Neutralizing Antibodies to IL-18 Ameliorate Experimental Autoimmune Neuritis by Counter-Regulation of Autoreactive Th1 Responses to Peripheral Myelin Antigen

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Abstract. Experimental autoimmune neuritis (EAN) is a demyelinating disease of the peripheral nervous system (PNS). This acute inflammatory disease is mediated by CD4+ T cells and bears significant similarities to the Guillain-Barré syndrome of humans. In the present study, we investigated the function of IL-18 in T cell-mediated autoimmunity of EAN in mice induced by P0 peptide 180–199 and Freund’s complete adjuvant. Our data indicate that in 2 different therapeutic regimens, anti-IL-18 monoclonal antibody (mAb) effectively ameliorates the clinical and pathological signs of EAN. The suppression is associated with reduced inflammatory cell infiltration into the PNS and an insufficiency of autoreactive Th1 cells, as reflected by a reduced mononuclear cell proliferation and IFN-γ-secretion in the spleen. Increased numbers of IL-4 expressing cells and decreased numbers of IFN-γ and TNF-α expressing cells were found in the PNS. Our results suggest that shifting the Th1/Th2 balance towards Th2 cells may be one mechanism underlying EAN suppression by anti-IL-18 mAb. In addition, anti-IL-18 mAb treatment reduced anti-P0 peptide 180–199 autoantibody responses, which may also contribute to EAN suppression. We conclude that endogenous IL-18 plays a critical role in the pathogenesis of autoimmune demyelinating disease of the PNS and that IL-18 antagonists may provide a new therapy for these diseases.

Key Words: Experimental autoimmune neuritis; Guillain-Barré syndrome; IL-18; Th1/Th2 cytokines; Therapy.

INTRODUCTION

Guillain-Barré syndrome (GBS) is a crippling disease of humans in which acute inflammation incited by CD4+ T cells causes demyelination in structures of the peripheral nervous system (PNS). Experimental autoimmune neuritis (EAN) is the laboratory model of GBS. EAN can be induced by active immunization with the synthetic peripheral nerve myelin components P2 and P0 peptide emulsified in Freund’s complete adjuvant (FCA) (1, 2). EAN can also be transferred to naive recipient rats by either CD4+ P2 or P0 reactive T cell lines (3–5). CD4+ Type 1 helper T (Th1) cells play a crucial role in the establishment and progression of EAN.

Interleukin-18 (IL-18) is a cytokine that was first identified in the liver of mice sequentially treated with Propionibacterium acne and lipopolysaccharide (LPS) (6). The molecule was originally identified as interferon-γ (IFN-γ) production by splenocytes, liver lymphocytes, and Th1 cell clones (7–9). IFN-γ is produced by a variety of cells, including activated macrophages and Kupffer cells. The molecule is related to the IL-1 family in terms of its structure, processing, receptor family, and signal transduction pathways (10, 11). The activation of IL-18 is mediated by IL-1β-converting enzyme (12). Increasing evidence shows that IL-18 is a pleiotropic cytokine (13, 14) that apparently shares its biological functions with IL-12. For example, a synergistic action of IL-18 and IL-12 induces the production of IFN-γ by lymphocytes (15–17). IL-18 also exerts pro-inflammatory properties by inducing the production of TNF-α, IL-1, GM-CSF, and chemokines, such as MIP-1, nitric oxide and prostaglandins (18, 19). TNF-α, IL-1, and MIP-1 have been shown to be involved in the pathogenesis of EAN (20, 21).

According to recent data, IL-18 is a central factor in the development of an efficient anti-microbial and anti-tumour immunity (22, 23), as well as in the onset of some autoimmune diseases (24–27). IL-18 is up-regulated in the nerve root of EAN rats and IL-18 serum levels are significantly higher in GBS patients (27). However, the function of IL-18 in T cell-mediated EAN needs further clarification. In the present study, we demonstrate that in 2 different therapeutic regimens, anti-IL-18 monoclonal antibodies (mAb) effectively ameliorate clinical and pathological EAN. The suppression was associated with insufficient stimulus for autoreactive Th1 cells, a shift of the Th1/Th2 balance towards Th2 cells, and a reduced autoantibody response. We conclude that IL-18 plays a critical role in the pathogenesis of autoimmune disease in this model and that IL-18 antagonists may have preventive and therapeutic effects on autoimmune demyelinating diseases of the PNS.

