}$ mice rescued this phenotype which could be attributed to the production of interleukin (IL)-10 by the transferred lymphocytes since adoptive transfer of IL-10-deficient B lymphocytes did not affect the lesion size or the neurological outcome after MCAO (Chen et al., 2012; Ren et al., 2011a). Ren et al. found that IL-10-producing B lymphocytes decrease the infiltration of neutrophils (Ren et al., 2011a). This might partly explain the beneficial effect of early B cell infiltration on infarct growth, as several research groups could show that the recruitment of peripheral neutrophils contributes to the ischemic damage (Neumann et al., 2015; Neumann et al., 2018; Otxoa-de-Amezaga et al., 2018). Furthermore, in the case of lung infection, it was demonstrated that neutrophil infiltration is increased in IL-10-deficient animals, whereas it is decreased in a model of pulmonary IL-10 overexpression. This demonstrates that indeed IL-10 affects neutrophil recruitment and thus might play a similar role after cerebral ischemia (Peñaloza et al., 2015; Sun et al., 2009).

Moreover, transfer of IL-10 producing B lymphocytes into wild-type mice significantly reduced infarct lesion size which correlated with a reduced infiltration of pro-inflammatory T cell subsets into the ischemic brain while the infiltration of regulatory T cells was enhanced (Bodhankar et al., 2014, 2015a). In addition to protective effects via IL-10 secretion, B cells may also limit immune cell infiltration and infarct growth through the programmed death-1 (PD-1) coinhibitory pathway. PD-1 is an immunoreceptor expressed by activated T and B cells. Upon binding of PD-1 to its ligands PD-L1 or PD-L2, inhibitory signal pathways and peripheral T cell anergy are induced (Ren et

al., 2011b). An additional line of research suggests that there are sex differences in B cell biology after MCAO. In brief, female mice develop smaller infarcts, the peripheral immune depression is less drastic and the regulatory B cell response is stronger (Bodhankar et al., 2015b; Seifert et al., 2017). However, a recent study found no major influence of B cells on infarct size and functional outcome for up to 3 days after experimental stroke (Schuhmann et al., 2017). Thus, further research is required to better understand the role of B cells in the acute phase of stroke.

The above-mentioned experimental studies investigated the role of B cells within the acute or sub-acute phase after experimental stroke and were focused on their cytokine-producing function, neglecting their capability to produce auto-antibodies specific to CNS antigens. It has been known for a long time that local antibody production can occur in the ischemic brain and oligoclonal bands can be found in the CSF of stroke patients (Prüss et al., 2012; Tsementzis et al., 1986). In an experimental model, B cells have been demonstrated to infiltrate into the ischemic hemisphere in a delayed manner starting after 7 days and at least over the following 12 weeks (Doyle et al., 2015). Findings from our group support these results. In our hands, B lymphocyte infiltration starts between day 7 and day 14 after MCAO. Thereafter, the number of B lymphocytes keeps increasing at least until 10 weeks after MCAO. Doyle et al. hypothesized that this accumulation of B cells is responsible for a delayed post-stroke cognitive decline. In fact, clinical data suggest that the risk of developing dementia after stroke is increased and a subgroup of patients shows a remarkable cognitive decline (Levine et al., 2015; Pendlebury and Rothwell, 2009). In experimental stroke, mice developed delayed cognitive deficits 7 weeks after stroke onset. This phenotype was verified in different experimental models as well as with different cognitive tests and ultimately linked to the production of MBP-specific antibodies (Becker et al., 2016). In contrast, cognitive deficits after stroke were prevented in B cell-deficient $\mu\text{MT}^{-/-}$ mice or after B cell depletion. On a functional level, this cognitive decline was mirrored in a deficient long-term potentiation in the hippocampus developing between week 1 and week 7 after stroke (Doyle et al., 2015). These findings are mirrored by data from human brains obtained from deceased patients demonstrating that the frequency of B cells is significantly higher in the group with post-stroke dementia compared to the stroke group without dementia (Doyle et al., 2015).

