



# Contribution of Dysregulated B-Cells and IgE Antibody Responses to Multiple Sclerosis

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Multiple sclerosis (MS), a debilitating autoimmune inflammatory disease that affects the brain and spinal cord, causes demyelination of neurons, axonal damage, and neurodegeneration. MS and the murine experimental autoimmune encephalomyelitis (EAE) model have been viewed mainly as T-cell-mediated diseases. Emerging data have suggested the contribution of B-cells and autoantibodies to the disease progression. However, the underlying mechanisms by which dysregulated B-cells and antibody response promote MS and EAE remain largely unclear. Here, we provide an updated review of this specific subject by including B-cell biology and the role of B-cells in triggering autoimmune neuroinflammation with a focus on the regulation of antibody-producing B-cells. We will then discuss the role of a specific type of antibody, IgE, as it relates to the potential regulation of microglia and macrophage activation, autoimmunity and MS/EAE development. This knowledge can be utilized to develop new and effective therapeutic approaches to MS, which fits the scope of the Research Topic “Immune Mechanism in White Matter Lesions: Clinical and Pathophysiological Implications”.

**Keywords:** B-cells, humoral antibody response, IgE, macrophage, microglia, neuroinflammation, multiple sclerosis, experimental autoimmune encephalomyelitis

## INTRODUCTION

Multiple sclerosis (MS) is the most prevalent chronic inflammatory demyelinating disease of the central nervous system (CNS), affecting approximately 2.8 million people worldwide (1, 2). MS varies between patients at presentation, displaying as one of three clinical forms, primary-progressive MS (PPMS), secondary-progressive MS (SPMS) and relapsing-remitting MS (RRMS). Approximately 85% of MS patients are diagnosed with RRMS, which is typically characterized by acute, episodic periods of aggressive symptomology (relapses), followed by periods of remission (3). Symptoms of MS include, but are not limited to, sensory loss, fatigue, visual impairments and ataxia in consequence of inflammation, neuron demyelination and the accumulation of white-matter lesions in the CNS. The progression of these disease manifestations consequently results in gradual

loss of mobility and cognition potentially leading to neurologic disability (2). Currently, no medications can prevent or reverse neurological deterioration (2).

MS is generally classified as an immune-mediated inflammatory disease, involving a complex combination of neurodegenerative processes amplified by immunological responses. During a relapse, immune cells are activated in the periphery and traffic into the CNS, where they are re-activated, trigger inflammation and recruitment of other peripheral immune cells, consequently resulting in neuron demyelination and tissue damage (3). The C57BL/6 (B6) murine experimental autoimmune encephalomyelitis (EAE) is the most widely used experimental model of MS due to the availability of transgenic and gene knock-out models on the B6 background that are used to investigate the disease pathogenesis (referring to reference 5 for details of other EAE models). The model is established by sensitizing mice to myelin oligodendrocyte glycoprotein MOG<sub>35-55</sub> peptide emulsified in complete Freund's adjuvant along with the co-adjuvant pertussis toxin (4). It can be actively induced through direct immunization, or passively through adoptive transfer of myelin-specific T-cells or CD4<sup>+</sup> T helper (T<sub>H</sub>) cells from a sensitized donor to a naïve recipient (5). EAE is characterized by the infiltration of autoreactive immune cells into the CNS with subsequent inflammation, demyelination, axonal damage and loss. Due to the potential immune mechanisms involved in both MS and murine MOG<sub>35-55</sub>-induced EAE, this model remains important in the MS research, despite that the lesions in this model, which are different from the MS pathology, appear to display extensive axonal injury and loss with little primary demyelination and are largely confined to the spinal cord (5).

Extensive studies on EAE and MS have focused on myelin-specific autoreactive T-cells. The involvement of B-cells in MS has also been appreciated, as evidenced by the presence of oligoclonal bands (OCB) in the cerebral spinal fluid (CSF) of MS patients (2, 6–8), and the effectiveness of recent B-cell depleting therapies in MS patients that highlights antibody-independent B-cell function in MS pathogenesis (9–12). The primary focus of this review will discuss our expanded understanding of B-cell involvement in autoimmune neuroinflammation with a focus on antibody-secreting B-cells. We will then discuss the role of a specific type of antibody, IgE, as it relates to autoimmunity and MS/EAE development.

## BIOLOGY OF B-CELLS

The role of B-cells in the maintenance of proper immune function and regulation displays profound importance in human health and disease. B-cells as a highly heterogeneous population with a great degree of functional plasticity are capable of modulating both innate and adaptive immune responses. Consequently, their development and effector functions are highly regulated, as an inappropriate development can lead to the generation of autoreactive B-cells (13).

