The Multiple Roles of B Cells in Multiple Sclerosis and Their Implications in Multiple Sclerosis Therapies

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Increasing evidence has suggested that both antibody-dependent and antibody-independent functions of B cells are involved in multiple sclerosis (MS). The contrasting results of distinct B-cell targeting therapies in MS patients underscores the importance of elucidating these multiple B-cell functions. In this review, we discuss the generation of autoreactive B cells, migration of B cells into the central nervous system (CNS), and how different functions of B cells may contribute to MS disease activity and potentially mitigation in both the periphery and CNS compartments. In addition, we propose several future therapeutic strategies that may better target/shape B-cell responses for long-term treatment of MS.

Although T cells have historically been considered the key players in multiple sclerosis (MS) pathogenesis, selective depletion of B cells with anti-CD20 antibodies has proven highly effective in limiting new MS disease activity (Bar-Or et al. 2008, 2014; Hauser et al. 2008, 2017; Kappos et al. 2011; Sorensen et al. 2014). The two independent phase III (OPERA I and OPERA II) clinical trials of the humanized anti-CD20 monoclonal antibody orelizumab showed a >94% decrease in new magnetic resonance imaging (MRI) lesion development with robust effects on MS relapses, as compared with the interferon (IFN)-β treated group (Hauser et al. 2017). Although essentially all approved immune therapies for relapsing remitting MS (including IFN-β, copaxone, tysabri, gilenya, tecfidera, and alemtuzumab) were developed largely with a view of how they may impact T cells in MS, all of these therapies are now also known to directly impact B-cell responses (Cupps et al. 1985; Genc et al. 1997; Duda et al. 2000; Salama et al. 2003; Duddy et al. 2007; Begum-Haque et al. 2010; Kala et al. 2010; Ramgolam et al. 2011; Miyazaki et al. 2014b; Nakamura et al. 2014; Li et al. 2017).

Of note, not all treatments targeting B cells have been beneficial for MS patients. In fact, atacicept (a fusion protein of TACI and Fc fragment of immunoglobulin (Ig)G that targets B cells and plasma cells but relatively spears memory B cells) appeared to worsen. In fact, atacicept (a fusion protein of TACI and Fc fragment of IgG that targets B cells and plasma cells but relatively spears memory B cells) appeared to worsen central nervous system (CNS) inflammatory disease in MS and optic neuritis studies (Kappos et al. 2014; Sergott et al. 2015). In au-

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toimmune encephalomyelitis (EAE) (a commonly used animal model for neuroinflammation), the outcome of targeting B cells can also be either beneficial or detrimental. The particular effect observed appears to hinge on several factors. Matsushita et al. (2008) showed that depleting B cells before immunization worsens disease activity while depleting B cells after disease induction improves disease activity, indicating that B cells may play different roles at different disease stages. In addition, the antigens used to induce EAE also seem to play an important role. For example, depleting B cells in an EAE model induced with recombinant myelin oligodendrocyte glycoprotein (MOG) protein results in reduced disease activity, although disease exacerbation was observed when B cells were depleted in an EAE model using the MOG35-55 peptide to induce disease (Weber et al. 2010).

The opposing outcomes of anti-CD20 and atacicept treatments in MS, together with the observations in EAE, highlights the need for more complete elucidation of the functional heterogeneity that exists among B cells and, in particular, their capacity to either promote or acquiesce CNS inflammation. In recent years, considerable work has expanded our understanding of the diverse functions of B cells in both health and disease. In addition to their potential to differentiate into antibody-producing plasmablasts/plasma cells, B cells can also efficiently present antigen to T cells, help T-cell activation and differentiation, contribute to the organization of normal and possibly also ectopic lymphoid structures, and modulate local immune responses through secretion of soluble products such as proinflammatory or anti-inflammatory cytokines. Abnormalities in several of these novel B-cell functions have been implicated in MS.