Experiments from Doyle et al. as well as our own group show that B lymphocytes are not randomly spread in the ischemic hemisphere but rather form organized cell clusters reminiscent of B cell follicles in secondary lymphoid

Figure 1: B Cells after stroke. A. Early after stroke, different immune cell subsets, such as T cells (red), B cells (green), and myeloid cells (blue) infiltrate into the ischemic brain region. Amongst them, IL-10 producing regulatory B cells exert a beneficial role by inhibiting the inflammatory process. B. Due to the tissue damage, brain-specific antigens are released and drained towards the cervical lymph nodes. C. In the lymph node, the antigens can be presented to T cells by APCs or directly recognized by autoreactive B cell clones. D/E. The activated autoreactive B and T cells then infiltrate in a delayed manner into the ischemic brain region and start forming ELS. F. Histological analysis of the mouse stroke brain 7 weeks after surgery. Left picture: Large B cell clusters (B220+, green) have formed in the infarct core and are surrounded by T cells (CD3+, red). Right picture: The B cells in the clusters express IgG (green) and surrounding the cluster IgG-producing plasma cells (CD138 and IgG double-positive, red/green respectively) can be observed. G. The antibodies produced in the local immune reaction in the ischemic brain can bind to neuronal antigens and cause delayed cognitive decline.

organs (Doyle et al., 2015) that were termed ectopic lymphoid structures (ELS). As described below, similar structures have been identified in MS, SCI and other models of autoimmunity and chronic inflammation (Aloisi and Pujol-Borrell, 2006; Corsiero et al., 2016; Pitzalis et al., 2014). Here, it has been demonstrated that ELS produce fully matured, CNS-specific B cells and antibody-secreting cells. The reactivity of these antibodies remains to be determined, but published data suggest that autoreactive antibodies recognizing CNS antigens are produced locally after stroke (Dambinova et al., 2003; Kaley-Zylinska et al., 2013; Ortega et al., 2015; Weissman et al., 2011). There is ample evidence that such antibodies might inflict dysfunction and even damage to the CNS. This can occur through binding cognate structures like receptors as well as by antibody-dependent cell-mediated cytotoxicity, complement-mediated mechanisms or direct induction of apoptosis. The latter is known to occur in MS or SCI as well.

On the other hand, antibodies against peripheral nerve antigens have been associated with beneficial

effects in traumatic injury to peripheral nerves. Endogenous, self-reactive antibodies accumulate in injured nerve tissue and opsonize degenerating myelin debris. This opsonization facilitates phagocytosis of the myelin debris by macrophages and thus promotes nerve regeneration. The authors suggest that similar mechanisms might occur in the CNS (Vargas et al., 2010).

Research in a mouse model of SCI demonstrated that B cells proliferate and produce CNS-reactive antibodies in peripheral lymphoid organs. Intracerebral injections of these CNS-reactive antibodies caused robust glia activation and neuronal cell death, demonstrating their neurotoxic effect. Such autoreactive antibodies were also found to be increased in human SCI patients in the subacute phase (Arevalo-Martin et al., 2018). Moreover, they observed that B lymphocytes infiltrate in a rather delayed manner into the injured spinal cord and form ELS in this disease setting (Ankeny et al., 2006). Based on their previous findings, Popovich et al. went on to show that mice lacking B cells develop much smaller lesions after spinal cord contusion and recover considerably faster than their wild-type coun-

terparts. They attribute this phenomenon to direct neurotoxic effects of the antibodies as well as their ability to activate complement and innate immune cells (Ankeny et al., 2009). It is also possible that autoantibodies do not lead to cell death, but influence neuronal function through binding of surface receptors (Vincent et al., 2011). This is well described for the case of autoimmune encephalitis. Patients suffering from this disease show symptoms like psychosis, seizures, dyskinesia and autonomic dysfunction. In the case of autoimmune encephalitis, it has been shown that NMDA receptor autoantibodies are sufficient to elicit this pathology through binding and altering the function of the NMDA receptor (Kreye et al., 2016). Hence, it is likely that autoreactive antibodies produced after stroke have an impact on the long-term outcome, notably the occurrence of delayed cognitive deficits.

Lessons from multiple sclerosis and its experimental model

Since relatively little is known about the formation and function of ELS in stroke pathology parallels may be drawn from recent findings in the field of multiple sclerosis (MS) and its experimental autoimmune encephalomyelitis (EAE) model. MS is a chronic inflammatory disease of the CNS with various manifestation forms. Although major progress has been achieved in the past 2 decades, the underlying pathomechanisms are far from being fully understood. In the past, brain-infiltrating autoreactive myelin-specific CD4⁺ T-helper (Th) cells have been considered the main drivers of neuroinflammation, demyelination and neurodegeneration in MS. The abundance of CD4 T cells and their products in MS lesions (Wu and Alvarez, 2011), as well as large-scale genomic studies (Beecham et al., 2013) and the observation that MS-like symptoms can be induced in the EAE model by transferring CNS-autoreactive Th cells (McPherson et al., 2014) support this paradigm. However, as B cell-depleting approaches are currently among the most effective treatment options for MS (Gelfand et al., 2017; Hauser et al., 2008; Menge et al., 2016; Naismith et al., 2010), B lymphocytes and their involvement in MS pathomechanisms have gained increasing interest in recent years. They may contribute to neuroinflammation by producing autoreactive antibodies and proinflammatory cytokines or presenting auto-antigens. It has been known for a long time, that CNS-specific antibodies and activated B lymphocytes can be found in MS patients' CSF (Dobson et al., 2013; Kabat et al., 1948; Reiber et al., 1998). Their involvement in complement-de-

