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Review article

Role of B cells and antibodies in multiple sclerosis

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ABSTRACT

Multiple sclerosis (MS) is a chronically progressive auto-immune mediated inflammatory demyelinating disease of the central nervous system (CNS) which manifests as disturbances in sensorimotor function and cognitive impairment. Although believed to be a T-cell mediated disease, the role of B cells has recently become a central issue in MS pathogenesis. Both antibody dependent and independent theories have been suggested to play a role in the initiation of inflammatory demyelination. Antibody dependent mechanisms include formation of auto-antibodies targeting specific tissues in the CNS and B cell antigen presentation to T cells, leading to subsequent activation and cytokine secretion. Antibody independent mechanisms entail formation of ectopic lymphoid structures, cytokine production and secretion of neurotoxic factors. Moreover, breach of peripheral tolerance mechanisms due to disturbances in regulatory T cell functioning has also been described. B cell depletion through anti-CD20 monoclonal antibody utilization and other immunomodulatory therapies have been promising in reducing episodes of relapse and slowing progression, further strengthening the concept that B cells and antibodies are significant players in formation of brain lesions in MS.

1. Introduction

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system of unknown aetiology. MS mainly affects young adults and is the most common cause of neurological disability in this age group. It seems that the disease onset and course may depend on infectious, genetic, immunological or environmental causes (Iwanowski and Losy, 2015). Diffuse gray and white matter demyelination results in reduction in brain volume. Throughout the course, MS manifests as sensorimotor disturbances and cognitive impairment of unpredictable onset and varying severity. Neurodegeneration, axonal and blood-brain barrier damage is believed to be the result of immunological activation of both adaptive and innate immunity. B- and T- lymphocyte infiltration are found to be responsible for the formation of lesions at particular locations of the CNS (Lassmann, 2019). MS commonly affects the young adult population and the pathomechanisms behind disease development is yet to be more clearly elucidated. The exact pathogenesis remains unknown, however, ongoing studies have shown evidence of neuroinflammatory contribution with promising effects after administration of anti-inflammatory and immunomodulatory drugs, although still unable to reverse disease progression (Ghasemi et al., 2017). This suggests the significance of inflammatory infiltration in the process of neuronal demyelination and damage (Dargahi et al., 2017). There are three main courses of MS: relapsing-remitting (RRMS), secondary progressive (SPMS) and primary progressive (PPMS). RRMS, which is the most common course, occurs in 85–90% of patients. RRMS is characterized by clinical episodes interspersed by periods of stability, affects twice as many women as men and 40–50% of patients develop into SPMS within a ten year period. Approximately 10% of patients experience PPMS, presenting with gradual neurological dysfunction without exacerbations. Compared with RRMS, the mean age of PPMS onset is a decade later and there is no female predominance (Iwanowski and Losy, 2015).

Although T cells are widely known to be of major contribution to inflammatory demyelination in MS, growing evidence suggests a significant role of B cells in the disease progression. Many genetic variants have been associated with immunological aspects of MS, including T-cell activity and B-cell expression of surface co-stimulatory molecules, enhancing ones susceptibility to disease development especially when environmental risk factors coexist (Parnell and Booth, 2017). Both B cell antibody-dependent and independent mechanisms have been proven to be involved in MS pathogenesis and exerts both protective and damaging effects to the CNS through secretion of pro- and anti-inflammatory cytokines [Li et al., 2018]. Besides differentiation into plasma cells producing autoantibodies, B cells are known for their ability to stimulate the activity of T cells through antigen presentation (Lisak et al., 2012), production of soluble neurotoxic factors triggering demyelination (Lassmann, 2019) and switching to memory cells which

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contributes to autoproliferation of CD4 + T-cells (Jelcic et al., 2018).

Presence of oligoclonal bands in the cerebrospinal fluid and brain tissue plaques of MS patients results from persistent intrathecal clonal expansion of various B cell populations that contribute to production of autoreactive antibodies (Wootla et al., 2011). Recent evidence suggests peripheral B cells as a potential source of intrathecal oligoclonal bands (Bankoti et al., 2014) due to the presence of clonally related populations of B cells in the peripheral blood and the CNS (Eggers et al., 2017). This strongly suggests that B cells are important players in the autoimmune processes observed in MS. However, more investigation is required to answer the question regarding whether disease onset is a result of peripheral immune cell migration or inflammation initiated centrally within the CNS.

Compartmentalized inflammation refers to inflammation limited within the boundaries of the blood-brain barrier. Trapped B cell aggregates, in concert with other chronically activated inflammatory cells within the central nervous system are associated with progression of MS and explains the persistence of brain tissue damage (Meinl et al., 2008, Machado-Santos et al., 2018). Recent studies have focused on novel B cell depletion therapies and promising effects have been observed after introduction of anti-CD20 monoclonal antibodies in clinical studies. This further signifies the role of B cells as a major source of inflammation.