B-CELL TOLERANCE IN MS

Immune tolerance is generally maintained even though self-reactive (autoreactive) B cells are present in the normal immune repertoire of healthy individuals (McHeyzer-Williams and Nossal 1988; Wardemann et al. 2003; Shlomchik 2008). The physiologic roles of such autoreactive B cells that exist as part of "normal autoimmunity" remain incompletely understood. Abnormalities in B-cell tolerance have been reported in several autoimmune diseases, including SLE, rheumatoid arthritis (RA), type 1 diabetes (T1D), and MS (Samuels et al. 2005; Yurasov et al. 2005; Henry et al. 2012; Kinnunen et al. 2013a). There are two major checkpoints that normally contribute to the elimination or control of autoreactive B cells: central tolerance and peripheral tolerance (Meffre 2011). Central tolerance of B cells is established in the bone marrow and eliminates ~75% of self-reactive B cells, while peripheral tolerance takes place in the secondary lymphoid organs where most other self-reactive B cells are controlled (Meffre 2011). B-cell receptor (BCR) and Toll-like receptor (TLR) signaling pathways play important roles during the bone marrow selection of B cells, although CD40 ligand, major histocompatibility complex (MHC) II, and regulatory T cells (Tregs) are important for the control of autoreactive B cells in the periphery (Meffre 2011). Using careful analysis of self-reactive antibody profiles, Meffre and colleagues implicated deficiencies of both central and peripheral B-cell tolerance in patients with SLE, RA, and T1D. In contrast, MS B cells appear to only display an abnormality in peripheral tolerance (Kinnunen et al. 2013a,b). This result is consistent with the observations that the function of Tregs is deficient in MS patients (Viglietta et al. 2004; Haas et al. 2005; Schwarz et al. 2013). In this regard, it is plausible that the tolerance abnormality observed in MS B cells may be the consequence of the dysfunction of Tregs. Relatively little is known about how Tregs regulate B-cell tolerance. A subset of CXCR5-expressing Tregs has been described within the classical germinal center (GC) architecture, referred to as follicular regulatory T (Tfr) cells (Chung et al. 2011; Linterman et al. 2011; Sage et al. 2014a; Vaeth et al. 2014). Subsequent studies showed that, in mice, Tfr cells control B-cell responses indirectly, through CTLA-4-mediated suppression of follicular helper T (Tfh) cells (Sage et al. 2014b; Wing et al. 2014). In MS, both the frequency and immune suppressive function of Tfr is reportedly

decreased as compared with healthy controls (Dhaeze et al. 2015). Questions remain as to whether and how we may be able to restore peripheral tolerance of B cells in MS patients. Some patients with MS undergoing selective B-cell depletion may experience durable quiescence of their MS disease activity even as their B cells (largely naïve) reemerge, suggesting that a form of tolerance has been achieved. In contrast, B cells reconstituting following less selective depletion (e.g., immune ablation and hematopoietic stem cell transplantation and, particularly, use of the approved anti-CD52 therapy for MS) may manifest with breach in tolerance and the development of secondary (typically antibody-mediated) autoimmune diseases (Coles et al. 2012).

B-CELL TRAFFICKING IN MS

B cells (as well as plasmablasts and plasma cells) appear to be fostered in the inflamed MS CNS, in which they have been observed in several subcompartments, including cerebrospinal fluid (CSF), parenchyma, and meninges (Michel et al. 2015). Unlike T cells, there is a relative gap in our understanding of the molecular mechanisms used by B cells to enter the CNS, both in health and disease. CXCL13, one of the most strongly implicated chemokines in regulating B-cell migration (Bagaeva et al. 2006; Henry and Kendall 2010), is abnormally increased in the CSF of MS patients (Krumbholz et al. 2006; Sellebjerg et al. 2009). In addition, a positive correlation has been reported between the number of CSF B cells and the level of CXCL13 in the MS CSF (Kowarik et al. 2012).