### B-Cell Developmental Subsets

B-cells develop from hematopoietic stem cells in the bone marrow (BM), supported by growth factors and cytokines

produced by resident stromal cells (14). The early B-cell development in the BM involves different stages and rearrangements of immunoglobulin (Ig) heavy and light gene segments by recombination activating gene-dependent processes, resulting in an enormous diversity of the antibody repertoire (15). In mice, these early developing B-cells finally differentiate into transitional B-cells which then migrate from the BM mainly to the spleen, while in humans transitional B-cells are present in the circulation and secondary lymphoid organs (SLOs), including the spleen (16). The late transitional B-cells give rise to mature B-cells, including follicular and marginal zone (MZ) B-cells. Upon activation, both follicular and MZ B-cells can develop into antibody-secreting cells (ASCs), including cycling plasmablasts and non-dividing plasma cells, in a T-cell-independent manner (17). When follicular B-cells encounter antigen recognition and T-cell help, they can also be fully activated, migrate into the follicle and induce the germinal center (GC) formation in SLOs (17). The cognate T-B interactions, namely T follicular helper (T<sub>FH</sub>)-GC B-cell interactions, in the GC facilitate GC B-cells to undergo Ig class switch recombination and somatic hypermutation followed by developing into memory B-cells or ASCs, including long-lived plasma cells producing class-switched antibodies (14, 16). Memory B-cells are primarily responsible for mounting the secondary immune response, triggered following a subsequent exposure to the same antigen they recognize for the first time, allowing them to proliferate and differentiate into plasma cells (18).

### Normal B-Cell Functions

A key characteristic of the mammalian adaptive immune response is the ability to rapidly produce and secrete high-affinity antibodies as they detect and help clear foreign pathogens or generate protective immunity to vaccination. B-cells are indispensable for the generation of plasmablasts and plasma cells, which are the only cell types capable of antibody production. There are five distinct antibody isotypes: IgA, IgD, IgE, IgG, and IgM, each possessing a unique effector function and distinct heavy chain. Each antibody contains a unique amino acid sequence and antigen-binding site that resides in the antigen-binding fragment (Fab) or the variable fragment (Fv) of Fab, conferring antigen specificity (19). Antibodies serve three primary functions: neutralization, activation of the complement cascade, and initiation of pathogen opsonization. Neutralization occurs when secreted antibodies bind to infectious pathogens and toxins, rendering them ineffective. Alternatively, antibodies can activate the complement cascade, a complex innate immune surveillance system that plays a primary role in protection against bacterial pathogens. Lastly, antibodies can initiate opsonization upon binding the foreign target, flagging it for destruction by phagocytic cells (20).

Although B-cells are most notable for their ability to generate and secrete antibodies, they also provide several other key effector functions, including antigen presentation, directing immune responses through cytokine secretion, and immunoregulatory roles. B-cells, recognized as professional antigen-presenting cells (APCs), constitutively express major histocompatibility complex class II (MHCII) molecules produced during B-cell development in

the BM. MHCII expression in mature B-cells permits the presentation of antigens to naïve CD4<sup>+</sup> T-cells, which triggers T-cell activation and proliferation when coupled with co-stimulatory signals (21). B-cells also possess the ability to modulate immune responses. Effector B-cells, Be1 or Be2 subsets, arising from naïve B-cells upon activation can influence CD4<sup>+</sup> T-cell differentiation into effector and memory subtypes through distinct cytokine production. T<sub>H1</sub> differentiation is promoted by Be1 cells that secrete tumor necrosis factor (TNF- $\alpha$ ), interferon- $\gamma$  (IFN $\gamma$ ), interleukin-12 (IL-12), and IL-6, while T<sub>H2</sub> differentiation is driven by Be2 cells producing IL-2, IL-13 and IL-4 (22–24). IL-6-secreting B-cells are also implicated in the development of autoimmunity and promote the development of proinflammatory T<sub>H17</sub> cells, a cell subset known to play a crucial role in MS pathogenesis (25). Finally, B regulatory cells (Bregs) can negatively regulate immune responses through the production of anti-inflammatory cytokines, IL-10, IL-35 and transforming growth factor  $\beta$  (TGF- $\beta$ ) (22, 26–28). Bregs also play an important role in maintaining invariant natural killer T-cells, which promote tolerance against autoantigens involved in autoimmune diseases (29). A continuous effort is being made to understand Breg properties and functions in healthy adults as a means of developing effective immunotherapies.

### Regulation of GC B-Cell Responses

Upon activation, B-cells undergo differentiation into ASCs that are classified as either plasmablasts or plasma cells (30). ASCs can be generated *via* an extrafollicular differentiation pathway and produce relatively low-affinity antibodies. Here we focus on ASCs derived from the GC, where high-affinity antibodies and memory B-cells are generated (17).

