The FcRγ Chain Is Not Essential for Induction of Experimental Allergic Encephalomyelitis (EAE) or Anti-Myelin Antibody-Mediated Exacerbation of EAE

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INTRODUCTION

Multiple sclerosis (MS) is a chronic degenerative disease of the central nervous system (CNS), with poorly understood etiology and pathogenesis. In experimental allergic encephalomyelitis (EAE), an animal model that is used to study (auto-) immune inflammation and demyelination in the CNS, both CD4⁺ T and CD8⁺ T cells specific for myelin antigens induce lesions highly reminiscent of MS lesions (1). Importantly, T cells critically depend on macrophages to initiate demyelinating disease (2). Abundant presence of activated microglia and macrophages containing intracellular myelin debris in active MS lesions suggests that macrophages contribute to the formation of lesions by myelin phagocytosis. Several receptor families are implicated in myelin phagocytosis, including complement receptors and IgG receptors FcγR (3–5). FcγR enhance phagocytosis of IgG-opsonized particles (6), thereby forming a bridge between adaptive and innate immunity. In MS lesions, expression of FcγR is enhanced on microglia and macrophages (7) and immunoglobulins are observed in a substantial proportion of active demyelinating MS lesions (8). At least part of these immunoglobulins specifically bind myelin antigens and can be found within phagocytic macrophages in association with degraded myelin (9). However, it is unknown to what extent FcγR-mediated myelin phagocytosis contributes to MS lesion formation.

The capacity of FcγR to contribute to myelin phagocytosis was demonstrated in vitro, where myelin-specific antibodies enhanced myelin phagocytosis in absence of active complement (4). In addition, cultured microglia produced inflammatory chemokines upon FcγR crosslinking, further supporting a pathogenic role for IgG-FcγR interactions in the CNS (10).

Knockout mice lacking FcγR have improved the understanding of Ig-FcγR interactions in health and disease, including experimental autoimmune diseases (11, 12). The murine leukocyte FcγR family consists of 3 subclasses (FcγRI, FcγRII, and FcγRIII). The activating FcγRI and FcγRIII are expressed predominantly on myeloid cells and mediate inflammatory effector functions upon crosslinking by IgG-containing immune complexes. For surface expression and signal transduction, both receptors depend on association with the FcγR chain (13). In FcγR chain-deficient mice...
Recent studies suggest an important role for both activating and inhibitory FcγRI in the induction of EAE. Disease in FcγRI−/− mice was monophasic with low incidence and mild clinical symptoms (20, 21), while autoimmune prone disease in FcγRII−/− mice exhibited more pronounced disease (21). This led to the conclusion that interactions between anti-myelin antibodies and FcγR are important for the induction of EAE. It remains unclear if IgG-FcγR interactions can contribute to ongoing CNS demyelinating disease. Injection of antibodies directed against the immunodominant myelin oligodendrocyte glycoprotein (MOG) exacerbated EAE in rats and mice (22, 23), implying that anti-MOG antibodies can contribute to ongoing CNS inflammation and demyelination. Antibody-mediated exacerbation of EAE was (partially) independent of complement (22, 24), suggesting involvement of FcγR.

We explored the role of FcγR in the effector phase of EAE, using the MOG35-55 model that is B cell independent (25). Our hypothesis was that the FcγR chain was not essential for the induction of MOG35-55 EAE, but that FcγR were instrumental in antibody-mediated exacerbation of EAE. Indeed, EAE was reproducibly induced in FcγRI−/− mice. However, injection of anti-MOG antibodies at onset of EAE rapidly exacerbated clinical EAE in both wt and FcγR−/− mice, demonstrating that anti-MOG antibodies can enhance clinical EAE independent of interactions with activating FcγR. Interestingly, sustained CNS inflammation and demyelination in wt but not FcγR−/− mice after injection of antibodies suggests that IgG-FcγR interactions may contribute to a sustained pathologic effect of anti-MOG antibodies.

**MATERIALS AND METHODS**

**Animals**

C57BL/6 mice were purchased from Harlan Olac (Horst, The Netherlands). FcγRII−/− mice generated on the C57BL/6 background in the lab of Dr. T. Saito (26). All mice were 10 to 20 weeks and weighed 18 to 25 g at the time of EAE induction. Mice were specific pathogen free and had access to chow and water ad libitum. All experiments were performed with approval of the relevant ethical committees.

