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An appraisal of antigen identification and IgG effector functions driving host immune responses in multiple sclerosis

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Increased immunoglobulin G (IgG) antibodies and oligoclonal bands (OCB) are the most characteristic features of multiple sclerosis (MS), a neuroinflammatory demyelinating disease with neurodegeneration at chronic stages. OCB are shown to be associated with disease activity and brain atrophy. Despite intensive research over the last several decades, the antigen specificities of the IgG in MS have remained elusive. We present evidence which supports that intrathecal IgG is not driven by antigen-stimulation, therefore provide reasoning for failed MS antigen identification. Further, the presence of co-deposition of IgG and activated complement products in MS lesions suggest that the IgG effector functions may play a critical role in disease pathogenesis.

Keywords: multiple sclerosis (MS); oligoclonal band; IgG; antigen; effector function

1. Introduction

Multiple sclerosis (MS) is the most common chronic inflammatory disease of the central nervous system (CNS), which causes a mild to severe disability in the majority of affected patients [1,2]. The increased intrathecal synthesis of IgG and oligoclonal bands (OCB) are present in over 95% of MS patients [2]. OCB were found to be associated with increased levels of disease activity and disability, the conversion from a clinically isolated syndrome (CIS) to early relapsing-remitting multiple sclerosis (RRMS), and more significant brain atrophy [3]. Furthermore, extensive pathological characterization of acute MS brain lesions

Abbreviations: V_H (IgG heavy chain variable region), FACS (fluorescence-activated cell sorting), RT-PCR (reverse transcription polymerase chain reaction), FcγR (Fc gamma receptors), FcγRIIB (Fcγ receptor IIB), FcRn (neonatal Fc receptor), ADCC (antibody dependent cellular cytotoxicity), CDC (complement dependent cytotoxicity), MAC (membrane attack complex), C1q (complement component 1q), NK (natural killer), IVIG (intravenous IgG), rAbs (recombinant antibodies), CDRs (complementarity-determining regions), HCDR3 (heavy chain CDR3)

has demonstrated the colocalization of IgG antibodies, complement activation products, and Fc gamma receptors (FcγR), suggesting an effector function for these antibodies in the early stages of the disease [4–6]. The successful B cell therapy, the persistence of OCB, and the consistent presence of codeposition of IgG and complements indicate the significance of IgG in MS disease pathogenesis. Yet, despite the intensive research over the last several decades, the antigen specificities of MS IgG have remained elusive. In this review, we consider the possible reasons for this failure to identify a key MS-associated antigen and present evidence supporting the role of IgG effector functions in disease pathogenesis.

2. Intrathecal IgG and Oligoclonal Bands in MS

A high IgG load in MS CNS and the presence of OCB are considered the hallmarks of disease and criteria for diagnosis of MS [7,8]. Increased IgG and OCB correlates with disease activity and disability [9,10]. In addition, OCB do not change within an individual patient over time [11], and OCB-specific peptides in MS stay identical or similar over time [12], but unique for individual patients [3]. The presumed antigenic specificity of the OCB in MS has yet to be determined and indeed is considered to be a form of 'holy grail' for MS immunologists. Identification of a causative antigen would be of great importance to the field of MS and also raise the possibility of primary prevention. However, as Hauser et al. pointed out, knowledge of the causative antigen(s) in other autoimmune disorders has so far not resulted in selective targeted therapy for any condition [13]. Further, OCB are also detected in several other neurological conditions such as neurosarcoidosis, neurosyphilis, and Cryptococcus meningitis [14] so, they are not necessarily disease-specific. Further, the overlapping, but different, OCB profiles observed in diverse regions of the same MS brain were thought to indicate that much of the IgG in MS plaques are nonsense antibodies resulting from random B cell activation and not relevant to the pathogenesis of MS [15,16]. Given the success of B cell therapies, and the consistent presence of increased IgG antibodies in the brain and CSF, it is plausible that the pathological role of OCBs in MS may be contributed by antibody effector functions.

Importantly, intrathecal IgG synthesis in MS was found to be genetically influenced [17–19], and OCB are also associated with specific genetic risk alleles [20] indicating that OCB in MS are genetically controlled.