Within the GC reaction, somatic hypermutation of the variable regions of Ig genes allows B-cells to produce high-affinity antibodies. However, random point mutations can also lead to nonfunctional or autoreactive antibody production, thus this process is tightly regulated by positive and negative selection mechanisms controlling for antibody affinity, while avoiding autoreactivity (31, 32). Two critical players in these regulatory processes include T<sub>FH</sub> and T follicular regulatory (T<sub>FR</sub>) cells. T<sub>FH</sub> cells are a specialized subset of CD4<sup>+</sup> T<sub>H</sub> cells, characterized by the expression of programmed cell death protein 1 (PD-1), chemokine receptor CXCR5 and B cell lymphoma 6 (Bcl6) transcription factor (33–36). T<sub>FH</sub> cells are localized in B-cell follicles, where they participate in the GC formation, promote the proliferation and differentiation of GC B-cells, and support the production of high-affinity antibodies *via* the cognate interactions with GC B-cells. T<sub>FH</sub>-derived IL-21 can promote GC responses by directly acting on B-cells while simultaneously promoting Bcl6 expression to further enhance T<sub>FH</sub> cell development (35–37). During affinity maturation, B-cells undergo division and Ig gene mutation in the GC dark zone followed by migrating to the light zone, where B-cells with higher affinity receptors present antigens to T<sub>FH</sub> cells for selection of high-affinity cells that cycle back to the dark zone for additional rounds of division and mutation (38, 39). This T<sub>FH</sub>-mediated selection process is accompanied by substantial cell death and apoptosis, which potentially provides self-antigens and induces autoreactive antibody production (40, 41), testifying a need for a tight regulation of this process. Although T<sub>FR</sub> cells share surface

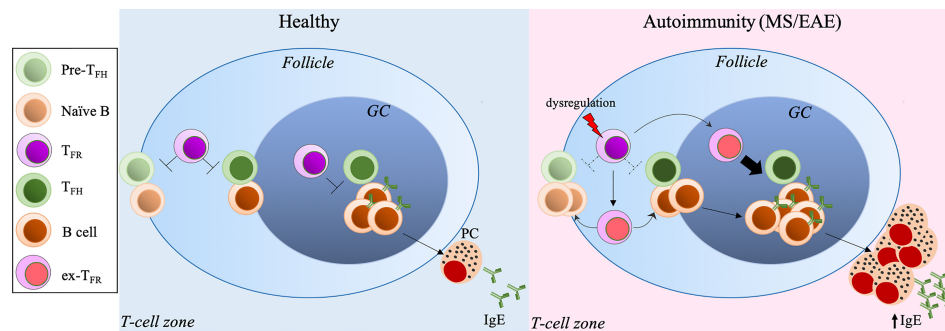
features with T<sub>FH</sub> cells and are also Bcl6<sup>+</sup>, they are the immunosuppressive counterpart of T<sub>FH</sub> cells, as a subset of Foxp3<sup>+</sup> regulatory T-cells (Tregs) with their primary role to control GC responses and maintain humoral self-tolerance (42–45). A precise control of GC responses requires the maintenance of the balance between T<sub>FH</sub> and T<sub>FR</sub> cell responses.

Our recent studies have demonstrated that dysregulated T<sub>FR</sub> cells result in aberrant T<sub>FH</sub> cell expansion and excessive GC responses with increased antibody production (42). The stability and suppressive capacity of T<sub>FR</sub> cells require the expression of the transcription factor, Blimp1. The deletion of Blimp1 in Foxp3<sup>+</sup> Tregs reprograms Tregs and T<sub>FR</sub> cells into effector T-cells that produce increased pro-inflammatory cytokines, such as IFN $\gamma$  and IL-17A, promoting the autoimmune responses. Additionally, unstable T<sub>FR</sub> cells migrate to the GC prematurely, thus promoting T<sub>FH</sub> and GC B-cell expansion, along with upregulated antibody and autoantibody production (42) (Figure 1).

### DYSREGULATED B-CELLS AND ANTIBODIES IN CNS AUTOIMMUNITY

Dysregulation of B-cells directly or secondary to aberrant T-cell responses due to the immune tolerance breakdown can lead to autoantibody production, which is a classic hallmark of B-cell-mediated autoimmune diseases (46). Autoantibodies directed against membrane-associated, extracellular and nuclear antigens are found in a plethora of autoimmune disorders, including systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and type I diabetes (T1D) (47–49), where they either directly injure target tissues or generate a polyclonal activation of the immune system *via* forming immune complexes and activating the complement cascade, resulting in unregulated inflammatory responses (46, 50–52). Conventionally, T<sub>H</sub> cells, particularly T<sub>H1</sub> and T<sub>H17</sub> subsets, are thought to contribute heavily to MS and EAE (53). However, emerging evidence suggests that B-cells play a comparably crucial role in mediating disease through their ability to serve as cytokine-producing regulatory cells, professional APCs and ASCs (54). The impaired Breg activity may contribute to the development of MS and EAE, as mice deficient in Breg-derived IL-10 and IL-35 develop exacerbated EAE with failed recovery, while elevated IL-35<sup>+</sup> or IL-10<sup>+</sup> Bregs ameliorate disease severity (55, 56). Here we focus on the contribution of dysregulated T/B responses and resultant autoantibody production to MS and EAE.