**Antibodies**

The monoclonal antibody (mAb) directed against MOG, Z12 mAb, is a mouse IgG2a. The hybridoma and ascites fluid were kindly provided by Dr. Sarah Piddelsden (27) and mAb was grown either at Charing Cross Hospital, London, UK, or at the VUMC, Amsterdam, The Netherlands. Z12 mAb was purified from supernatant or ascitic fluid by affinity chromatography using a protein A Sepharose FF column (Amersham, Roosendaal, The Netherlands). Z12 F(ab′)2 fragments were produced in the laboratory of Dr. Van de Winkel. Hybridomas producing rat-anti-mouse mAbs 6B2 (anti-B220), KT3.1 (anti-CD3), M1/70 (anti-MAC-1), and M5/114 (anti-HLA-DR) were purchased from American Type Culture Collection (Manassas, VA) and grown in our laboratory. Supernatants were used to detect T cells, B cells, macrophages, and MHC Class II expression, respectively. The 2.4G2 antibody (Pharmingen, Alphen a/d’ Rijn, The Netherlands) was used to detect expression of FcγRII/III.

**Induction of EAE and Assessment of Clinical Disease**

Animals were immunized subcutaneously with 200 µg MOG peptide residues 35-55 corresponding to the mouse MOG peptide sequence (M-E-V-G-W-Y-R-S-P-F-S-R-V-V-H-L-Y-R-N-G-K) (Ansylth, Roosendaal, The Netherlands) emulsified in complete Freund’s adjuvant (Difco, Detroit, MI) (1:1, total volume 200 µL) supplemented with 600 µg heat killed *Mycobacterium tuberculosis* (Difco). After 24 hours, animals were injected intraperitoneally (i.p.) with 400 ng pertussis toxin derived from *Bordatella pertussis* (Sigma, Zwijndrecht, The Netherlands) in 200 µL saline (NaCl).

Animal were weighed and scored daily for clinical signs of EAE. Clinical disease was graded as follows: 0 = no clinical signs; 1 = limp tail; 2 = unsteady gait, hindlimb weakness; 3 = incomplete hindlimb paralysis; 4 = complete hindlimb paralysis; and 5 = moribund (euthanized) or death. Animals exhibiting signs of a lesser severity than typically observed were scored as 0.5 less than the indicated grade (22). Mice were killed at day 16 or day 35 using O2/CO2. Serum was collected and stored at −80°C. CNS tissue was collected and fixed at −80°C for immunocytochemistry or fixed in formalin before embedding in paraffin wax for histology.

**Administration of MOG Z12 Monoclonal Antibody (Z12 mAb)**

EAE was induced in C57BL/6 wt or FcγR−/− mice and at the onset of clinical signs (limp tail, grade 0.5–1), animals were injected i.p. with 1 mg of Z12 mAb, 1 mg Z12 F(ab′)2, or an equal volume of saline (NaCl). As the day of onset varied between animals, mice were not all treated on the same day. To limit the variation in day of disease onset (and thus the day of antibody injection) between treatment groups, animals were injected alternately with NaCl, Z12 mAb or Z12 F(ab′)2. The first animal to develop EAE was injected with NaCl, the second with Z12 mAb, the third with Z12 F(ab′)2, the fourth with NaCl, etc. As a result, the average day of disease onset was comparable for all treatment groups within one strain. As a control, C57BL/6 wt mice were immunized with CFA, MTB, and pertussis toxin in absence of MOG35-55 peptide, and at the time corresponding to onset of EAE in wt mice (day 14), the animals were injected i.p. with 1 mg Z12 mAb.

**Histology, Immunohistochemistry, and Immunocytochemistry**

Mice were killed 35 days after immunization, and Kluver-Barrera (Luxol fast blue/cresyl violet) staining was performed on formalin-fixed sections of spinal cord and
cerebellum to assess demyelination (28). Semiquantitative evaluation of demyelination was performed blindly and each section was evaluated three times. Perivascular demyelination, small rims of demyelination centered around blood vessels, and plaque-like demyelination (larger areas of myelin loss that were not obviously associated with blood vessels) were scored independently as absent (−), minor (+), moderate (++), intermediate (+++), or extensive (++++). Total demyelination, the cumulative score for perivascular and plaque-like demyelination, was used for statistical analysis.