3. Disease-causing antibodies in MS

To date, there is no convincing evidence of specific antibodies that play a critical role in MS pathogenesis. However, the involvement of antibodies in disease pathogenesis is supported by the clinical response of some patients to treatments known to inhibit antibody-mediated effects in other diseases [21–26], as well as the observation that actively demyelinating lesions are commonly associated with deposition of immunoglobulins and complement activation products [4–6]. Local deposition of immunoglobulins and complement is also observed following antibody-mediated demyelination in animal models of MS [4], providing further credibility for the hypothesis that autoantibody-dependent mechanisms

are involved in the immunopathogenesis of MS [27,28]. However, it should be appreciated that antibodies produced in MS, such as those produced by CD5+ B cells, are polyspecific indicating the absence of a single antigen driving autoimmunity in MS [29,30]. While one study suggested that MS sera contain antibodies to oligodendrocytes, which form myelin in the CNS [29], this observation was not confirmed in other studies [31,32]. The absence of disease-causing antibodies is not consistent with the notion of a single antigen driving the harmful immune response seen in MS patients.

4. Clonal B cells, plasmablasts, and V_H4 dominance in MS and other diseases

4.1. IgG heavy chain variable region (V_H) family dominance in MS

Owens et al (1998) reported the restricted use of V_H4 germline segments in an acute MS brain. The IgG heavy chain variable region repertoire expressed in lesions of an acute MS brain were predominantly V_H4 clones, and CDR3(+) sequences showed extensive somatic mutation and the preferential accumulation of amino acid replacement mutations [33]. A subsequent study from this laboratory reported expanded CD138(+) cells from 11 MS patients representing differing clinical courses and stages of disease that contained dominant V_H4 sequences in the CSF [34]. Figure 1 highlights the three CDR regions in the IgG gene. This data suggests that the IgG antibodies in MS may be antigen-driven.

However, a study found that the human Immunoglobulin V_H gene repertoire was genetically controlled and unaltered by chronic autoimmune stimulation [35]. Quantitative analysis (anchored PCR-ELISA) of μ and γ transcripts in peripheral blood lymphocytes from 10 pairs of adult monozygotic twins revealed that the V_H gene family expression was controlled by genetic factors and could often be distinguished from one another. It remained stable despite the passage of time and duration of disease [35].

4.2. V_H family gene expression and immunoglobulin specificity

IgG B cells are derived from IgM B cells after antigenic stimulation. Therefore, one would expect that the expressed IgG would depend upon environmental stimuli, while the expressed IgM would be dependent on genetic and developmental factors. However, in this study, the μ and γ V_H gene expression patterns were similar in all subjects [35]. Thus, exogenous antigens do not normally skew the basic inherited pattern of Ig V_H gene expression by peripheral B lymphocytes. The V_H family gene expression pattern does not necessarily correlate with immunoglobulin specificity [35]. Hence, we argue that the dominant V_H4 gene expression in MS CSF is likely due to specific enrichment of B cells rather than antigen-stimulation. Our recent study that distinct sets of oligoclonal IgG-reactive peptides were identified by individual MS CSF, support the notion that the