VLA-4 is an adhesion molecule that is involved in immune cells rolling, activation, and arrest during immune cell *trans*-endothelial trafficking (Takeshita and Ransohoff 2012). Functional blockade of the adhesion molecule VLA-4 using the monoclonal antibody natalizumab substantially decreases new relapsing MS disease activity (Polman et al. 2006; Ransohoff 2007), an effect largely attributed to limiting T-cell trafficking into the CNS (Hyun et al. 2009). However, B cells—and especially memory B cells—also express high levels of VLA-4 (Alter et al. 2003; Niino et al. 2006; Putzki et al. 2010). Blocking VLA-4 in vitro decreases human B-cell migration across endothelial cells to a greater extent than the decreases observed for T cells (Alter et al. 2003). In EAE mice, selective knockout of VLA-4 from B cells, substantially reduced accumulation of both B cells and T cells in the CNS, and was associated with less severe disease (Lehmann-Horn et al. 2015).

Although classical work using somatic hypermutation analysis of MS CSF B-cell immunoglobulin genes (summarized in Michel et al. 2015) initially pointed to clonal expansion of B cells within the CNS, more recent work using similar techniques has identified shared B-cell clones between the CNS and the periphery, including the CNS draining deep cervical lymph nodes of the same patients (von Budingen et al. 2012; Palanichamy et al. 2014; Stern et al. 2014). The molecular analysis of related clones revealed bidirectional trafficking of these B cells (both into and out of the CNS), and suggested that much of the clonal expansion (and presumably activation) of the B cells may in fact occur in the deep cervical lymph nodes (von Budingen et al. 2012; Palanichamy et al. 2014; Stern et al. 2014). These same studies also identified shared clones present in the different CNS subcompartments, namely, the CSF, parenchyma, and meninges of the same patients. When and how B cells enter the CNS through what are now recognized as distinct interfaces (traditional blood–brain barrier endothelial cells, meningeal, and choroidal interfaces), how they migrate among different CNS subcompartments, and what determines their egress from the CNS (e.g., into the cervical lymph nodes), are topics of active investigation.

ABNORMAL ANTIBODY RESPONSES IN MS

Abnormal antibody production within the CNS has been a well-recognized feature commonly seen in patients with MS. Elevated levels and synthesis rates of both IgG and IgM can be found in the CSF of patients, which, when run on an electrophoretic gel, frequently display a pattern of oligoclonal bands (OCBs) consistent with a restricted number of clonally expanded antibody-producing plasma cells (Ivers et al. 1961; Kostulas et al. 1987; Villar et al. 2002).

IgG OCBs can be found in the great majority of MS patients. IgM OCBs are present in ~30%–40% (Weber et al. 2011), and their presence has been associated in different studies with more active disease (Tintore et al. 2001; Lourenco et al. 2013) and potentially with therapeutic response to B-cell-directed therapy (Villar et al. 2014). Studies have indicated that the CSF antibodies in patients with MS can correspond to the immunoglobulin gene sequences of B cells and plasma cells isolated from the CSF as well as within CNS tissues (both in typical white matter lesions and in the meninges) of the same patients, indicating sharing of the same B clones and their antibody products in different subcompartments of the same inflamed MS CNS (Lovato et al. 2011; von Budingen et al. 2012; Palanichamy et al. 2014; Stern et al. 2014). Within MS lesions, antibodies can be seen within phagocytic myeloid cells, which may include myelin fragments (Zhou et al. 2006). Such lesions may have distinct imaging features and may be more amenable to antibody-depleting interventions such as plasmapheresis (Breij et al. 2008; Sadaba et al. 2012).

Despite the strong implication of abnormal antibody responses in MS, direct showing of their pathogenicity has been difficult to establish. For example, in contrast to the ability of activated CNS-specific T cells to transfer EAE to naïve animals, antibodies alone appear unable to induce such CNS inflammation (Genain et al. 1995; Mathey et al. 2007; Derfuss et al. 2009). It has also been difficult to elucidate disease-relevant antigenic targets of B cells, plasmablasts, and plasma cells isolated from the CNS of patients. Similarly, the antigenic specificities of the majority of abnormal CSF antibodies in MS (including the overall IgG or IgM as well as the OCB) have not been elucidated despite considerable efforts (reviewed in Michel et al. 2015). Most recently, thorough examination of MS patient OCB-identified antibodies that largely recognized ubiquitous intracellular self-proteins, suggesting that the OCB antibodies may be generated as response to debris (Brandle et al. 2016; Hohlfeld et al. 2016a,b; Winger and Zamvil 2016).