Immunocytochemistry on frozen material was used to detect infiltration of macrophages, T cells, B cells, the extent of immune activation (estimated by MHC Class II expression), and expression of FcγRII and FcγRIII. CNS tissue sections (5 μm) were fixed in acetone, followed by incubation with phosphate buffered saline (PBS) containing 0.1% bovine serum albumin (BSA; PAA Laboratories, Linz, Austria) and 5% normal mouse serum to block nonspecific and Fcγ-mediated interactions. After rinsing in PBS, sections were incubated with primary antibody in PBS/0.1% BSA (1 hour, 20°C), followed by another rinse with PBS and incubation with peroxidase (HRP)-conjugated rabbit-anti-rat Ig secondary antibody (DAKO, Glostrup, Denmark) in PBS/0.1% BSA (1 hour, 20°C). After rinsing with PBS, peroxidase activity was visualized using 0.5 mg/mL 3', 3'-diaminobenzidine tetrahydrochloride (DAB) (Sigma) in 0.05 mol/L Tris-HCl buffer (pH 7.6) and 0.03% H2O2. Immunostaining was assessed quantitatively using the computer program AnalySis (Soft Imaging System GmbH, Münster, Germany), and expressed as the percentage of DAB-positive area in the cerebellar white matter relative to the total cerebellum white matter area. In each group, sections from at least five mice were analyzed, unless stated otherwise.

**Statistical Analysis**

Differences in day of disease onset, clinical score, and macrophage infiltration between experimental groups were assessed using ANOVA and Student t-test. Disease incidence and survival were analyzed using Pearson’s χ2 test. The extent of demyelination in different experimental groups was compared using Mann-Whitney U test. Kaplan-Meier analysis and logrank tests were used to analyze differences in survival of wt and FcγR−/− mice after injection of Z12 mAb or saline.

**RESULTS**

**FcγR−/− Mice Develop Chronic EAE**

EAE was induced in C57BL/6 wt and FcγR−/− mice using MOG 35-55 peptide. FcγR−/− mice developed chronic disease with similar clinical characteristics as wt mice, albeit with significantly delayed onset (day 15.8 ± 3.6 vs day 9.4 ± 3.1, respectively; p < 0.05) (Fig. 1a). No significant differences were observed between FcγR−/− and wt mice with respect to disease incidence (13 of 16 and 28 of 31, respectively), maximal clinical score (4.3 ± 0.5 and 4.0 ± 0.5, respectively) and survival (9 of 13 and 8 of 9, respectively) (Table 1).

Histopathology of EAE in wt and FcγR−/− mice was evaluated at 35 days after immunization. CNS macrophage infiltration, estimated by the mac-1-positive area in the cerebellar white matter, did not differ between wt and FcγR−/− mice (Fig. 2; Z12 mAb injection versus NaCl injection, p < 0.05, day 1–4, day 9–12). The disease-modifying effect of Z12 mAb was dependent on the Fc portion of the antibody, as injection of 1 mg Z12 F(ab′)2 fragments did not exacerbate clinical EAE (Fig. 2).

The experiment was repeated using FcγR−/− mice and a wt control group. Injection of Z12 mAb dramatically enhanced clinical EAE in both wt and FcγR−/− mice. Survival of saline-injected mice after 35 days was 7 of 7 in both strains, whereas survival after injection of Z12 mAb was significantly reduced in both wt and FcγR−/− mice (2 of 7 and 3 of 7 respectively; p < 0.05 when compared with saline-injected mice) (Fig. 3). C57BL/6 wt mice that died after injection Z12 mAb succumbed at 2.8 ± 0.4 days after injection, FcγR−/−
mice died significantly later at 4.0 ± 0.8 days (p < 0.05). The effect of antibody injection on survival was short-lived; animals either died within 5 days after antibody injection or survived for the remainder of the experiment. The maximal clinical score in wt mice was significantly higher after Z12 injection than after saline injection (4.6 ± 0.8 and 3.5 ± 0.8, respectively; p < 0.05), no such difference was observed in FcR⁻/⁻ mice (4.6 ± 0.5 and 4.3 ± 0.3, respectively). It must be noted that the maximal clinical score of wt mice in this experiment was somewhat lower than in the previous experiment, whereas clinical scores of FcR⁻/⁻ mice were similarly high (compare Table 1 with Table 2). As a result, an increase of clinical scores after injection of Z12 mAb is easier to measure in wt mice than in FcR⁻/⁻ mice, because in the latter a possible increase in clinical signs may be obscured by high clinical scores of EAE even in absence of antibody. Exacerbation of EAE after Z12 injection in wt mice was observed in 3 independent experiments. This demonstrates that the effect of anti-MOG antibody injection is reproducible, even if there is variability in clinical scores between experiments, a well-known problem of EAE in C57BL/6 mice.