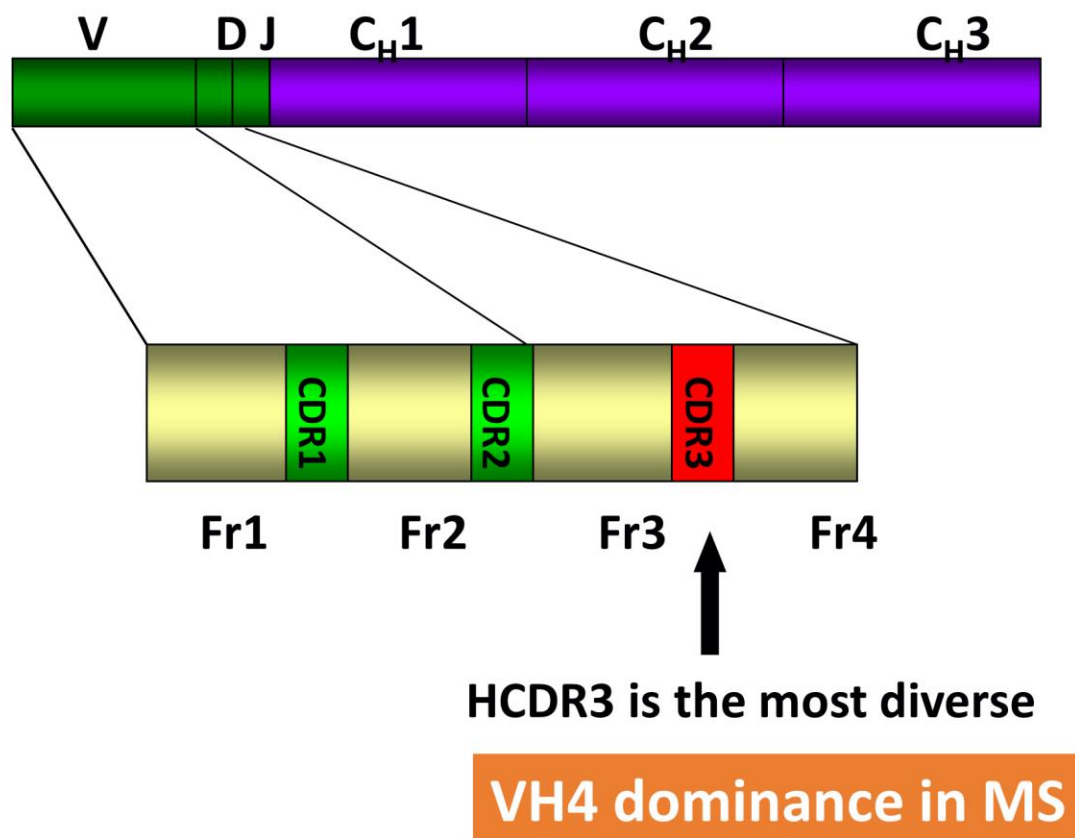


Figure 1: IgG heavy chain variable region V_H4 dominance in MS. CD19(+) B cells and CD138(+) plasma cells are sorted by fluorescence-activated cell sorting (FACS), and reverse transcription polymerase chain reaction (RT-PCR) is performed for V_H regions to identify the CDR3 sequences [34].

increased IgG in MS may not be antigen driven [36]. Moreover, expression of CD5 on B lymphocytes correlates with disease activity in patients with MS [37] and CD5+ B cells produce polyspecific antibodies [30].

4.3. V_H family usage in autoimmune diseases

Studies in known autoimmune diseases have shed further light on this issue. Thus, $V_H4.34$ antibodies (Abs) represent a major component of the IgG autoantibody repertoire in lupus, and it binds to a 220-kDa glycoform of CD45/B220 on the surface of human B lymphocytes [38]. The investigators showed that lupus IgG $V_H4.34$ Abs target a developmentally regulated B220-specific glycoform of CD45 protein. Their findings suggest that heterogeneity of auto-antigens may potentially change specific naive B cell populations. Many different human autoantibodies use genes from the V_H4 family, and positive selection by autoantigen [39] is one possible explanation for the predominance of V_H4 genes.

Restricted V_H gene family usage has been shown in several other scenarios. These include early in fetal development [40,41], in malignant B cells [42], in CD5+ B1 B cells [43], and in

autoantibody repertoires [44], resulting in the generation of higher levels of serum antibodies, and a higher percentage of human plasmablasts and plasma cells in vivo.

5. The failure of identification of MS antigens by clonal B cell-derived recombinant antibodies

The findings of V_H4 dominance in MS have generated much interest in recombinant antibody generation and antigen identification. Figure 2 illustrates the scheme for generation of recombinant antibodies (rAbs) from single cells in MS CSF.