Like other APCs, such as macrophages and dendritic cells, B-cells can present antigens to T-cells as an MHCII: peptide complex once antigens are recognized through their B-cell receptor (BCR) to activate T-cells, which in turn induce B-cell proliferation and differentiation into ASCs in SLOs. As expected, unchecked T/B response to self-antigens, like myelin-associated antigens, can promote CNS pathology. The expanded autoreactive B-cell clones are found in both the periphery, including draining cervical lymph nodes, and CNS compartments (meninges, CSF and parenchyma)



**FIGURE 1** | Excessive  $T_{FH}$ -GC-B cell response and IgE production secondary to dysregulated  $T_{FR}$  cells exacerbate MS/EAE. Under normal conditions, IgE production is tightly controlled by the  $T_{FH}$ - $T_{FR}$  cellular pair. Dysregulation of  $T_{FR}$  cells leads to  $T_{FH}$ /GC B-cell expansion and excessive IgE production, inducing autoreactive IgE, resulting in exacerbated autoimmune diseases, such as MS and EAE. PC, plasma cell. x- $T_{FR}$ , dysregulated  $T_{FR}$  cells.

of MS patients (57). In particular,  $IgG1^+$  B-cells expressing the chemokine receptor CXCR3 and the transcription factor T-bet are recruited and enriched in the CNS of some MS patients, likely reflecting high levels of CXCR3 ligand CXCL10 in the CSF of these patients (58, 59). These studies imply that autoreactive B-cells can traffic across the blood-brain barrier (BBB) into the CNS where they may undergo further differentiation into ASCs, promoting MS pathology (58, 60). Interestingly, histological analysis has revealed structures resembling lymphoid follicles compartmentalizing T, B, plasma cells, and follicular dendritic cells within the meninges of the CNS, termed as ectopic lymphoid structures (ELSs) (61). The presence of these follicle-like structures within the CNS further suggests that T/B-cell activation and proliferation *in situ* contribute to disease pathogenesis (62).  $T_{FH}$  and GC B-cells are found in these ELSs, but the presence of  $T_{FR}$  cells has not been reported in the inflamed CNS until our recent study (63), despite that the regulatory activity of  $T_{FR}$  cells in the lesions still require further investigation. Dysregulated  $T_{FH}$  cell-GC-antibody responses secondary to dysfunctional  $T_{FR}$  cells are the root of autoimmune disorders, including MS and EAE (64, 65) (**Figure 1**). MS patients have been found to harbor substantially reduced circulating  $T_{FR}$  cells compared to healthy controls, and those residual cells in the circulation resemble a more  $T_{H17}$ -effector like phenotype with impaired suppressive activity (66). Our recent study has also shown that mice with dysfunctional  $T_{FR}$  cells due to the deletion of Blimp1 develop more severe EAE and fail to recover compared to control mice (63). In this MOG<sub>35-55</sub>-induced EAE model, Blimp1-deficient  $T_{FR}$  cells become unstable and produce  $T_{H17}$ -associated cytokines, including GM-CSF and IL-17A. Moreover, these unstable  $T_{FR}$  cells acquire the  $T_{FH}$  helper activity, and promote GC B-cell expansion and antibody production, leading to augmented disease (63) (**Figure 1**).

Although the contribution of antibodies, particularly antibody isotypes, to the pathogenesis of MS and EAE remains largely unclear, antibodies specific to self-antigens, including myelin-derived lipids and proteins, are often detected in the CSF of MS patients (67–69). The emergence of oligoclonal bands (OCB) in the CSF, which are locally produced by clonally expanded antigen-experienced B-cells, is one of the hallmarks of MS, with more than