This review will look into the major contributions of B cells and immunoglobulins in the pathogenesis of MS, including their interactions with other inflammatory cells and their role in promoting a pro-inflammatory environment through processes of antigen presentation, cytokine production and antibody secretion. Benefits and limitations of emerging therapies will also be explored.

2. Antibody dependent and independent functions of B cells

Growing interest has been directed towards the involvement of B cells in the pathogenesis of inflammatory demyelination in MS. B cells are believed to be the source of autoantibodies targeting specific tissues of the CNS. Studies have found meningeal infiltration of B cell follicle-like structures, deposition of immunoglobulins and complement, suggesting the presence of an environment that nurtures B cell proliferation and clonal expansion (Pröbstel et al., 2015). The involvement of antibody-independent mechanisms is mainly supported by the findings of studies on B cell depletion therapy. Levels of antibodies remained the same after administration of rituximab, an anti CD20 monoclonal antibody. Rituximab does not target plasma cells, which is explanatory for the findings, however reductions in inflammatory damage and relapse observed after B cell depletion despite the same levels of antibodies suggests other mechanisms of B cell involvement independent of antibody mediated effects (Hauser et al., 2008). In this section, autoantibodies identified in MS will be discussed. Antibody-independent mechanisms of inflammatory injury including antigen presentation, formation of ectopic lymphoid organs and T cell, macrophage and glial activation through cytokine signaling will also be elucidated (Miyazaki and Niino, 2014).

2.1. Autoantibodies as potential biomarkers

Oligoclonal bands, a major pathological feature present in MS patients proves the participatory activities of B cells in axonal damage and demyelination. Oligoclonal immunoglobulins secreted from plasma cells are present intrathecally. Evidence supports the presence of affinity maturation and somatic hypermutation following clonal expansion of B cells in the CSF. The antigens potentially responsible for the initiation of these processes still demands further investigation (Qin et al., 2003; Qin et al., 1998). It remains debatable whether B cell activation occurs peripherally in the germinal centers before migration into the CNS, occurs locally in germinal centers in the CNS as a result of antigenic challenge behind the blood-brain barrier or a combination of both (von Büdingen et al., 2011), since ectopic B cell follicular like structures containing proliferating B cells are also present in the meninges (Magliozzi et al., 2007; Serafini et al., 2004). Antibody mediated phagocytic damage of myelin may also be involved in neuronal and axonal damage since antibodies were found in phagocytic macrophages from active demyelinating lesions [Breij et al., 2008). MS lesions also harbor autoantibodies, B cells and plasma cells (Prineas and Wright, 1978).

Various antibodies targeting autoantigens in the CNS have been identified in the serum and CSF of MS patients, signifying the involvement of humoral immunity in the process of inflammatory demyelination. One extensively studied autoantigen and target of autoantibodies worth mentioning is myelin oligodendrocyte glycoprotein (MOG) present on oligodendrocyte and myelin sheath surfaces (Peschl et al., 2017). Antibodies to MOG (anti-MOG) of the IgG isotype are believed to be involved in a number of immunological processes including complement fixation and activation of antibody dependent cellular cytotoxicity (Ramanathan et al., 2016). Cells expressing MOG are targeted through extracellular domain epitope binding of anti-MOG and subsequent natural killer cell mediated killing (Brilot et al., 2009). Their direct damaging effects remains controversial since the increase in the levels of anti-MOG is able to be alternatively depicted as a secondary inflammatory response triggered by the products of degraded myelin protein (Ramanathan et al., 2016). High titers of anti-MOG is correlated with increased severity at disease onset, however, they are not useful as a predictor of disease progression (Cobo-Calvo et al., 2019). Waters et al. (2015) discovered that none of the patients tested positive for MOG IgG1 antibodies had a clinical diagnosis of MS, therefore suggesting that detection of serum anti-MOG may allow us to differentiate between MS and non-MS acquired demyelinating syndromes such as acute disseminated encephalomyelitis (ADEM). Recent evidence, however, supports that MOG-specific T cells may be present in patients with MS (Bronge et al., 2019).

Damage to the blood-brain barrier, potentially following leptomeningeal inflammation (Absinta et al., 2015) allows entry of peripheral inflammatory cells which may lead to formation of aggregates of B cells within the CNS. Investigation of the detrimental effects of B cell dependent neuroinflammation in experimental models of MS demonstrated disruption in blood-brain barrier integrity, varying in location and magnitude of injury in each model (Bell et al., 2019).