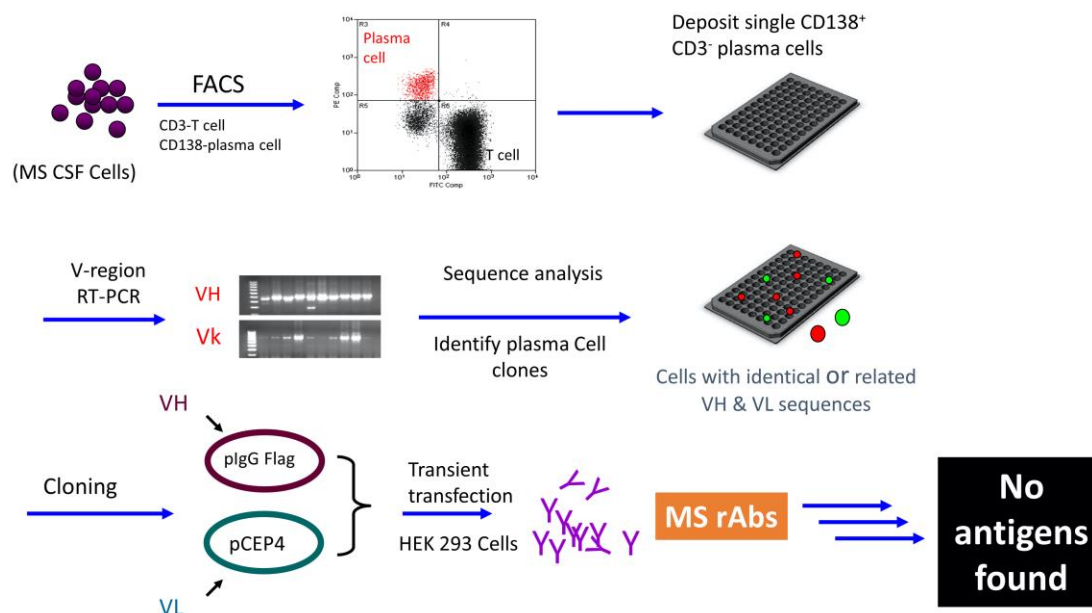


Figure 2: Flow chart of single cell PCR and generation of recombinant antibodies from MS CSF. CSF cells are sorted by FACS (CD3⁻) and CD138(+). Single cells are deposited into a 96 plate followed by RT-PCR for V_H and V_L sequences and CDR3 regions are identified. Cells with identical V_H and V_κ sequences are considered clonally expanded populations. The overrepresented IgG V_H and V_κ sequences are cloned into IgG expression vectors to generate recombinant antibodies (rAbs). However, no antigens specific for MS antibodies have been found.

We showed that specific phage peptides were identified by recombinant antibodies (rAbs) generated from MS clonal expanded plasma cells, but no common antigens were found [12,45]. Owens et al. found that humanized control rAbs derived from anti-myelin hybridomas and anti-myelin monoclonal antibodies readily detected myelin antigens in multiple immunoassays. In contrast, none of the rAbs derived from MS CSF displayed immunoreactivity to the three myelin antigens tested [46]. Brändle et al. showed that OCB in MS target ubiquitous intracellular antigens released in cellular debris [47]. Using recombinant antibodies cloned from laser captured single plasma cells from MS brain, we recently identified high-affinity peptides which bound to OCB but failed to demonstrate

that IgG also recognized these peptides from other MS patients [48]. Further, we showed that MS OCB target patient-specific antigens [36].

A general point to emphasize is that patients with autoimmune diseases frequently produce autoantibodies to a large variety of antigens, but for many of these, it has not been possible to determine their relevance to the pathogenesis of the disease. In some cases, even autoantibodies with the same specificity are not equally pathogenic. The pathogenicity of different autoantibodies with the same specificity cannot be determined with the polyclonal autoantibodies present in the serum of individual patients. Ditzel et al. pointed out that much of the antibody repertoire is concerned with polyreactive antibodies capable of interacting with multiple antigenic species. In their study of the determinants of polyreactivity in a large panel of recombinant human antibodies from HIV-1 infection, these authors found that there was skewed VL gene usage in that 75% of the Ig Fab fragments used one of two germlines [49]. The importance of the heavy chain, in particular the heavy chain CDR3 (HCDR3), in dictating the polyreactive phenotype was demonstrated for the prototype Fab, and they hypothesized that antibody polyreactivity is associated with conformationally flexible HCDR3 regions.