95% of MS patients containing the OCB of IgG class (8). RRMS patients with intrathecal IgG synthesis, manifested by the presence of OCB, are also associated with a higher risk of and shorter time to disability worsening (as reflected by the Expanded Disability Status Scale score) over a four-year period of follow-up (70). The antigen specificity of OCB remains elusive. Using an approach that allows concurrent analysis of the full-length sequences of matching Ig heavy and light chains from distinct OCB followed by producing recombinant OCB antibodies and antigen searches, Brändel et al. have revealed that six OCB antibodies from four MS patients recognize three ubiquitous intracellular proteins not specific to brain tissue (71). These interesting findings suggest that part of MS OCB antibodies target autoantigens released through tissue destruction (71). Additionally, Liu et al. have tested the specificity of recombinant IgG1 antibodies produced from clonally-expanded plasmablasts isolated from MS CSF. The application of these antibodies onto mouse organotypic cerebellar slices has shown that these antibodies bind to the surface of oligodendrocytes and myelinating axons inducing rapid demyelination accompanied with enhanced microglia activation in the presence of complement, suggesting their specificity to myelin-derived antigens (72). Another study has demonstrated that higher CSF IgM levels in treatment-naïve MS patients positively correlate with the CSF levels of molecules related to B-cell immunity (IL-10), recruitment (CXCL13 and CCL21), and macrophage/microglial activity (IL-12p70, CX3CL1 and CHI3L1), as well as white matter lesion numbers and disease activity after two years of follow-up, suggesting a potential role of IgM in the MS disease course (73). Several additional studies also implicate that intrathecal IgM synthesis may serve as a predictor of the onset of new relapses and worsened disease progression (74–77). In contrast, gut commensal-specific IgA-producing plasma cells have been shown to recirculate into the CNS of EAE mice and active MS patients during disease relapse (78, 79). Despite their unclear function in MS patients, these cells suppress neuroinflammation in EAE mice *via* the production of IL-10 (79), suggesting the anti-inflammatory role of IgA-producing cells which may serve as a predictor for MS disease course (78). Finally, the IgE isotype has only recently been implicated in taking part in MS pathology, as sera from some MS

patients contain significantly higher levels of IgE reactive against myelin protein-derived peptides whereas peptide-reactive IgA or IgG is often undetectable (80). Our recent study has also pointed to a disease-promoting role of IgE in EAE (63). We will further discuss the pathogenic role of IgE in autoimmune diseases with an emphasis on MS and EAE in the following sections.

## CONTRIBUTION OF IGE TO AUTOIMMUNE DISEASES

### Regulation of IgE Production and Maintenance

B-cells undergo isotype switching, a complex process that requires precise and sequential genomic DNA splicing and recombination, to express surface membrane-bound IgE, and to secrete it as well. IgE is an antibody isotype with the lowest abundance and the shortest serum half-life *in vivo*, suggesting that IgE responses are generally limited at steady states (81). IgE can be derived from direct class-switching where IgM directly converts to IgE, or from sequential steps by initially converting IgM to IgG1 that then converts to IgE, or alternatively from IgG1 directly (81). These differing mechanisms for IgE generation are suggested to distinguish the IgE<sup>+</sup> B-cell fates. While direct class-switching is associated with the generation of IgE<sup>+</sup> GC B-cells and the production of low-affinity IgE, the sequential generation of IgE is more related to developing plasma cells with a greater affinity of IgE (82–85). Interestingly, the membrane-bound IgE (i.e., IgE<sup>+</sup> BCR) has been shown *in vivo* and *in vitro* to autonomously promote B-cell differentiation into antibody-secreting plasma cells in the absence of cognate antigen, suggesting that BCR signals restrict IgE<sup>+</sup> GC B-cell responses (86). Upon release into circulation, IgE binds to the high-affinity FcεRI receptor expressed on the surface of mast cells, basophils and other cell types (87). Binding of IgE to FcεRI expressed on dendritic cells and macrophages induces activation through the internalization of IgE-bound antigens, and production of a cytokine milieu (e.g., IL-4) favoring T<sub>H</sub>2 differentiation (81), which may in turn facilitate IgE class-switching, implying a positive feedback mechanism in the regulation of IgE production.

The IgE production is also tightly regulated by the T<sub>FH</sub>-T<sub>FR</sub> cellular pair (Figure 1). T<sub>FH</sub> cells have been shown to undergo progressive maturation after entering the GC to regulate GC B-cell differentiation, starting with an IL-21<sup>+</sup> T<sub>FH</sub> cells that enable the selection of high-affinity antibodies to become IL-4<sup>+</sup> T<sub>FH</sub> cells that promote the differentiation of ASCs, including IgE-producing cells (88). Although T<sub>FR</sub> cells can positively induce IgE under certain settings (89, 90), we and others have reported that T<sub>FR</sub> cells, particularly Blimp1<sup>+</sup> T<sub>FR</sub> cells, are key suppressors of IgE production (42, 63, 91–95). Using a unique T<sub>FR</sub> cell-deleter mouse strain, T<sub>FR</sub> cells have been demonstrated to control IgG and IgE responses and regulate IL-13-producing T<sub>FH</sub> cell-induced IgE specifically in house dust mite models (94). A most recent study by Dr. Carola Vinuesa's group has further shown that T<sub>FR</sub> cells produce neuritin -a neuropeptide known to regulate synaptic plasticity and neuronal growth, migration, and survival- which regulates GC B-cells to block the emergence of autoantibodies

and excessive IgE (95). The deletion of neuritin in Tregs or ablation of T<sub>FR</sub> cells expedites the differentiation of GC B-cells into plasma cells and IgE class-switching (95). Thus, the immune system has adopted various mechanisms to restrain IgE production and keep it at proper levels under normal conditions.