Injection of Z12 mAb in CFA control mice did not cause EAE or reduce survival, confirming that anti-MOG antibodies can exacerbate but not cause clinical EAE and that injection of Z12 in absence of an ongoing CNS inflammatory response is not lethal (Table 2).

**Sustained Effect of Z12 mAb Injection on Inflammation and Demyelination in wt but Not FcR⁻/⁻ Mice**

Mice that survived injection of Z12 mAb and Z12 F(ab')₂- and saline-injected mice were killed 35 days after immunization and the CNS was isolated for histopathologic examination. This was on average 21 days (range, 18–25 days) after injection of Z12 mAb, Z12 F(ab')₂ or saline. Spinal cords from Z12 mAb-injected mice but not from NaCl-injected mice were in such a poor condition, presumably due to the severity of disease in the CNS, that they could not be extracted. Therefore, we examined cellular infiltration and demyelination in the cerebellum, which is also a good and relevant measure of disease activity in chronic EAE (29, 30).

C57BL/6 wt mice injected with Z12 mAb showed extensive plaque-like and perivascular demyelination, compared to limited perivascular demyelination in saline-injected mice (Fig. 4A, B; Table 2). The difference between saline and Z12 mAb-injected wt mice was significant (p < 0.05). Unlike previous studies (22, 23, 27), we carried out this pathologic examination of the brains approximately 3 weeks after injection of Z12 mAb, demonstrating that the effect of antibody administration was not limited to the first days after injection. In wt mice that were injected with Z12 F(ab')₂,

**FIGURE 2.** Disease modifying effect of Z12 mAb on MOG35-55 EAE in C57BL/6 wt mice. EAE was induced in C57BL/6 wt mice and at first appearance of clinical signs (arrow) animals were injected with 1 mg Z12 mAb (crosses, n = 8), Z12 F(ab')₂ fragments (open circles, n = 8), or an equal volume of NaCl (filled triangles, n = 9). Injection of Z12 mAb, but not Z12 F(ab')₂ fragments resulted in exacerbation of clinical EAE. Figure is representative of 3 independent experiments (black lines: NaCl vs Z12 mAb, Student t-test: p < 0.05; dashed lines: Z12 F(ab')₂ vs Z12 mAb, Student t-test: p < 0.05).

**FIGURE 3.** Kaplan-Meier analysis of survival of C57BL/6 wt and FcR⁻/⁻ mice after injection of Z12 mAb at onset of MOG35-55 EAE. EAE was induced in wt (triangles, n = 7) and FcR⁻/⁻ (circles, n = 7) mice, and animals were injected with 1 mg of Z12 mAb (open symbols) or and equal volume of saline (filled symbols) at disease onset (arrow). Z12 mAb significantly reduced survival in both wt and FcR⁻/⁻ mice within the first 5 days after injection (*, p < 0.05, logrank test).
fragments, demyelination at day 35 was comparable to demyelination in wt mice (data not shown), suggesting that the sustained effect of anti-MOG antibody injection is dependent on the Fc part of the antibody. Interestingly, FcRγ−/− mice did not show sustained CNS pathology after injection of Z12 mAb. Three weeks after injection of anti-MOG antibodies, demyelination in Z12 mAb-treated FcRγ−/− mice did not differ from demyelination in saline-treated FcRγ−/− or wt mice (Fig. 4E, F; Table 2). This suggests that IgG-FcγR interactions contribute to the sustained effect of Z12 mAb on demyelination.

Macrophages are thought to actively contribute to demyelination by myelin phagocytosis, therefore we subsequently evaluated macrophage infiltration in the CNS. In wt mice, macrophage infiltration at day 35 was enhanced after injection of Z12 mAb (Fig. 4C, D; Table 2). Quantitative analysis of MAC-1 staining confirmed enhanced macrophage infiltration in wt mice after injection of Z12 mAb (Fig. 4I). This difference did not reach statistical significance, probably as a result of the high variation within experimental groups and as consequence FcRγ signaling in the preclinical phase of EAE. Furthermore, interactions between IgG and activating FcγR are not essential for anti-MOG antibody-mediated exacerbation of EAE. However, IgG-FcγR interactions may contribute to a sustained effect of anti-MOG antibodies on CNS inflammation and demyelination.