Despite evidence of associations between anti-MOG and demyelinating diseases, a study (Owens et al., 2009) utilizing recombinant antibodies from CSF of MS subjects assessing the antigenic targets of intrathecal oligoclonal bands showed no immunological reaction towards MOG, providing us an insight towards other potential antigenic targets as triggers of inflammatory demyelination. This includes viral involvement, such as Ebstein-Barr virus (Guan et al., 2019; Mameli et al., 2012), IgG4 autoantibodies towards self-proteins such as neurofascin (Stich et al., 2016), ion channel protein anoctamin 2 (Ayoglu et al., 2016), contactin, transaldolase (Jaśkiewicz, 2004) and cytoskeletal protein alpha actinin (Pandey et al., 2013). Antibodies targeting neurofascin, an axo-glial protein present around the node of Ranvier are involved in paranodopathy, a damaging process leading to nerve conduction blockade as a consequence of disturbances in protein interactions (Kira et al., 2018). However, due to the overlapping presence of these biomarkers in other diseases, their specificity is still questionable and their usefulness as potential biomarkers on disease progression and prognosis requires further research.

Moreover, there has been recent discovery of novel autoantibodies against talin1, a cytoskeletal protein, in MS patients. Levels were found to be increased in MS patients in comparison to controls and these antibodies may play a role in transmigration of lymphocytes, negatively correlating with IgG levels, presumably providing a protective effect against pathological progression (Muto et al., 2015).

Other antibodies detected in MS which are considered as valuable diagnostic or prognostic biomarkers include anti-glycan antibodies, anti-ganglioside and antibodies toward neurofilament light (NFL) and

neurofilament medium (NFM). In a panel of four anti-glycan IgM antibodies (anti-GAGA2, anti-GAGA3, anti-GAGA4 and anti-GAGA6), presence of at least one was found to be associated with imminent early relapse and disease progression (Freedman et al., 2009, Freedman et al., 2012). Moreover, increased IgM antibodies targeting alpha-glucose antigens, produced by self-replenishing B1 B-cells, were found early in the disease course of MS, which may predict conversion to RRMS (Dotan et al., 2006). Neurofilament proteins were found to be indicative of axonal degeneration. Elevated NFL correlates with degree of axonal damage and worse disease outcome, with autoantibodies toward NFL being higher in patients with progressive MS. There is also increased intrathecal IgG and IgM towards NFM in MS patients (Iwanowski and Losy, 2015). Studies also revealed elevated anti-ganglioside antibodies in MS, which triggers local immune response and influences neuronal tissue damage (Iwanowski and Losy, 2015). High titers of anti-GM1 and anti-GM3 IgG antibodies in MS patients were found to be associated with demyelination and blood-brain barrier damage, respectively (Kolyovska et al., 2017; Zaprianova et al., 2004).

2.2. Antigen presentation and regulation of cytokine secretion

Interactions between T cells and B cells capable of antigen presentation initiate neuroinflammatory reactions. MHCII dependent antigen presentation by B cells, together with costimulatory molecules such as CD80, CD86 and CD40, promotes T cell proliferation and secretion of cytokines, initiating autoimmunity through T cell activation. Increased B cells positive for CD80 were found in patients with active MS which is presumably responsible for activation of Th1, causing episodic exacerbations (Genç et al., 1997).

B cells are able to recognize soluble antigens and conformational epitopes, internalize and express them on the surface alongside MHC, ready for recognition by T cells (Claes et al., 2015). Errors in peripheral autoantigen processing by specific proteases may be the cause of myelin reactive T cells persistence in circulation due to failed tolerance (Stoeckle and Tolosa, 2010). Reactivation of autoreactive T cells by antigen presenting cells after migration into the CNS triggers neuroinflammation. Recently, researchers have found that peripheral B cell activation of T cells and subsequent migration into the CNS leads to destruction of myelin. Whereas depletion of B cells led to decreases in T cell proliferation (Jelcic et al., 2018).

The capability of B cell antigen presentation could potentially be enhanced by CD40-CD40L interactions. In MS, elevated levels of CD40L expressing CD4 + T cells were identified. After binding to CD40 present on B cells, neuroinflammatory processes are initiated through recruitment of inflammatory cells by upregulation of cell adhesion molecule expression, enhanced expression of MHCII, other surface co-stimulatory molecules, B cell proliferation, antibody production and cytokine secretion. Furthermore, activation of NF-κB pathways through CD40 stimulation also occurs, depicted by enhanced memory B cell proliferation due to NF-κB hyperphosphorylation in MS patients and increased production of proinflammatory cytokine IL-6 in comparison to controls. Lower B cell proliferation rates were observed in the absence of CD40 (Grewal et al., 1996). Inhibiting the proinflammatory signaling through NF-κB pathway mediation is yet another therapeutic aim (Chen et al., 2016). Additionally, ubiquitination and degradation of Casitas-B-lineage lymphoma-b (Cbl-b) is known to be mediated by CD40 co-stimulation. Normally, Cbl-b is responsible for B cell response inhibition, thus Cbl-b ubiquination following BCR-CD40 stimulation dampens the negative regulation of B cell activation and proliferation. It is hypothesized that Cbl-b ubiquitination may be responsible for setting the threshold of B cell activation (Tang et al., 2019).