6. Evidence for IgG effector functions in MS

While extensive research has failed to identify the antigen specificity of the IgG antibodies in MS, there is nevertheless evidence to support IgG effector functions and their role in disease pathogenesis. IgG Fc domain mediates a wide range of effector functions including antibody dependent cellular cytotoxicity (ADCC) and complement dependent cytotoxicity (CDC). For ADCC, engagement of the various types of Fc γ Rs by the Fc domain can activate distinct immunomodulatory pathways with pleiotropic functional consequences for several leukocyte types. For CDC, binding of complement component 1q (C1q) triggers the activation of the complement cascade and leads to the formation of the membrane attack complex (MAC), which forms pores causing the lysis of target cells [Fig. 3]. Several lines of evidence support the pathological role of IgG in MS, summarized as follows:

6.1. Co-deposition of complement activation products and IgG in acute MS lesions

The complement system is central to innate and adaptive immune responses. Complement is activated through the classical, lectin and alternative pathways that generate anaphylatoxins C3a and C5a and opsonins, including C3b [50].

Prominent deposition of IgG antibodies and complement activation are common features of acute demyelinating plaques [4–6]. Complement activation products are consistently present in active lesions and cortical grey matter lesions [52]. Watkins et al (2016) showed that complement is activated in the MS cortical grey matter lesions in areas of elevated numbers of complement receptor-positive microglia, and suggests that complement over-activation may contribute to the worsening pathology that underlies the irreversible progression of MS [53]. These studies provide strong evidence that complement-dependent

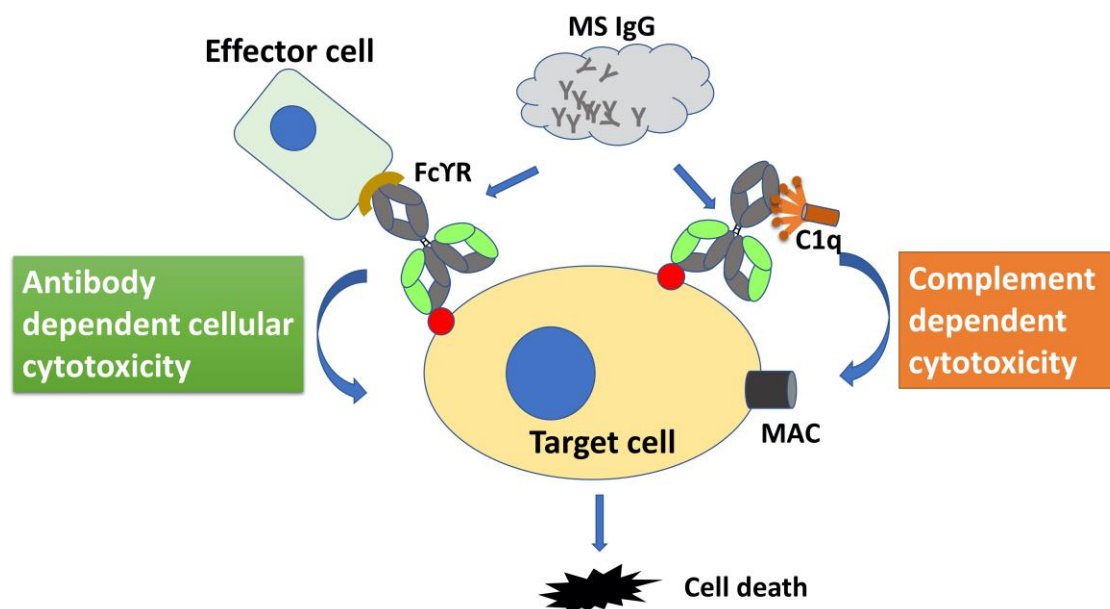


Figure 3: The effector functions of IgG antibodies (modified based on a figure from Wu and Lefranc at IMGT) [51].

antibody cytotoxicity (Fc effector function) may play important role in demyelination and neuronal death.