The relevance of B cells and antibodies in EAE is debated, and the interpretation of data is complicated by the variety of models that are used. The role of B cells is best characterized in MOG-induced EAE in C57BL/6 and DBA/1 mice. Consequently, the role of FcγR has been addressed in these models (20, 21).

In C57BL/6 mice, the origin of the MOG protein is crucial for the role of B cells in EAE. Induction of EAE using recombinant human MOG (rhMOG) is B cell-dependent, whereas immunization protocols using rat derived MOG35-55 peptide or recombinant rat MOG (rMOG) are independent of B cells (25, 31). MOG35-55- and rrMOG-induced EAE in B cell-deficient C57BL/6 mice are indistinguishable from EAE in wt mice with regard to disease incidence, onset, severity, and CNS pathology (25). This is in line with our finding that C57BL/6 FcγR−/− mice are susceptible to MOG35-55-induced EAE. Delayed onset of EAE in FcγR−/− mice may be related to absence Fcγ chain signaling functions that are unrelated to IgG receptors. Observations on the role of B cells and FcγR in EAE in DBA/1 mice support this. B cell-deficient DBA/1 mice develop EAE after immunization with rrMOG, although clinical severity and demyelination are lower than in wt DBA/1 mice (32). Interestingly, the effect of FcγR deficiency is more dramatic: EAE in FcγR−/− DBA/1 mice was nearly absent (21).

The Fcγ chain associates with at least six FcγR-unrelated receptor complexes in leukocytes, including the γδT cell receptor (33–37). The role of FcγR chain in these receptor complexes is ill defined and as consequence FcγR−/− mice have been considered almost exclusively as mice lacking activating FcγR, thereby possibly ignoring less obvious deficiencies.

Earlier studies reported severely attenuated MOG35-55 EAE in B6129PF2 FcγR−/− mice (20, 38). The immunization protocol was similar to ours and mice were of the same H2

**DISCUSSION**

This study demonstrates that induction and progression of MOG35-55 EAE are independent of the Fcγ chain, although delayed onset of EAE in FcγR−/− mice suggests a role for Fcγ signaling in the preclinical phase of EAE. Additionally, interactions between IgG and activating FcγR are not essential for anti-MOG antibody-mediated exacerbation of EAE. However, IgG-FcγR interactions may contribute to a sustained effect of anti-MOG antibodies on CNS inflammation and demyelination.

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haplotype (H-2b), suggesting that responses to the immunizing antigen and antigen presentation may be comparable. Genetic variation in mouse strains (e.g. C57BL6/129 F2 vs C57BL/6) probably accounts for the different results. Importantly, backcrosses of 129 and C57BL/6 mice may have unpredictable phenotypes in models of autoimmunity, presumably through epistatic interactions between 129 and C57BL/6 genes (39). This emphasizes that comparisons between results obtained in different EAE experiments, using mouse strains of different origin, should be drawn very cautiously. Similarly, mast cell expressed FcγRIII has been proposed to play an important role in MOG35-55 EAE (40). The data presented here, together with our unpublished results that FcγRIII−/− mice develop full-blown EAE, demonstrate that absence of FcγRIII on mast cells does not ameliorate MOG35-55 EAE, at least not in C57BL/6 mice.

Another aspect of murine FcγR that may be relevant to our observations is residual function of FcγRI in FcγR−/−

**FIGURE 4.** CNS inflammation and demyelination in antibody-exacerbated EAE in wt and FcγR−/− mice. Brains were isolated 35 days after immunization and the cerebellum white matter was analyzed for demyelination using Kluver-Barrera staining (A, B, E, F) and inflammation using mac-1 staining (C, D, G, H). In wt mice, injection of Z12 mAb resulted in enhanced demyelination (B) and inflammation (D) when compared to saline-injected animals (A and C, respectively). In FcγR−/− mice, injection of Z12 mAb did not change demyelination (F) or inflammation (H) compared to saline-treated mice (E, G). Areas of demyelination are indicated by arrows. Original magnification: 40×. (I) Quantitative analysis of macrophage infiltration (percentages calculated as [MAC-1 area/total cerebellum white matter area] × 100). Data represent average of 7 mice (Wt-NaCl; FcγR−/−NaCl), 2 mice (Wt-Z12 mAb), or 3 mice (FcγR−/−Z12 mAb).
mice and possible FcRγ chain independent regulation of FcγRI (15, 41). It is not known to what extent residual FcγRI function affects the immune response in FcγRI−/− mice, as FcγRI−/− mice and FcγRI/III−/− mice (lacking expression FcγRI and FcγRII, but not the FcRγ chain) showed similar responses in a model of immune complex-mediated nephritis (42).