Upregulation of B cell survival factor B cell activation factor (BAFF) was found in MS lesions, enhancing persistence of cytokine producing B cells (Kannel et al., 2015). Decreased level of BAFF in CSF at MS onset suggests uptake by intrathecal B cells and correlates with increased IgG production (Puthenparampil et al., 2016). Strict regulation of BAFF is important in the balance of pro-inflammatory and regulatory activities of B cells (Claes et al., 2015). Administration of agents targeting BAFF and APRIL led to disease worsening which is supposedly due to enhanced memory B cell activity (Kappos et al., 2014). Concerning cytokine production, pro-inflammatory B cells are known to secrete IL-6, IL-12, IL-15, TNF-α and lymphotoxin-α. Granulocyte-monocyte colony stimulating factor (GM-CSF) is also secreted by B cells, implying interactions with myeloid cells and opposing regulating effects of IL-10 (Li et al., 2015). On the other hand, B cells may also harbor protective effects through secretion of anti-inflammatory cytokines such as IL-10, IL-35 and TGF-β (Li et al., 2016). Targeting memory B cells and promoting balance of pro- and anti-inflammatory properties of B cells are major considerations for future therapies.

2.3. Formation of ectopic lymphoid structures

Aggregates of B- and T- lymphocytes form tertiary lymphoid organs (TLO) and structures resembling germinal centers (GC) in meninges of MS patients. Within germinal centers, B cells proliferate and undergo processes of affinity maturation and somatic hypermutation. After a series of GC reactions, B cells are capable of differentiation into plasma cells and memory cells producing autoantibodies. Moreover, B lymphocytes residing in ectopic TLOs are resistant to anti-CD20 therapy with persistence of antibody production despite complete B cell depletion, likely due to local secretion of B cell survival factors such as BAFF (Thaunat et al., 2008). Creation of a special inflammatory niche promotes both formation and maintenance of TLO. Besides inflammatory cells, evidence supports the role of stromal cells, which are non-immune cells, as an important player in lymphocyte recruitment and retention within the meninges. A pro-inflammatory milieu is achieved through secretion of cytokines (TNF-α, IL-6, IL-23), chemokines (CXCL13) and B cell regulatory factors (Pikor et al., 2015).

Besides formation of TLOs, B cells are also contributory to the maintenance of these structures through cytokine, chemokine and lymphotoxin signaling (Corsiero et al., 2016). The chemokine, CXCL13 which binds to CXCR5 expressed on B cells is elevated in active MS lesions. Such signaling is involved in the control of immune cell localization, shifting of B cells between light and dark zones and activation of microglia. Formation of ectopic follicles are associated with enhanced disease severity, likely due to favored affinity maturation and clonal maturation toward autoantigens (Corsiero et al., 2016). IL-22 is an important cytokine involved in mediating expression of lymphoid chemokines, namely CXCL12 and CXCL13 which are B-cell chemoattractants, playing a role in formation of TLOs and thereby promoting constitution of autoantibody-producing B cell aggregates. Blockade of IL-22 has been discovered to interfere with TLO formation and significant reduction in autoantibody production (Barone et al., 2015).

3. Failure of tolerance

Contrary to other autoimmune diseases where both central and peripheral tolerance are breached, MS exhibits only failure of peripheral tolerance due to disturbances in regulatory T cell (T_{reg}) functioning (Kinnunen et al., 2013). Defects in the CD4 + CD25 + regulatory T cell population is involved in MS. Further look into the subdivisions of T cells expressing CD4 + CD25 +, high expression of IL-7 receptor α chain (CD127) is associated with increased pro-inflammatory cytokine production, mainly IL-2, IFN-γ and TNF-α which in turn, promotes proliferation of CD25- T cells, further eliciting inflammatory damage. The subgroup with low CD127 expression however, showed no defects in T regulatory activities in comparison to normal subjects (Michel et al., 2008), proposing that elimination of cells highly expressing CD127 may be beneficial in reducing T cell proliferation, pro-inflammatory cytokine production and due to normal T_{reg} functions, may restore tolerance.

Expression of migration inhibitory factor (MIF) and their receptors

CXCR4 and CD74 are highly regulated through negative feedback. Early in the course of MS, downregulation of MIF correlates with decreased CD74 but increased CXCR4 expression, leading to B cell maturation disturbances responsible for arrest of B cells in the earlier stages of maturation. Coinciding with overexpression of CXCR4, which downregulates expression of Fas, an important mediator of apoptosis essential for removal of autoreactive immune cells, naïve B cells are allowed to escape tolerance (Rijvers et al., 2018). Increased MIF level, which correlates with disease severity and progression, was found in patients with progressive MS (Benedek et al., 2017). Administration of ibudilast, a small molecule inhibitor of MIF and phosphodiesterase have shown promising results in slowing the rate of brain atrophy in progressive MS (Fox et al., 2018).