### Unconventional Role of IgE in Autoimmune Disorders

Conventionally, IgE is known for mediating immediate, allergen-specific reactions, commonly referred to as type 1 hypersensitivity. Effector functions are triggered by the cross-linking of allergen-specific IgE to the FcεRI receptor on mast cells and basophils, inducing the subsequent degranulation and release of potent proinflammatory mediators, such as histamine and T<sub>H</sub>2 cytokines, to cause inflammatory responses (96). IgE also binds to low-affinity receptors known as FcεRII or CD23 on B-cells and other cells to mediate the uptake of IgE-antigen complexes (81, 97). Additionally, IgE plays an important evolutionary role in host protection against venoms and parasitic infections (98), particularly those caused by helminths and specific protozoans (99).

The association of elevated serum IgE levels with autoimmunity has been understudied, but recent clinical evidence linking autoreactive IgE beyond its conventional role in inducing allergic responses to autoimmune diseases has attracted more attention from the research community (100, 101). IgE has been implicated in contributing to the onset of inflammatory and autoimmune diseases such as RA, SLE, T1D, atopic dermatitis, bullous pemphigoid, atherosclerosis, obesity, and coronary heart disease (102–106). Autoreactive IgE, including antinuclear IgE antibodies, are found in a significant portion of these patient populations (103, 104), despite that the exact pathogenic role of IgE remains largely unclear, and in some cases, autoreactive IgE levels are comparable to autoreactive IgG levels making a definitive causal relationship challenging to establish (100, 107). Notably, a key study of SLE patients demonstrates that double-stranded DNA (dsDNA)-reactive IgE can trigger IFNα production *via* activating plasmacytoid dendritic cells (pDCs) upon binding to FcεRI on these cells, and that the serum concentrations of these dsDNA-reactive IgE correlate with disease severity (108). These studies have justified and stimulated the application of IgE blocker (omalizumab), which is used to treat allergic asthma, as a therapeutic option for some autoimmune disorders (109).

Supporting evidences from clinical and experimental data suggest the involvement of IgE in both MS and EAE (63, 80, 110). The discovery of significant serum levels of IgE specific to a panel of short, unique myelin protein-derived peptides in the cohort of 26 MS patients irrespective of clinical subtype based on an author-developed radioimmunoassay suggests that autoreactive IgE against CNS target antigens may hold valuable diagnostic potential in some MS patients (80). Indeed, IgE<sup>+</sup> cells are detectable in all lesions of MS brains from 14 different patients, including areas with active immune infiltration (110). These studies also point out that the encephalitogenic potential of IgE may rely on its abundance in the CNS, and the presence of other pathogenic Ig isotypes, as they may compete with IgE for

the same targets. Consistent with the findings that mice with disrupted Ig Fc receptors, including FcεRI, display ameliorated EAE (111), we have recently revealed the increased CNS deposition of total and MOG-specific IgE in MOG<sub>35-55</sub>-induced EAE mice with dysregulated Tregs and T<sub>FR</sub> cells, and the serum IgE levels positively correlate with EAE disease severity (63). The increased IL-17A and IL-4 produced by over-activated T<sub>H</sub> cells and unstable Tregs in these mice may account for the elevated IgE (63), although other mechanisms, such as reduced neuritin expression by dysregulated T<sub>FR</sub> cells, may be at play and are worth further investigation. Additionally, MOG-IgE (specific to the model antigen MOG<sub>35-55</sub>) but not MOG-IgG are elevated in these mice. Although MOG-IgG has become a new diagnostic marker for neuromyelitis optica (NMO) but not MS (112), we do not know if MOG-IgE is derived from MOG-IgG *via* class-switching in this pre-clinical study and if MOG-IgE may potentially contribute to NMO or MS. It will also be interesting to investigate if the IgE-mediated pathogenesis in other autoimmune disorders, such as activation of pDCs and production of IFNα, contributes to MS and EAE, despite that the role of type 1 IFNs in MS has been a contentious subject (113, 114). As one of the conventional target cells of IgE, earlier studies have suggested that mast cells in the CNS as a direct result of intravascular myelin-reactive IgE penetrating the BBB promote MS and EAE (80, 111, 115, 116). Our recent study has also suggested that CNS myeloid cells, including microglia and infiltrating macrophages, are targeted by IgE to induce their activation (63) (**Figure 2**). We will provide a more detailed discussion of this topic in the following section.