pendent demyelination and loss of oligodendrocytes in MS lesions is a more recent discovery, however (Liu et al., 2017). Concordantly, antibodies found in MS patients were directed against myelin membrane lipids but also intracellular protein expressed ubiquitously (Brändle et al., 2016; Brennan et al., 2011). It has been shown, that removing antibodies from the peripheral blood by therapeutic plasma exchange is effective in some patients (Keegan et al., 2005). On the other hand, B cell depletion with anti-CD20 antibody effectively reduces relapses in MS without affecting intrathecal autoantibody titers (Piccio et al., 2010). Therefore, it is likely that B cells contribute to MS pathology beyond the production of autoantibodies. B cells are also known to secrete different cytokines, depending on their polarization state. Pro-inflammatory B cells have been described to induce interferon (IFN) γ , tumor necrosis factor α (TNF α), lymphotoxin α (LT α) and IL-6 production in active MS or EAE (Bar-Or et al., 2010; Barr et al., 2012), whereas anti-inflammatory cytokines such as IL-10 and transforming growth factor β (TGF β) are expressed by regulatory B cells during early EAE induction (Matsushita et al., 2008).

Very recently it was demonstrated that IgA-producing plasma cells migrate from the gut to the CNS attenuating disease activity in the EAE model. Mice that were deficient of plasmablasts and/or plasma cells showed earlier and more severe EAE onset that could be rescued by adoptive transfer of plasma cells. This protective effect was attributed to IL-10 secretion by the plasma cells populating the CNS (Rojas et al., 2019). These new insights into the role of the gut-brain axis in regulating immune responses during neuroinflammation guide increasing interest towards the gut microbiome as a therapeutic target in stroke (Winek et al., 2016). Nevertheless, several studies indicate that pro-inflammatory B cells outweigh their regulatory counterpart in MS (Bar-Or et al., 2010; Barr et al., 2012; Ireland et al., 2012) promoting neuroinflammation. Interestingly, the imbalance between pro- and anti-inflammatory B cell cytokine expression was found to be highest in patients with more disabling MS subtypes (Piancone et al., 2016), indicating a direct link of cytokine expression levels to disease severity. B cells are also important antigen-presenting cells. In case of CNS-autoreactivity, B cells internalize and process myelin components such as MOG and MBP which then are presented on the cell surface, where antigen recognition and interaction with co-stimulatory proteins such as CD80 lead to activation of T cells. Increased CD80 expression in B cells has been observed in MS patients (Aung and Balashov, 2015) and could be reversed by IFN β therapy (Genç et al., 1997). Under healthy conditions, the blood brain barrier limits

lymphocyte entry into CNS tissue. Antigen recognition and presentation by lymphocytes takes place in perivascular compartments called Virchow-Robin space. Highly organized, B cell rich lymphoid structures were described in the Virchow-Robin space in MS patients already in 1979 (Prineas, 1979). Only recently, however, have these findings regained researchers' attention as several studies observed inflammatory B cell infiltrates in the meninges of some early- and late-stage MS patients (Lucchinetti et al., 2011; Serafini et al., 2004). These structures vary in complexity from simple B cell aggregates to highly organized lymphoid structures (Serafini et al., 2004). Recent studies also provide evidence for germinal center formation in ELS (Lehmann-Horn et al., 2016; Serafini et al., 2004). Germinal centers are the site in lymphoid tissue where B cells expand and immunoglobulin gene hypermutation and

selection is induced (Jacob et al., 1991; MacLennan, 1994; MacLennan and Gray, 1986). In other words, B cells with low affinity to CNS-antigens proliferate and differentiate to highly specific memory B cells and antibody producing plasma cells. As a result, long-lived autoreactive B cells and plasma cells can maintain chronic inflammation in the brain for many years (Corsiero et al., 2016). Therefore, it seems that formation of meningeal ELS with germinal centers play a pivotal role in the development of MS. This assumption was reinforced by recent experiments that show a reduction in axonal damage by depleting CNS B cell aggregates with anti-CD52 antibody treatment in mice (Simon et al., 2018). In this context, it seems plausible, that B cells play a major role in MS pathology through various pathways.