Clonal deletion, clonal ignorance and anergy are tolerance mechanisms essential for clearance of autoreactive B cells. C-ets-1 is a transcription factor involved with inducing peripheral B cell anergy and clonal ignorance. Russell et al. (2015) investigated the effects of c-ets-1 deficiency on immune tolerance and discovered that although central clonal deletion was intact, B cells failed to achieve tolerance through peripheral clonal ignorance and anergy. Besides maintenance of clonal ignorance to antigens exhibiting low affinity, c-ets-1 is also fundamental for inhibition of anergic B cell differentiation into autoantibody producing cells. Defects in apoptosis mediated by aberrant B cell specific Fas-FasL interactions led to uncontrollable production of autoantibodies, signifying the importance of Fas in maintaining tolerance (Hueber and Koncz, 2012).

4. Currently investigated treatments

Various therapeutic strategies are under investigation, aiming to improve prognosis, prevent relapse and minimize the extent of disability. Extensive research revealed benefits of using monoclonal antibodies (mAb) against CD20 in both progressive and relapsing-remitting variants of MS. Administration of CD20-mAb rituximab successfully slowed disease progression and lowered the rate of relapse (Alcalá et al., 2018). A newer CD-20mAb, ocrelizumab has been used in relapsing-remitting MS and is the first agent approved for the primary progressive form, diminishing disease activity and progression (D'Amico et al., 2019; Bigaut et al., 2019). Moreover, ocrelizumab targets both B cells and CD20 + T-cells, which might explain why CD20 targeted therapy is so efficacious in reducing inflammation (Gingele et al., 2018). Another mechanism by which B cell depletion can be beneficial in MS is its effect on increasing the pool of regulatory T cells and reducing activation of T cells since low numbers of B cells are available for antigen presentation after therapy (Lovett-Racke et al., 2019). Adverse effects of long term use, route of administration, infusion times, including the risks and benefits of different novel monoclonal antibodies should be carefully addressed (Ancau et al., 2019).

Besides anti-CD20 therapy, other agents are under investigation as future therapeutic candidates. Cladribine has recently been found to also have memory B cell depleting properties (Ceronie et al., 2018). Small-molecule therapies are investigated for their B cell modulatory actions and are beneficial due to higher blood-brain barrier penetration and higher flexibility in treatment initiation and discontinuation (Gregson et al., 2019). Increasing activity of IL-10 producing regulatory B cells through usage of fingolomod and glatiramer acetate have been explored (Sabatino et al., 2019). Recently in a phase II clinical trial (Montalban et al., 2019), evobrutinib, a Bruton's tyrosine kinase (BTK) enzyme inhibitor was used to target B cell activation with results showing reduction in enhancing lesions. With further research, the possibility of targeting B cell function without the need for depletion minimizes the risk of acquiring infections, which occurs as a complication of anti-CD20 therapy due to decreased number of immune cells in circulation (Sabatino et al., 2019).

5. Conclusion and future implications

To conclude, further research is certainly required to disentangle complexities in the immunological pathways and precise roles of B cells in MS pathogenesis in order to develop effective targeted therapeutic agents. This involves identifying, in greater detail, the antibody dependent and independent mechanisms of disease development. Antigen presentation, B cell-T cell interactions, formation of ectopic lymphoid tissues, cytokine signaling, defects in peripheral B cell tolerance, production of autoantibodies and correct identification of immunological targets of B cells are all important issues to address. Regardless, future work could continue to search for effective therapeutic strategies aimed at reducing inflammation, disease relapse, progression and promoting remyelination together with thorough assessment of drug safety and tolerability.

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Declaration of Competing Interest

None.