## IgE-Mediated Regulation of Microglia and Macrophages in MS and EAE

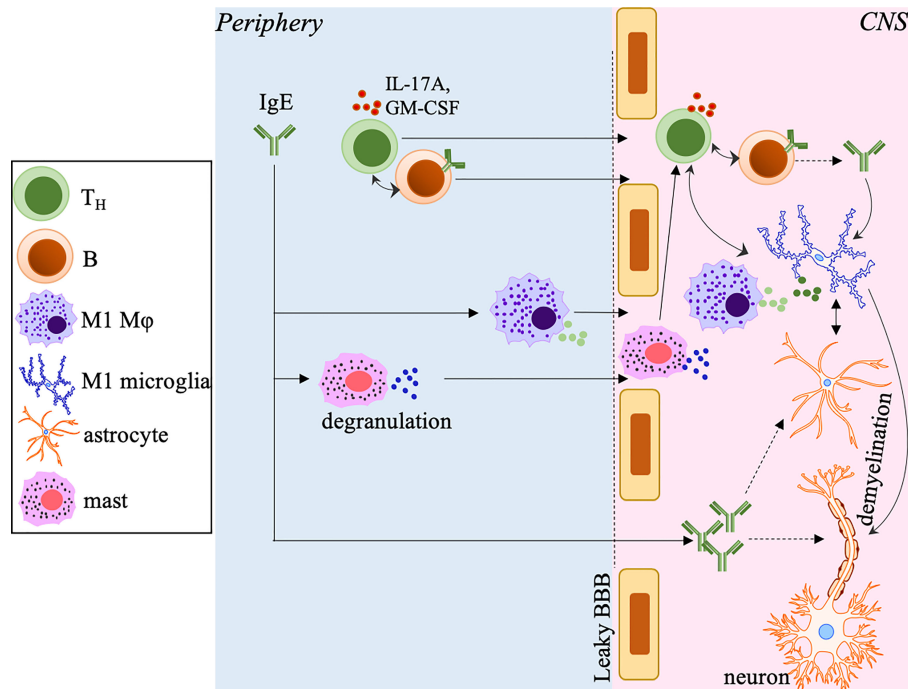
The crosstalk between the innate and adaptive arms of the immune system often occurs to ensure proper immune responses. Disruption within this complex network of cell communication can result in devastating consequences. In addition to T/B-cells and myeloid cells/macrophages that infiltrate into the CNS during MS and EAE progression, microglia, non-circulating tissue resident macrophages of the CNS, are critical for the regulation of neuroinflammation. Microglia are the cell types responsible for removing and pruning damaged and unnecessary neurons and synapses to maintain CNS homeostasis (117). Besides serving as APCs to induce T-cell activation, microglia and monocyte-derived macrophages are armed with several receptors equipped to remove aged, necrotic tissues and toxic molecules from their surroundings while eliciting endocytosis of immunocomplexes and complement-opsonized proteins through Fc receptors (118, 119). Upon homeostatic dysregulation, microglia and CNS-infiltrated macrophages can be pushed towards an M1 pro-inflammatory phenotype to mediate secretion of TNFα, IL-12, IL-6, IL-23, and TGFβ at elevated levels, promoting T<sub>H</sub>1 and T<sub>H</sub>17 differentiation, which in turn provide feedback to facilitate M1 polarization, and ultimately leading to MS pathology (120, 121). In MS and EAE, activated microglia and macrophages are hallmarks of active demyelinating lesions (122–124). Upon activation, microglia and macrophages can produce inflammatory cytokines, free radicals, protease and other mediators to augment CNS inflammation,

destroy oligodendrocytes and cause axon injury and demyelination (125). The importance of microglia and macrophages in MS and EAE has been evidenced by the fact that the inhibition of microglial activation or downregulation of molecules in these cells to diminish their function results in disease attenuation along with reduced demyelination (125–127). However, it should be noted that microglia and macrophages can also provide neuroprotection by aiding in axonal remyelination and regeneration. Their beneficial and harmful effects are possibly attributed to the heterogeneity of these cells and temporal and spatial requirements during disease progression (125, 128, 129).

The impact of IgE on macrophages has been mainly investigated in atherosclerosis and cardiovascular diseases and more recently, in cancer (102, 130, 131). Using mice lacking IgE or FcεRI combined with atherosclerosis prone models, IgE is reported to bind to FcεRI on macrophages to induce activation, accumulation into the inflammatory lesions and skewed differentiation towards the pro-inflammatory M1 phenotype (102, 130, 131). Treatment of quiescent M0 and immunosuppressive M2 macrophages with IgE results in elevated levels of M1-associated molecules. In contrast, treatment of pro-inflammatory M1 cells retains the levels of these molecules, including CD80, TNFα, IFNγ and IL-1β (131), suggesting a favorable role of IgE in driving M1 type inflammatory responses. Our recent study has for the first time reported that IgE can activate CNS myeloid cells in the context of EAE (63). This study shows that supplementing sera from EAE mice into the CNS CD11b<sup>+</sup> myeloid cell culture promotes activation and M1 polarization of these cells *via* upregulation of CD68, MHCII, and TNFα. Most notably, pre-incubation of sera with anti-IgE to neutralize IgE activity diminishes the activation of CD11b<sup>+</sup> cells, suggesting a direct regulation of myeloid cells by IgE (63) (**Figure 2**), despite that a follow-up experiment is needed to distinguish the relative impact of IgE on microglia to CNS-infiltrated macrophages. The impact of IgE on other CNS resident cells, such as astrocytes, which may influence the disease course, is also warranted for future investigation. Moreover, further *in vivo* study and exploration of IgE's mechanistic action are required to establish the importance of IgE in MS and EAE (**Figure 2**).