Considerable efforts have also been invested over the years to detect and establish the significance of circulating anti-CNS antibodies in both adult and pediatric populations with MS and related disorders (Bar-Or et al. 2016). Challenges have included important subtleties of the methodologies used to detect the antibodies, selection of control populations, the aforementioned potential for autoreactive antibodies to develop as a response to (rather than cause of) injury, as well as the realization that self-directed antibodies (including CNS-reactive antibodies) can be commonly detected as part of the normal circulating humoral repertoire. Such normal antibodies may nonetheless contribute to CNS inflammatory disease—for example, individuals who happen to have antimyelin antibodies in their circulation as part of their normal humoral repertoire, but also develop MS, may have a more aggressive presentation—suggesting that presence of such antibodies (themselves normal) can modulate disease expression if they access the CNS (O'Connor et al. 2010).

Despite ongoing efforts to assess whether particular circulating CNS autoantibodies may serve as clinically useful biomarkers (whether for diagnosis, prediction of disease severity or course, or to distinguish pathophysiologic entities that may warrant different therapeutic approaches), the field of MS has not yet implicated CNS autoreactive antibodies in the same compelling way that anti-AQP4 antibodies are implicated in the neuromyelitis-optica spectrum disorders (NMOSDs) or antineuronal antibodies in the spectrum of antibody-mediated encephalitides. Within the broader spectrum of CNS inflammatory demyelinating syndromes, presence of anti-MOG antibodies has been associated in some studies with less aggressive disease, lesser likelihood of relapse and improved outcomes, and may emerge as a non-MS disease phenotype (Sato et al. 2014; Ketelslegers et al. 2015). Anti-MOG antibodies occur more commonly in the pediatric than adult age group (McLaughlin et al. 2009; Probstel et al. 2011; Mayer and Meinl 2012; Bar-Or et al. 2016), although their significance in children (including putative biomarker value) may not be the same as in adults. In addition to considering traditional myelin antigens (such as MOG) as potential antibody targets, serum antibodies to other

CNS targets have been studied. Circulating antibodies specific to KIR4.1 (ATP-sensitive inward rectifying potassium channel that is largely expressed by glial cells) were reported in approximately half of both adults with MS (Srivastava et al. 2012) and children with acute CNS demyelination (Kraus et al. 2014), although their presence did not appear to associate with a particular clinical phenotype. Other studies did not reproduce the original results (Brickshawana et al. 2014; Nerrant et al. 2014), highlighting the impact of different methodologies used and the importance of direct assay comparison (Waters et al. 2012).