6.2. ADCC and Fc gamma receptors in neurons and microglia of MS lesions

Antibodies forming complexes with antigens can initiate important cell-based functions such as antibody dependent cellular cytotoxicity (ADCC), triggering the release of pro- and anti-inflammatory mediators and enzymes, as well as modulating antigen presentation and the clearance of pathogenic complexes [54]. Both IgG1 and IgG3 bind to FcγRIIa, FcγRIIIa, and FcγRIIIb effector cells such as neutrophils, monocytes, macrophages, or natural killer (NK) cells [55]. Early studies demonstrated that in active MS lesions, reactive microglia have an increased expression for Fc gamma receptors FcγRI, FcγRII, and FcγRIII [56]. Fc gamma receptors have been shown to be involved in the uptake of IgG-coated particles and immune complexes in MS lesions [6]. In inflammatory demyelinating areas, immunostaining for FcγRI, FcγRII, and FcγRIII was observed within macrophages in intracellular vesicle-like structures, and on the cell surface. Further, double-labeling studies have demonstrated colocalization of FcR with IgG, C1q in phagocytic macrophages, suggesting a role for FcR-mediated myelin phagocytosis in established MS [6]. This data supports that the IgG effector function may be critical for MS disease pathogenesis.

6.3. Higher IgG1 and IgG3 in MS lesions and are major components of oligoclonal bands

The predominant IgG subclasses in MS CSF are IgG1 and IgG3 [57,58], and the elevation of both IgG1 and IgG3 indices in MS is observed more frequently than the elevation of the general IgG index [9]. Furthermore, the susceptibility to MS is associated with an IgG3 restriction fragment length polymorphism [59], and intrathecal IgG synthesis in MS is

associated with IgG3 heavy chain gene polymorphism [17]. Recent studies support the concept that total IgG as well as IgG3 may play significant role in MS disease pathogenesis. For example, 1) MS patients have higher levels of total IgG in serum [60]; 2) higher serum IgG3 levels may predict the development of MS from clinically isolated syndrome [61], 3) IgG3+ B cells are associated with the development of MS [62]. Thus, both the major IgG1 and minor IgG3 may play major role in their effector functions in MS. Rozanolixizumab is a neonatal Fc receptor (FcRn) inhibitor that has been shown clinical benefit in patients with Myasthenia Gravis [63]. We speculate that Rozanolixizumab may have the potential to treat MS patients in the near future.

6.4. Higher levels of IgG glycosylation in MS

The IgG subclasses contain a highly conserved asparagine-linked (N-) oligosaccharide located in the CH2 domain of the Fc region, and glycans are also present in about 15% of variable domains [64]. Glycosylation on the immunoglobulin plays a strong role on the binding to Fc receptors. Variations in IgG Fc N-glycosylation have been shown to be associated with increased autoimmune disease activity since they influence binding to Fc γ Rs on both effector cells and immune mediators [65–67]. Furthermore, it was shown that antibodies with lower levels of terminal sugar residues might be more pathogenic [68–70]. Relevant to this was the finding that IgG galactosylation was significantly altered in CSF but not in the serum of MS patients, and that this modification had a relationship with an active progression of MS [68]. We recently demonstrated the presence of aberrant IgG glycosylation in MS [71]. We showed the presence of lower levels of IgG sialylation in the CSF compared to paired serum and higher levels of sialylated and galactosylated serum IgG in MS compared to other neurological disorders and normal healthy controls. The unique IgG glycosylation profiles in MS suggest a complex nature of the IgG antibodies which may influence its effector functions in the disease.

7. The importance of Fc γ RIIB in autoimmunity

Although a potential link between MS autoimmunity and physiological autoimmunity is unclear, there has been significant progress in learning more about specific mechanisms that can be driving autoimmune responses. There is now a body of evidence to suggest that the Fc γ receptor IIB (Fc γ RIIB) plays a significant role in the generation of autoimmunity. Baerenwaldt et al. showed that the inhibitory Fc γ -receptor is a checkpoint of humoral tolerance in the human immunity. Impaired human Fc γ RIIB function resulted in the generation of higher levels of serum immunoglobulins, the production of different autoantibody specificities, and a higher proportion of human plasmablasts and plasma cells *in vivo*. These results suggest that Fc γ RIIB may be an essential checkpoint of humoral tolerance in the human immune system [72]. Tiller et al. found that loss of Fc γ RIIB was correlated with an increase in poly- and autoreactive IgG+ germinal center B cells, including anti-nuclear antibody-expressing cells. In the mice deficient in Fc γ RIIB, autoreactive B cells actively participated in germinal center reactions, and it was found that somatic mutations contributed to the generation of highly autoreactive IgG antibodies [73]. It would be of particular value if a specific immunological response could also be identified in MS.