## THERAPEUTIC TARGETING B-CELLS AND ANTIBODY RESPONSE TO TREAT MS AND EAE

B-cell depletion therapy using monoclonal antibodies (mAbs) that target CD20 expressing B-cells is a highly effective treatment option for relapsing MS patients (132). Anti-CD20 mAbs work by depleting circulating CD20<sup>+</sup> B-cells, with treatments lasting up to 9 months (133). There are currently three clinically approved anti-CD20 mAbs used in the treatment of MS patients: rituximab (RTX), ocrelizumab (OCR), and ofatumumab (OFA). These drugs differ in their clinical effectiveness based on their molecular structure and mechanism of action targeting B-cells, as reviewed elsewhere (132). The first of the three mAbs, RTX, a chimeric mouse-



**FIGURE 2** | The potential pathogenic role of IgE in MS and EAE. In the periphery, IgE, including myelin-specific or autoreactive IgE, polarizes macrophages toward the M1 phenotype and induces mast cell degranulation, which promotes a leaky BBB allowing increased infiltration of T/B-cells, macrophages and mast cells into the CNS. IgE may also penetrate the BBB allowing the deposition into the CNS. In the CNS, IgE activates and polarizes microglia into the M1 phenotype. The M1 microglia and infiltrated macrophages produce inflammatory mediators to further drive the differentiation of encephalitogenic  $T_H$  cells, which in turn amplify the M1 polarization of these cells. IgE may directly activate astrocytes that cooperate with microglia to enhance neuroinflammation and induce axonal demyelination and destruction. IgE may also potentially directly target oligodendrocytes (not depicted) to promote axonal damage. The accumulation of  $T_H$  cells and B-cells may form ELSs that perpetuate inflammation, demyelination and disease progression. The small circles with different colors close to different cell types represent different secreted inflammatory mediators.

human mAb, was initially developed to target B-cell lymphomas, but is repurposed as an off-label treatment for MS patients and is now widely used in several autoimmune diseases (134–136). Its primary mechanism of action is complement-dependent cytotoxicity, but antibody-dependent cellular cytotoxicity (ADCC) also plays an important role in its effectiveness (137). OCR is used in patients with RRMS and PPMS. Currently, it is the only approved treatment for patients with the primary progressive form of the disease. OCR is a fully-humanized lytic mAb with ADCC as its primary mechanism of action; however apoptotic and antibody-dependent phagocytosis assist in B-cell depletion (138). OFA is a fully human mAb and is the only approved anti-CD20 mAb that uses a subcutaneous route of administration (139). Anti-CD20 clinical trials involving patients with RRMS show significant reductions in brain lesion formation, clinical relapse rates and no substantial side effects. However, a caveat is that CD20 is expressed on B-cells beginning in the late pre-B developmental stage, until the cells are terminally differentiated as antibody-secreting plasmablasts and plasma cells (140). Thus, pro-B cells and all ASCs are spared with anti-CD20 mAbs as they are CD20 negative (140), which may underlie the potential ineffectiveness, if any occurs, in some patients. The efficacy of B-cell depleting therapy may also need to consider the abundance and activity of Bregs, as transfer of these

cells leads to disease mitigation, at least reported in EAE mice (141, 142). With the emergence of a critical pathogenic role of IgE in promoting EAE and MS, therapies against MS could be developed to neutralize IgE or block IgE activity, such as the use of omalizumab in other autoimmune disorders (109).

## CONCLUSIONS AND PERSPECTIVES

Considerable progress has been made in uncovering the mechanisms guiding CNS autoimmunity, particularly in MS. However, there are many critical knowledge gaps that remain. It is essential to understand the emerging role of B-cells and IgE in triggering autoimmune diseases. Current and future areas of interest should include defining the effector activity of IgE in mediating macrophage/microglial activation, influencing the CNS resident cells and promoting a pro-inflammatory milieu in the CNS. Better delineation of autoreactivity of autoantibodies may enable immunological phenotyping of MS patients, facilitate the development of a diagnostic test and lead to new treatment directions. In addition, as our knowledge of B-cell involvement in MS progression, elucidating the mechanisms by which  $T_{FR}$ ,  $T_{FH}$ , GC-B cells and antibody production (particularly IgE) are properly regulated is crucial in discovering disease-promoting factors. This

represents a new era for identifying therapeutic targets to manipulate B-cell activity for targeted immunotherapies.

## AUTHOR CONTRIBUTIONS

MRS, MMM, JDL, and JWJ drafted the manuscript, revised it critically, and approved this final version for publication.

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