B-CELL ANTIGEN PRESENTATION AND CNS INFLAMMATION

For a T cell to be fully activated, it requires antigen presenting cells (APCs) to process and present its antigenic epitope as well as providing the necessary costimulatory signals. Professional APCs include monocyte-derived dendritic cells (mDCs), plasmacytoid dendritic cells (pDCs), and tissue-resident macrophage. These cells sense the antigen/pathogen often through innate immune receptors (such as TLRs), digest these protein molecules into peptides, and present them to T cells through either MHC or non-MHC molecules (Guermonprez et al. 2002; Brigl and Brenner 2004). B cells can also present antigen to T cells, a process that usually occurs within the secondary lymphoid tissue (Rodriguez-Pinto 2005; Rodriguez-Pinto and Moreno 2005). Compared with professional APCs (that specialize in linear epitope presentation), B cells (that recognize 3-dimensional "conformational" epitopes) can more efficiently present protein antigens and seem to be the main source of APCs when the antigen level is low (Pierce et al. 1988; Rivera et al. 2001). B cells are also highly effective APCs when they recognize the same antigen as T cells (cognate interaction) (Pierce et al. 1988; Rodriguez-Pinto 2005). Cognate interactions appear important for both effector T-cell activation and Treg-cell generation (Barnett et al. 2014; Walters et al. 2014). APC function of B cells has been highlighted in many disease contexts, including infectious diseases, transplantation, and autoimmune diseases (Milich et al. 1997; Serreze et al. 1998; Molnarfi et al. 2013; Zeng et al. 2014). In EAE, B-cell-specific MHC II knockout mice are resistant to recombinant human MOG-induced disease—an EAE model strongly dependent on the presence of B cells (Weber et al. 2010; Molnarfi et al. 2013). Interestingly, knocking out MHC II on B cells also results in a total abrogation of anti-MOG antibody; however, injecting these mice with anti-MOG antibody only partially recovers the EAE phenotype, indicating an antibody-independent but MHC II–dependent role of B cells in EAE (Molnarfi et al. 2013). In the same study, the investigators also found that crossing MOG BCR-specific mice with MOG TCR-specific mice substantially enhanced the incidence of spontaneous EAE (Molnarfi et al. 2013), suggesting that cognate interactions between B cells and T cells may be required for optimal EAE induction.

The second signal required for T-cell activation is the costimulatory signal. So far, >20 costimulatory molecule pairs have been verified. Of those, CD80/86 and their T-cell-activating binding partner CD28 are the best characterized. Human memory B cells express CD80 and a much smaller subset of B cells express CD86 in the resting state (Bar-Or et al. 2001). Both molecules can be further induced by various B-cell-activating stimuli (both innate and adaptive) in vitro (Bar-Or et al. 2001; Henn et al. 2012). In vivo, specific knockout of CD80 and CD86 on B cells alone, has been associated with decreases of both primary and secondary T-cell responses (O'Neill et al. 2007). In humans, B cells can also stimulate T cells through both CD80 and CD86 (Gimmi et al. 1991; Bar-Or et al. 2001). Genc and colleagues reported that the frequency of circulating $CD80^+$ B cells is increased in patients with active MS (Genc et al. 1997). In addition to costimulatory molecules, B cells also express coinhibitory molecules that are involved in down-regulating the responses of effector T cells. For instance, it has been reported that B-cell PD-L1 expressed by B cells can protect against EAE by down-regulating T-cell responses through PD-1 (Bodhankar et al. 2013). In addition, GITRL, another coinhibitory molecule expressed by B cells, can

directly induce Treg differentiation through glucocorticoid-induced tumor necrosis factor receptor–related (GITR) protein (Ray et al. 2012). In mice, memory B cells can be divided into two subsets, PD-L2$^+$ CD80$^+$ and PD-L2$^-$ CD80$^-$ B cells, independent of their antibody isotype (Zuccarino-Catania et al. 2014). Double-positive B cells become antibody-secreting cells rapidly but cannot induce GC reaction while double-negative B cells can induce GC reaction, but very few of them can become antibody-secreting cells (Zuccarino-Catania et al. 2014). This provides an initial basis to define functionally distinct B-cell subsets, based on their different profiles of costimulatory or coinhibitory molecule expression. Whether this annotation will prove useful in humans and how different costimulatory molecule-defined B-cell subsets may contribute to MS remain to be explored.

CYTOKINE-DEFINED B-CELL RESPONSES IN MS

Cytokines are important for B cells to modulate (up- or down-regulate) local immune responses in both health and disease (Shen and Fillatreau 2015). An imbalance of B-cell pro- and anti-inflammatory cytokines is now implicated in the pathophysiology of both MS and EAE (Li et al. 2015a).