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References

Absinta, M., Vuolo, L., Rao, A., et al., 2015. Gadolinium-based MRI characterization of leptomeningeal inflammation in multiple sclerosis. Neurology 85, 18–28.
Alcalá, C., Gascón, F., Pérez-Miralles, F., et al., 2018. Efficacy and safety of rituximab in relapsing and progressive multiple sclerosis: a hospital-based study. J. Neurol. 265, 1690–1697.
Ancau, M., Berthele, A., Hemmer, B., 2019. CD20 monoclonal antibodies for the treatment of multiple sclerosis: up-to-date. Expert. Opin. Biol. Ther. 19, 829–843.
Ayoglu, B., Mitsios, N., Kockum, I., et al., 2016. Anoctamin 2 identified as an autoimmune target in multiple sclerosis. PNAS 113, 2188–2193.
Bankoti, J., Apeltsin, L., Hauser, S.L., et al., 2014. In multiple sclerosis, oligoclonal bands connect to peripheral B-cell responses. Ann. Neurol. 75, 266–276.
Barone, F., Nayar, S., Campos, J., et al., 2015. IL-22 regulates lymphoid chemokine production and assembly of tertiary lymphoid organs. Proc. Natl. Acad. Sci. U S A 112, 11024–11029.
Bell, L., Koeniger, T., Tacke, S., et al., 2019. Characterization of blood-brain barrier integrity in a B-cell-dependent mouse model of multiple sclerosis. Histochem. Cell Biol. 151, 489–499.
Benedek, G., Meza-Romero, R., Jordan, K., et al., 2017. MIF and D-DT are potential disease severity modifiers in male MS subjects. Proc. Natl. Acad. Sci. U.S.A. 114, E8421–E8429.
Bigaut, K., De Seze, J., Collongues, N., 2019. Ocrelizumab for the treatment of multiple sclerosis. Expert Rev. Neurother. 19, 97–108.
Breij, E.C.W., Brink, B.P., Veerhuis, R., et al., 2008. Homogeneity of active demyelinating lesions in established multiple sclerosis. Ann. Neurol. 63, 16–25.
Brilot, F., Dale, R.C., Selter, R.C., et al., 2009. Antibodies to native myelin oligodendrocyte glycoprotein in children with inflammatory demyelinating central nervous system disease. Ann. Neurol. 66, 833–842.
Bronge, M., Ruhrmann, S., Carvalho-Queiroz, C., et al., 2019. Myelin oligodendrocyte glycoprotein revisited-sensitive detection of MOG-specific T-cells in multiple sclerosis. J. Autoimmun. 102, 38–49.
Ceronie, B., Jacobs, B.M., Baker, D., et al., 2018. Cladribine treatment of multiple sclerosis is associated with depletion of memory B cells. J. Neurol. 265, 1199–1209.
Chen, D., Ireland, S.J., Remington, G., et al., 2016. CD40-mediated NFκB activation in B cells is increased in multiple sclerosis and modulated by therapeutics. J. Immunol. 197, 4257–4265.
Claes, N., Fraussen, J., Stinissen, P., et al., 2015. B cells are multifunctional players in multiple sclerosis pathogenesis: insights from therapeutic interventions. Front. Immunol. 6.
Cobo-Calvo, A., Sepúlveda, M., d'Indy, H., et al., 2019. Usefulness of MOG-antibody titres at first episode to predict the future clinical course in adults. J. Neurol. 266, 806–815.
Corsiero, E., Nerviani, A., Bombardieri, M., et al., 2016. Ectopic lymphoid structures:

powerhouse of autoimmunity. Front. Immunol. 7.
D'Amico, E., Zanghì, A., Gastaldi, M., et al., 2019. Placing CD20-targeted B cell depletion in multiple sclerosis therapeutic scenario: present and future perspectives. Autoimmun. Rev. 18, 665–672.
Dargahi, N., Katsara, M., Tselios, T., et al., 2017. Multiple sclerosis: immunopathology and treatment update. Brain Sci. 7.
Dotan, N., Altstock, R.T., Schwarz, M., et al., 2006. Anti-glycan antibodies as biomarkers for diagnosis and prognosis. Lupus 15, 442–450.
Eggers, E.L., Michel, B.A., Wu, H., et al., 2017. Clonal relationships of CSF B cells in treatment-naive multiple sclerosis patients. JCI Insight. 2.
Fox, R.J., Coffey, C.S., Conwit, R., et al., 2018. Phase 2 trial of Ibudilast in progressive multiple sclerosis. New Eng. J. Med. 379, 846–855.
Freedman, M., Laks, J., Dotan, N., et al., 2009. Anti-α-glucose-based glycan IgM antibodies predict relapse activity in multiple sclerosis after the first neurological event. Mult Scler 15, 422–430.
Freedman, M., Metzig, C., Kappos, L., et al., 2012. Predictive nature of IgM anti-α-glucose serum biomarker for relapse activity and EDSS progression in CIS patients: a benefit study analysis. Mult. Scler. 18, 966–973.
Genç, K., Dona, D.L., Reder, A.T., 1997. Increased CD80(+) B cells in active multiple sclerosis and reversal by interferon beta-1b therapy. J. Clin. Invest. 99, 2664–2671.
Ghasemi, N., Razavi, S., Nikzad, E., 2017. Multiple sclerosis: pathogenesis, symptoms. Diagn. Cell-Based Therapy. Cell J. 19, 1–10.
Gingele, S., Jacobus, T.L., Konen, F.F., et al., 2018. Ocrelizumab depletes CD20$^+$ T cells in multiple sclerosis patients. Cells 8.
Gregson, A., Thompson, K., Tsirka, S.E., et al. Emerging small-molecule treatments for multiple sclerosis: focus on B cells. F1000Res [Internet]. 2019. [cited 2019 Aug 27];8. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6402079/.
Grewal, I.S., Foellmer, H.G., Grewal, K.D., et al., 1996. Requirement for CD40 ligand in costimulation induction, T cell activation, and experimental allergic encephalomyelitis. Science 273, 1864–1867.
Guan, Y., Jakimovski, D., Ramanathan, M., et al., 2019. The role of Epstein-Barr virus in multiple sclerosis: from molecular pathophysiology to in vivo imaging. Neural. Regen. Res. 14, 373–386.
Hauser, S.L., Waubant, E., Arnold, D.L., et al., 2008. B-Cell depletion with rituximab in relapsing–remitting multiple sclerosis. New Engl. J. Med. 358, 676–688.
Hueber, A.-O., Koncz, G., 2012. The Fas/CD95 receptor regulates the death of autoreactive B cells and the selection of antigen-specific B cells. Front. Immunol. 3.
Iwanowski, P., Losy, J., 2015. Immunological differences between classical phenotypes of multiple sclerosis. J. Neurol. Sci. 349, 10–14.
Jaśkiewicz, E., 2004. Epitopes on myelin proteins recognized by autoantibodies present in multiple sclerosis patients. Postep. Hig. Med. Dosw. (Online) 58, 472–482.
Jelcic, I., Al Nimer, F., Wang, J., et al., 2018. Memory B cells activate brain-homing, autoreactive CD4+ T cells in multiple sclerosis. Cell 175, 85–100.e23.
Kannel, K., Alnek, K., Vahter, L., et al., 2015. Changes in blood B cell-activating factor (BAFF) levels in multiple sclerosis: a sign of treatment outcome. PLoS ONE 10, e0143393.
Kappos, L., Hartung, H.-P., Freedman, M.S., et al., 2014. Atacicept in multiple sclerosis (ATAMS): a randomised, placebo-controlled, double-blind, phase 2 trial. Lancet Neurol. 13, 353–363.
Kinnunen, T., Chamberlain, N., Morbach, H., et al., 2013. Specific peripheral B cell tolerance defects in patients with multiple sclerosis. J. Clin. Invest. 123, 2737–2741.
Kira, J., Yamasaki, R., Ogata, H., 2018. Anti-neurofascin autoantibody and demyelination. Neurochem. Int.
Kolyovska, V., Pavlova, V., Iliev, I., et al., 2017. Demyelination and neurodegenerative changes in serum IgG antibodies to GM1, GD1a and GM3 gangliosides in a patient on dialysis. Neurol. Disord. Therap. 1.
Lassmann, H., 2019. Pathogenic mechanisms associated with different clinical courses of multiple sclerosis. Front Immunol. 9.
Li, R., Patterson, K.R., Bar-Or, A., 2018. Reassessing B cell contributions in multiple sclerosis. Nat. Immunol. 19, 696–707.
Li, R., Rezk, A., Healy, L.M., et al., 2016. Cytokine-Defined B cell responses as therapeutic targets in multiple sclerosis. Front. Immunol. 6.
Li, R., Rezk, A., Miyazaki, Y., et al., 2015. Proinflammatory GM-CSF-producing B cells in multiple sclerosis and B cell depletion therapy. Sci. Transl. Med. 7, 310ra166.
Lisak, R.P., Benjamins, J.A., Nedelkoska, L., et al., 2012. Secretory products of multiple sclerosis B cells are cytotoxic to oligodendroglia in vitro. J. Neuroimmunol. 246, 85–95.
Lovett-Racke, A.E., Gormley, M., Liu, Y., et al., 2019. B cell depletion with ublituximab reshapes the t cell profile in multiple sclerosis patients. J. Neuroimmunol. 332, 187–197.
Machado-Santos, J., Saji, E., Tröscher, A.R., et al., 2018. The compartmentalized inflammatory response in the multiple sclerosis brain is composed of tissue-resident CD8+ T lymphocytes and B cells. Brain 141, 2066–2082.
Magliozzi, R., Howell, O., Vora, A., et al., 2007. Meningeal B-cell follicles in secondary progressive multiple sclerosis associate with early onset of disease and severe cortical pathology. Brain 130, 1089–1104.