Fc γ RIIB appears to be an essential negative regulator of inflammation in autoimmune diseases and infections [74]. In B cells, Fc γ RIIB is vital for peripheral tolerance, as Fc γ RIIB-deficient mice develop a higher frequency of autoreactive B cells [75–78]. Furthermore, mice with a polymorphism in the Fc γ RIIB promoter region showed a lower expression of Fc γ RIIB on B cells and are prone to develop autoimmunity [79,80].

Studies demonstrated that blocking of activating Fc γ Rs or changing the activating to inhibitory ratio can suppress autoantibody-induced inflammation in mice and man [79,81]. Indeed, one of the many speculated mechanisms by which intravenous IgG (IVIG) exerts its anti-inflammatory properties is upregulation of Fc γ RIIB and simultaneous downregulation of activating Fc γ Rs on macrophages to clear immune complexes without detrimental cell activation [65,82]. Significantly, the effect is most effective in IgG1-mediated inflammation as Fc γ RIIB binds IgG1 with a much higher affinity than IgG2a. The A/I ratios for IgG2a and IgG2b are 69 and 7 as compared with 0.1 for IgG1 [79]. In summary, the inhibitory Fc γ RIIB may play a role in regulating autoimmune diseases.

A very recent report shows that Fc γ RIIB expression is decreased on naive and marginal zone-like B cells from females with MS [83]. This data, together with findings of genetically controlled V_H4 dominance and intrathecal IgG in MS, collectively provide reasons for the failed antigen identification, provide a strong rationale for investigating the effector arms of the IgG antibodies.

8. Effective B cell therapies

The established effectiveness of B cell therapies using anti-CD20 monoclonal antibodies to treat patients with MS has demonstrated the critical role of this immune cell type in disease pathogenesis. Nevertheless, it is acknowledged that B cell therapies' reported success in MS could be interpreted differently from the view expressed here. Accumulating data has demonstrated that B cell depletion leads to reduced clinical and magnetic resonance imaging (MRI) evidence of disease activity, although the clinical improvement is less evident in progressive MS [84]. The actual depletion of B cells by anti-CD20 antibodies is mediated through several molecular mechanisms [84]. The exact mode of action of this therapy, however, remains unclear. B cell depletion is known to be associated with interruption of B cell trafficking from the peripheral compartment to the CNS, reduced B cell antigen presentation to T cells, modulation of proinflammatory cytokine secretion, and also reduced activation and differentiation to immunoglobulin-secreting plasmablasts [24,85]. When all B cells are removed from the blood, MS disease activity essentially ceases. The effect is rapid in onset [24], and probably in this scenario, the blockade of antigen presentation by B cells is much more important than any effect on antibody production. It has already been mentioned that MS-derived CD5+ B cells produce polyspecific antibodies, and the data so far on B cell therapy adds to the considerable weight of other evidence that a single antigen does not drive the host immune response seen in MS patients.

9. Conclusions

While there is abundant evidence that immune mechanisms unquestionably play a central role in the pathogenesis of MS, particularly evident in the form of intrathecal IgG synthesis and CSF oligoclonal IgG, it has not been possible hitherto to identify a single antigen capable of driving the observed immune responses in the disease. While there is convincing evidence for V_H gene family dominance in MS along with several autoimmune diseases, so far, the use of clonal B cell-derived recombinant antibodies has failed to identify any candidate MS antigens. However, there is convincing evidence to support IgG effector functions and their role in MS pathogenesis. The interpretation of effective B cell therapies in MS is open to question. Since MS is clinically heterogeneous, more than one antigenic stimulus may be involved in the pathogenesis of the spectrum of clinical phenotypes in MS.

Author Contributions

Conceptualization, X.Y.U.; outline of section topics, X.Y.U.; writing-original draft preparation, X.Y.U.; writing-review and editing, Z.Z. and P.G.K.; visualization, X.Y.U (figures in paper) and Z.Z. (graphical abstract). All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

The authors declare no conflict of interest.

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