Interleukin-10-Producing B Cells

Interleukin (IL)-10 is a cytokine with pleiotropic effects in inflammation and immunoregulation (Saraiva and O'Garra 2010) and IL-10-producing B cells have been extensively studied. Various stimuli can induce IL-10 production from B cells, including TLRs, CD40, microbiota, and cytokines (Lampropoulou et al. 2008; Yoshizaki et al. 2012; Rosser et al. 2014). In mice, knocking-out IL-10 selectively from B cells resulting in more severe EAE (Fillatreau et al. 2002), and adoptive transfer of in vitro–induced IL-10-producing B cells suppresses EAE in an IL-10-dependent manner (Lampropoulou et al. 2008; Matsushita et al. 2008; Yoshizaki et al. 2012). Inducing EAE in IL-10 reporter mice implicates the draining lymph nodes (rather than spleen or spinal cord) as the sites where IL-10$^+$ B cells regulate disease-relevant immune responses (Matsumoto et al. 2014); of note, the IL-10$^+$ B cells in this study showed plasma cell/plasmablast markers, highlighting previously unappreciated antibody-independent functions of plasma cells.

Both naïve and memory B cells can produce IL-10 in humans in a context-dependent manner (Duddy et al. 2004; Rieger and Bar-Or 2008; Blair et al. 2010; Iwata et al. 2011). Human CD27$^-$ (naïve) B cells, but not CD27$^+$ (memory) B cells, can produce IL-10 on CD40-ligand stimulation (Correale and Farez 2007; Duddy et al. 2007; Bar-Or et al. 2010; Miyazaki et al. 2014a), a response found to be abnormally deficient in MS patients' B cells (Duddy et al. 2007). Alternatively, IL-10$^+$ B10 cells are induced within the CD27$^+$ memory pool by stimulation through TLR4 and TLR9 and can suppress tumor necrosis factor (TNF)-α production by monocytes through an IL-10-dependent mechanism. B10 cells were unexpectedly reported as increased on stimulation in several human autoimmune diseases (MS included) (Iwata et al. 2011). A better understanding of these cells, which would include defining surface markers and master transcriptional regulators, would facilitate future cell-based therapies for MS.

Transforming Growth Factor (TGF)-β-Producing B Cells

TGF-β belongs to the TGF superfamily. So far, three isoforms of TGF-β has been identified: TGF-β1, 2, 3. As an anti-inflammatory cytokine, TGF-β has been shown to down-regulate immune responses in various contexts (Li et al. 2006). Although TGF-β-producing B cells were mainly studied in transplantation (Lee et al. 2014), relatively little is known about their role in CNS inflammation. In EAE, selective depletion of TGF-β from B cells exacerbated EAE, in association with increased Th1 and Th17 responses (Bjarnadottir et al. 2016). Documenting functional TGF-β production by human B cells has been difficult and their role of any in MS is not established.

IL-35-Producing B Cells

IL-35 is an anti-inflammatory cytokine that belongs to the IL-12 family (Vignali and Kuchroo 2012) and was initially described in Tregs (Collison et al. 2007; Seyerl et al. 2010; Chaturvedi et al. 2011). Of late, IL-35-producing B cells were found to have important roles in recovery from both EAE and experimental autoimmune uveitis (Shen et al. 2014; Wang et al. 2014). In these contexts, IL-35-producing B cells inhibited proinflammatory immune responses either directly through IL-35 (Shen et al. 2014) or indirectly through induction of IL-10-producing B cells (Wang et al. 2014). The same IL-35-producing B cells also showed plasma cell phenotypic markers (Shen et al. 2014). Whether human B cells/plasma cells can produce IL-35 and, if so, their potential relevance in MS, remain unclear.