The capacity of anti-MOG antibodies to contribute to an ongoing CNS inflammatory and demyelinating response was previously demonstrated in models of antibody augmented EAE (22, 23). The present study demonstrates that anti-MOG antibody-mediated disease exacerbation is dependent on the Fc part of the injected antibody, but independent of the FcRγ chain. This implicates that the pathologic effect of antibodies results from Fc-mediated complement activation. Although the role of complement activation in MOG35-55-induced EAE has been debated (43–45), complement activation may be relevant in the context of antibody exacerbated EAE. In rats, the in vivo demyelinating potential of anti-MOG antibodies was correlated to their complement fixing capacity (27). Z12 mAb has high complement fixing capacity in vitro (27), possibly explaining the severe effect of Z12 mAb injection on clinical EAE in both wt and FcRγ−/− mice. Deposition of C9, indicative of full complement activation, was observed in CNS lesions in association with exogenous anti-MOG antibodies, 2 days after injection in animals with EAE (27). At 6 days after antibody injection, C9 deposition was markedly lower, demonstrating that complement activation after antibody injection is a short-term event (46). This supports the idea that the rapid effect of antibody injection in both wt and FcRγ−/− mice is complement-mediated, although redundancy of FcγR and complement in antibody-exacerbated EAE cannot be excluded. Indeed, wt mice succumbed faster to antibody exacerbated EAE than FcRγ−/− mice, possibly reflecting a delayed response due to absence of FcγR-mediated actions. In addition, previous studies demonstrated that complement depletion cannot (24), or not completely (22), prevent acute exacerbation of EAE by anti-MOG mAb, whereas the present study demonstrates that deletion of the FcγR does not abolish the acute effect of anti-MOG mAb. This suggests redundancy of FcγR and complement-mediated pathways, as previously described in a model of antibody-dependent vitiligo (47).

Although the immediate effect of Z12 mAb on EAE severity was independent of FcγR, interactions between IgG and FcγR may contribute to a sustained effect of anti-MOG antibodies on inflammation and demyelination. On average, 3 weeks after injection of Z12 mAb, wt mice showed enhanced CNS demyelination and inflammation, whereas FcγR−/− mice did not. The half-life of IgG2a in serum is 6 to 8 days (48), therefore, enhanced cerebellum pathology after up to at least 25 days after injection is unlikely to result from direct deposition of Z12 mAb. Furthermore, at the time of antibody injection, blood-brain barrier damage in the cerebellum is limited in comparison with the spinal cord (49). Two mice that were killed 2 days after Z12 mAb injection for ethical reasons showed severe inflammation in the spinal cord, whereas infiltration of the cerebellum was negligible (data not shown). This suggests that Z12 mAb cannot directly reach the cerebellum parenchyma and that the effect of Z12 mAb is indirect. IgG2a complexed to a soluble protein can enhance both B and T cell responses against that protein through interactions with activating FcγR (50). Similarly, FcγR-mediated uptake of Z12 mAb opsonized myelin breakdown products, either at the site of demyelination or after capture of antigens in the periphery (51), could contribute to amplification of the immune response directed against myelin. Although it was beyond the scope of this study, it would be interesting to study MOG-specific T cell responses in wt and FcRγ−/− mice at different time points after anti-MOG antibody administration.

The data presented here may be relevant for the pathology and treatment of MS. Enhanced levels of anti-myelin antibodies in serum and CSF have been described in MS patients (52–54) and in a subgroup of early MS patients, deposition of IgG and complement was observed in active demyelinating lesions. This suggests that antibody-mediated activation of complement plays a role in a subpopulation of MS patients (8). In addition, intrathecal IgG production has been described as a prognostic marker for MS disease progression (55), suggesting that antibodies may contribute to sustained CNS inflammation and demyelination in MS.

In conclusion, MOG35-55-induced EAE in FcRγ−/− mice is delayed in onset, but otherwise indistinguishable from EAE in wt mice. This demonstrates that activating FcγR are not essential for the initiation of CNS inflammation and demyelination, although FcRγ chain-mediated signal transduction may contribute to the preclinical phase of EAE. In addition, we show that anti-MOG antibodies can induce rapid exacerbation of CNS inflammation in the absence of the FcγR chain, but that IgG-FcγR interactions may contribute to a sustained effect of anti-MOG antibodies on the CNS inflammatory and demyelinating response.

REFERENCES


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