Table 1: Immune responses in stroke compared to multiple sclerosis. Similarities and differences between the B cell immune response after stroke or during MS/EAE are listed in the following table.

♦ marks patient data, whereas • indicates results from experimental animal research.

Immune responses in stroke compared to multiple sclerosis		
	Stroke	MS
Regulatory B cells	<ul style="list-style-type: none"> • IL-10-producing B cells limit infarct volume, mortality and immune cell infiltration (Ren et al., 2011) • Enhance Treg response (Bodhankar et al., 2013) 	<ul style="list-style-type: none"> • B regs are protective in early phase of EAE-induction by suppressing IL-17 and IFNγ (Matsushita et al., 2008)
Effector B cells/ Plasma cells	<ul style="list-style-type: none"> ♦/• Antibody production (Dambinova et al. 2003; Ortega et al., 2015) • Minor or no effects known in the acute phase (Schuhmann et al. 2017; Doyle et al., 2015) • Delayed cognitive impairment (Doyle et al., 2015) 	<ul style="list-style-type: none"> ♦/• Function: Secretion of IFNγ, TNFα, LTα, IL-6 Antibody production Antigen presentation (Staun-Ram & Miller, 2017) • Promote T cell infiltration and expansion (Matsushita et al., 2008)
CSF pleocytosis	<ul style="list-style-type: none"> ♦ Lymphocytic pleocytosis in 18.1 % of patients (Prüss et al., 2012) 	<ul style="list-style-type: none"> ♦ Activated B lymphocytes in 59 % of patients (Reiber et al., 1998)
Oligoclonal bands in CSF	<ul style="list-style-type: none"> ♦ Found in 24.8 % of stroke patients (Prüss et al., 2012) 	<ul style="list-style-type: none"> ♦ Found in 87.7 % of MS patients (Dobson et al., 2013)
Frequently found auto-antibodies	<ul style="list-style-type: none"> ♦ In Serum: Myelin basic protein (22 %) Proteolipid protein (17 %) NMDA-receptor (44 %) (Dambinova et al., 2003; Becker et al. 2011) 	<ul style="list-style-type: none"> ♦ In CSF: Myelin membrane lipids Ubiquitous intracellular protein (Brändle et al., 2016 Brennan et al., 2011)
Antibody effects	<ul style="list-style-type: none"> ♦ MBP antibodies in Serum associated with cognitive decline (Becker et al., 2011) 	<ul style="list-style-type: none"> ♦ Antibody-mediated demyelination (Lucchinetti et al., 2000)
Antigen-priming	<ul style="list-style-type: none"> • CNS antigen is presented in cervical lymph nodes after stroke (Planas et al., 2012; van Zwam et al., 2009) 	<ul style="list-style-type: none"> ♦ B cell maturation in cervical lymph nodes (Stern et al., 2014)
ELS localization	<ul style="list-style-type: none"> • Infarct lesion (Doyle et al., 2015) 	<ul style="list-style-type: none"> ♦ Leptomeningeal (Serafini et al., 2006)

Conclusion

As outlined above, B lymphocytes seem to play an increasingly appreciated role in the pathology of stroke. In the acute phase, regulatory B lymphocytes may be recruited to the injured CNS and dampen inflammatory processes. On the other hand, a delayed activation and infiltration of autoreactive B cells possibly has a detrimental effect on cognitive function through the production of CNS-specific autoantibodies. The production and role of CNS-autoantibodies have been well studied in the case of MS/EAE. Nevertheless, recent findings as well as old publications suggest that similar phenomena occur after ischemic stroke. Further studies are needed to shed light on the reactivity of locally produced antibodies and their mechanisms of action. Once better understood, B lymphocytes might become an attractive therapeutic target to treat post-stroke cognitive decline and increase the quality of life of stroke survivors.

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Glossary

APCs	Antigen presenting cells
CNS	Central nervous system
CSF	Cerebrospinal fluid
EAE	Experimental autoimmune encephalitis
ELS	Ectopic lymphoid structures
IFN	Interferon
Ig	Immunoglobulin
IL	Interleukin
MBP	Myelin basic protein
MCAO	Middle cerebral artery occlusion
MOG	Myelin oligodendrocyte glycoprotein
MS	Multiple sclerosis
MZ	Marginal zone
NMDA	N-Methyl-D-Aspartate
PD-1	Programmed death-1
SAP	Stroke-associated pneumonia
SCI	Spinal cord injury
TGFβ	Transforming growth factor β
Th	T helper
TNFα	Tumor necrosis factor α
LTα	Lymphotoxin α

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