TNF-α and TNF-β (LT-α)-Producing B Cells

TNF-α and lymphotoxin (LT)-α are actively involved in promoting proinflammatory immune responses to protect against pathogen invasion (Bradley 2008). TNF-α is known to have pathogenic roles in several autoimmune diseases including RA (Feldmann and Maini 2001) and inflammatory bowel disease (IBD) (Neurath 2014) in which TNF-α-blocking therapies have been highly successful (Feldmann and Maini 2001). However, in MS, TNF-α blockade increased disease activity (Arnason 2011), which highlights the issue of largely targeting individual cytokines versus targeting particular cytokine-expressing cells. Stimulation through a combination of CD40 and the BCR significantly increases TNF-α and LT-α secretion from human B cells compared with either stimulation alone (Duddy et al. 2004). With this type of dual stimulation, the B cells of MS patients produce abnormally higher levels of both TNF-α and LT-α (Duddy et al. 2007; Bar-Or et al. 2010; Miyazaki et al. 2014a). In addition, TNF-α and LT-α from B cells are particularly important for Th1 and Th17 responses that are implicated in MS and that decrease in patients after B-cell depletion (Bar-Or et al. 2010). Miyazaki et al. (2014a) showed that a microRNA(miR)-132:SIRT1 axis modulates the expression of TNF-α and LT-α by human B cells and further showed that abnormally increased expression of miR-132 by MS B cells resulted in inhibition of the B-cell SIRT1 expression and enhanced proinflammatory cytokine production. In vitro addition of the SIRT1-agonist resveratrol normalized the exaggerated proinflammatory cytokine expression of MS B cells (Miyazaki et al. 2014a), pointing to a potential therapeutic target.

IL-6-Producing B Cells

IL-6, a cytokine that has been ascribed both proinflammatory and anti-inflammatory properties, can be produced by both immune and nonimmune cells (Kishimoto 2005). Proinflammatory effects of IL-6 include induction of Th17 cell differentiation from naïve T cells (Bettelli et al. 2006) and inhibition of Tregs (Korn et al. 2008; Kimura and Kishimoto 2010; Schneider et al. 2013). In contrast, IL-6 may induce IL-10-producing regulatory B and myeloid cells (Mauer et al. 2014; Rosser et al. 2014). B cells of MS patients are fond to secrete abnormally high levels of IL-6 (Barr et al. 2012) and IL-6 knockout selectively from B cells resulted in lower Th17 responses and diminished the severity of EAE (Barr et al. 2012; Molnarfi et al. 2013). What remains unknown is how B-cell IL-6 is regulated, and whether it also contributes to Th17 differentiation and Treg-cell dysfunction in MS.

IL-15-Producing B Cells

IL-15 can be produced by multiple cell types and belongs to the four α-helix bundle family of cytokines (Ma et al. 2006). IL-15 knockout mice develop more severe EAE (Gomez-Nicola et al. 2010), which in part is attributed to IL-15's ability to inhibit pathogenic Th17 cell differentiation (Pandiyan et al. 2012), and to induce regulatory $CD8^+$ $CD122^+$ T cells (Yu et al. 2014). However, in patients with MS, IL-15 in both serum and CSF is abnormally increased (Blanco-Jerez et al. 2002; Rentzos et al. 2006), where it may have the potential to promote rather than

inhibit disease (Saikali et al. 2010; Schneider et al. 2011). MS patients' B cells reportedly produce more IL-15 than controls, and activation of B cells through CD40 and the BCR induces IL-15 secretion, enhancing both the migratory capacity of $CD8^+$ T cells across a model of the blood–brain barrier, as well as $CD8^+$ T-cell cytotoxicity toward oligodentrocytes (Schneider et al. 2011).