Mameli, G., Poddighe, L., Mei, A., et al., 2012. Expression and activation by Epstein Barr virus of human endogenous retroviruses-W in blood cells and astrocytes: inference for multiple sclerosis. PLoS ONE 7, e44991.
Meinl, E., Krumbholz, M., Derfuss, T., et al., 2008. Compartmentalization of inflammation in the CNS: a major mechanism driving progressive multiple sclerosis. J. Neurol. Sci. 274, 42–44.
Michel, L., Berthelot, L., Pettré, S., et al., 2008. Patients with relapsing-remitting multiple sclerosis have normal Treg function when cells expressing IL-7 receptor α-chain are excluded from the analysis. J. Clin. Invest. 118, 3411–3419.
Miyazaki, Y., Niino, M., 2014. Molecular targeted therapy against B cells in multiple sclerosis. Clin. Exp. Neuroimmunol. 5, 16–27.
Montalban, X., Arnold, D.L., Weber, M.S., et al., 2019. Placebo-Controlled trial of an oral BTK inhibitor in multiple sclerosis. N. Engl. J. Med. 380, 2406–2417.
Muto, M., Mori, M., Hiwasa, T., et al., 2015. Novel serum autoantibodies against talin1 in multiple sclerosis: possible pathogenetic roles of the antibodies. J. Neuroimmunol. 284, 30–36.
Owens, G.P., Bennett, J.L., Lassmann, H., et al., 2009. Antibodies produced by clonally expanded plasma cells in multiple sclerosis cerebrospinal fluid. Ann. Neurol. 65, 639–649.
Pandey, S., Dioni, I., Lambardi, D., et al., 2013. Alpha actinin is specifically recognized by multiple sclerosis autoantibodies isolated using an N-Glucosylated peptide epitope. Mol. Cell. Proteomics. 12, 277–282.
Parnell, G.P., Booth, D.R., 2017. The multiple sclerosis (MS) genetic risk factors indicate both acquired and innate immune cell subsets contribute to MS pathogenesis and identify novel therapeutic opportunities. Front Immunol. 8.
Peschl, P., Bradl, M., Höftberger, R., et al., 2017. Myelin oligodendrocyte glycoprotein: deciphering a target in inflammatory demyelinating diseases. Front Immunol. 8, 529.
Pikor, N.B., Prat, A., Bar-Or, A., et al., 2015. Meningeal tertiary lymphoid tissues and multiple sclerosis: a gathering place for diverse types of immune cells during CNS autoimmunity. Front. Immunol. 6, 657.
Prineas, J.W., Wright, R.G., 1978. Macrophages, lymphocytes, and plasma cells in the perivascular compartment in chronic multiple sclerosis. Lab. Invest. 38, 409–421.
Pröbstel, A.-.K., Sanderson, N.S.R., Derfuss, T., 2015. B cells and autoantibodies in multiple sclerosis. Int. J. Mol. Sci. 16, 16576–16592.
Puthenparampil, M., Miante, S., Federle, L., et al., 2016. BAFF is decreased in the cerebrospinal fluid of multiple sclerosis at clinical onset. J. Neuroimmunol. 297, 63–67.
Qin, Y., Duquette, P., Zhang, Y., et al., 1998. Clonal expansion and somatic hypermutation of V(H) genes of B cells from cerebrospinal fluid in multiple sclerosis. J. Clin. Invest. 102, 1045–1050.
Qin, Y., Duquette, P., Zhang, Y., et al., 2003. Intrathecal B-cell clonal expansion, an early sign of humoral immunity, in the cerebrospinal fluid of patients with clinically isolated syndrome suggestive of multiple sclerosis. Lab. Invest. 83, 1081–1088.
Ramanathan, S., Dale, R.C., Brilot, F., 2016. Anti-MOG antibody: the history, clinical phenotype, and pathogenicity of a serum biomarker for demyelination. Autoimmun. Rev. 15, 307–324.
Rijvers, L., Melief, M., van der Vuurst de Vries, R.M., et al., 2018. The macrophage migration inhibitory factor pathway in human B cells is tightly controlled and dysregulated in multiple sclerosis. Eur. J. Immunol. 48, 1861–1871.
Russell, L., John, S., Cullen, J., et al., 2015. Requirement for transcription factor Ets1 in B cell tolerance to self-antigens. J. Immunol. 195, 3574–3583.
Sabatino, J.J., Zamvil, S.S., Hauser, S.L., 2019. B-Cell therapies in multiple sclerosis. Cold Spring Harb. Perspect. Med. 9.
Serafini, B., Rosicarelli, B., Magliozzi, R., et al., 2004. Detection of ectopic B-cell follicles with germinal centers in the meninges of patients with secondary progressive multiple sclerosis. Brain Pathol. 14, 164–174.
Stich, O., Perera, S., Berger, B., et al., 2016. Prevalence of neurofascin-155 antibodies in patients with multiple sclerosis. J. Neurol. Sci. 364, 29–32.
Stoeckle, C., Tolosa, E., 2010. Antigen processing and presentation in multiple sclerosis. Results. Probl. Cell. Differ. 51, 149–172.
Tang, N., Yang, L., Li, D., et al., 2019. Modulation of B cell activation threshold mediated by BCR/CD40 costimulation by targeting Cbl-b for ubiquitination. Biochem. Biophys. Rep. 18, 100641.
Thaunat, O., Patey, N., Gautreau, C., et al., 2008. B cell survival in intragraft tertiary lymphoid organs after rituximab therapy. Transplantation 85, 1648–1653.
von Büdingen, H.-C., Bar-Or, A., Zamvil, S.S., 2011. B cells in multiple sclerosis: connecting the dots. Curr. Opin. Immunol. 23, 713–720.
Waters, P., Woodhall, M., O'Connor, K.C., et al., 2015. MOG cell-based assay detects non-MS patients with inflammatory neurologic disease. Neurol. Neuroimmunol. Neuroinflamm. 2, e89.
Wootla, B., Denic, A., Keegan, B.M., et al., 2011. Evidence for the role of B cells and immunoglobulins in the pathogenesis of multiple sclerosis. Neurol. Res. Int. 2011.
Zaprianova, E., Majtényi, K., Deleva, D., et al., 2004. Serum IgG and IgM ganglioside GM1 antibodies in patients with multiple sclerosis. Ideggyogy. Sz. 57, 94–99.