Granulocyte Macrophage Colony-Stimulating Factor–Producing B Cells

During infection and autoimmune disease, granulocyte macrophage colony-stimulating factor (GM-CSF), which is an important growth factor for myeloid lineage cell development and function, is secreted by both immune and nonimmune cells (Hamilton 2008). GM-CSF knockout mice are resistant to active EAE induction (McQualter et al. 2001) and GM-CSF-deficient Th17 cells fail to induce passive EAE (Ponomarev et al. 2007; Codarri et al. 2011; El-Behi et al. 2011). Because GM-CSF-producing T cells are reportedly increased in the circulation of MS patients (Hartmann et al. 2014; Noster et al. 2014; Rasouli et al. 2015), T cells have been thought to be the main source of GM-CSF of relevance to MS and EAE (Kleinewietfeld et al. 2013; Hartmann et al. 2014; Noster et al. 2014; Rasouli et al. 2015). A murine B-cell population generated from B1a cells, termed innate response activator (IRA) B cells (Rauch et al. 2012), was described to produce GM-CSF and found to play a GM-CSF-mediated protective role during infections (Rauch et al. 2012; Weber et al. 2014), as well as a GM-CSF-mediated pathogenic role in atherosclerosis (Hilgendorf et al. 2014). Human GM-CSF-producing B cells ($B_{GM\text{-}CSF}$) were recently described (Li et al. 2015b), which, in contrast to the murine IRA cells, belong to the memory B-cell pool. Human GM-CSF-expressing B cells coexpress particularly high levels of TNF-α and IL-6 but not IL-10 (Li et al. 2015b), and efficiently enhance myeloid cell proinflammatory responses in a GM-CSF-dependent manner. These GM-CSF-expressing B cells are abnormally increased in MS patients and anti-CD20-mediated B-cell depletion results in a B-cell-GM-CSF-dependent decrease of proinflammatory myeloid cell responses, which highlights the potential pathogenic role of this B-cell population in vivo. It also reveals a novel disease-implicated axis involving B cells that are myeloid cell interactions (Li et al. 2015b). These proinflammatory B cells are also decreased following treatment of MS patients with either fingolimod or dimethyl fumarate (DMF) (Li et al. 2017). The recent discovery that STAT5 and STAT6 signaling reciprocally regulates human B-cell IL-10 and GM-CSF expression underscore the rationale for selective targeting of distinct B-cell populations in MS and points to novel therapeutic approaches.

B CELLS AND MENINGEAL INFLAMMATION IN THE MS CNS

There has been considerable interest in the cortical injury present in MS, and particularly the subpial cortical injury, which can be quite extensive and may represent the pathologic substrate underlying nonrelapsing progressive disease (Peterson et al. 2001; Magliozzi et al. 2007; Lucchinetti et al. 2011). In this regard, documentation of meningeal inflammation has sparked interest in the potential that immune cells fostered adjacent to the brain may contribute importantly to the subpial cortical injury (Magliozzi et al. 2010; Howell et al. 2011; Choi et al. 2012). In some cases, meningeal inflammation in MS may be organized to the extent that it recapitulates features of ectopic lymphoid structures (Magliozzi et al. 2007) as described in other contexts of chronic inflammation such as chronic infections, cancer, and autoimmune diseases (Takemura et al. 2001; Drayton et al. 2003; Pitzalis et al. 2014).

B cells tend to represent the predominant cell type within such immune cell collections (Magliozzi et al. 2007; Lucchinetti et al. 2011). T cells, follicular dendritic cells (FDCs), and stromal cell can also be found, but to a lesser extent (Magliozzi et al. 2007; Lucchinetti et al. 2011). Presence of such meningeal inflammation has been associated with earlier disease onset and more severe cortical pathology, characterized by abnormal microglia activation and

apoptotic neuronal loss, consistent with the possibility that B-cell-rich meningeal inflammation somehow promotes propagation subpial injury and progressive MS pathology (Magliozzi et al. 2007). Emerging work has documented that soluble products of B cells isolated from MS patients can be toxic and induce apoptosis of both oligodendrocytes and neurons (Lisak et al. 2012, 2017). Tracking and targeting meningeal inflammation and particularly B cells fostered within the inflamed MS CNS has now become a new therapeutic focus in MS.

CONCLUDING REMARKS

Dysregulation of multiple immune cell subsets has been implicated in MS disease activity. Although traditionally considered a T-cell-mediated disease, important pathogenic roles of B cells have emerged in recent years. The contrasting results of different B-cell-targeted treatments in MS patients (despite predicted benefit from animal models) call for a better understanding of the multiple roles that distinct human B-cell subsets likely play in this illness. There remain substantial gaps in our knowledge of pathogenic and potentially regulatory B-cell responses in MS. Better understanding of their functions, how they are generated and regulated, and phenotypic markers that may reliably distinguish them from other functionally distinct subsets will eventually help develop more selective B-cell-targeting therapy in MS.

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