MATERIALS AND METHODS

Animals

Wild-type C57BL/6 mice were bred at the animal housing facilities of the Microbiology and Tumor Biology Center, Karolinska Institutet, Stockholm, Sweden.
Antibodies to IL-18 Ameliorate EAN

The neuritogenic P0 protein peptides, corresponding to amino acids 180–199 of rat PNS myelin P0 protein, were synthesized by solid-phase stepwise elongation using a Tecan/Syro peptide synthesizer (Multisyntech, Bochum, Germany).

Anti-IL-18 Antibody Treatment

Both the rat anti-mouse IL-18 mAb and the rat isotype control IgG were purchased from R&D Systems (Minneapolis, MN). Using activated mouse T cells, we determined that the neutralization dose50 (ND50) for this lot of anti-IL-18 mAb was determined to be approximately 0.3 to 1.0 μg/ml in the presence of 15 ng/ml of rmIL-18. Mice were separated into 4 groups. Before onset of disease, on days −1, 0, and 3 post-immunization (p.i.), 2 groups of mice were injected intraperitoneally (i.p.) with either IL-18 mAb (20 μg/mouse) (the treatment group 1, T1), or with an isotype IgG (20 μg/mouse) used as the control (the control group 1, C1). After disease onset, on days 14, 17, 20 p.i., the other 2 groups were injected i.p. with either IL-18 mAb (30 μg/mouse) (the treatment group 2, T2), or with an isotype control IgG (30 μg/mouse) (control group 2, C2).

Induction of EAN and Assessment of Clinical Signs

A total of 56 male wild type C57BL/6 mice, 4- to 5-wk old and weighing 15 to 18 g were used in the present study. All mice were immunized twice (designated as days 0 and 7) by subcutaneous injection with 100 μg of P0 peptide 180–199 and 0.5 mg Mycobacterium tuberculosis (strain H 37 RA; Difco, Detroit, MI) in 25 μl saline and 25 μl Freund’s complete adjuvant (FCA). All mice received 400 ng pertussis toxin (Sigma, St. Louis, MO) by intravenous injection on days −2 and +1 p.i., respectively. Clinical scores were assessed immediately before immunization (day −1) and thereafter every second or third day until day 71 p.i. Severity of paresis was graded as follows: 0, normal; 1, flaccid tail; 2, moderate paraparesis; 3, severe paraparesis; 4, tetraparesis; 5, death; or 0.5, intermediate clinical signs.

Histopathological Assessment

Six mice from each group were killed and used as the source of sciatic nerve segments, which were excised close to the lumbar spinal cord. The segments were dissected, fixed in 4% formaldehyde and embedded in paraffin. Multiple serial 5- to 6-μm longitudinal sections of the sciatic nerve were stained with hematoxylin and eosin for evaluation of the extent of mononuclear cell (MNC) infiltration. Replicate sections were stained with luxol fast blue violet to determine demyelination. Tissue areas were measured by image analysis, and the numbers of inflammatory cells counted at ×20 magnification. The results were averaged and expressed as cells per mm² tissue section.

Immunohistochemistry

Segments of sciatic nerves were dissected and snap-frozen in liquid nitrogen. Cryostat sections (10 μm) were exposed to the following mAbs: rat anti-mouse macrophage, rat anti-mouse CD4, rat anti-mouse CD8 (all from Harlan Sera-Lab, Leicestershire, UK), rabbit anti-rat IL-4, rabbit anti-rat TNF-α, rabbit anti-rat IFN-γ (these antibodies also react with mouse IL-4, TNF-α and IFN-γ), all from the Central Laboratory Animal...
Institute (CLAI), Utrecht, The Netherlands), as well as rat anti-mouse IL-12 (Biosource, Camarillo, CA). Sections were stained according to the avidin-biotin technique (Vectastain Elite Kit; Vector Labs, Burlingame, CA). Omission of primary antibodies served as negative controls. Non-specificity of the staining was also controlled on tissue sections. The tissue areas were measured by image analysis, and the numbers of stained cells were counted at ×40 magnification in the entire section areas. The results were averaged and expressed as cells per mm² tissue section.

Isolation of MNC from Spleen

The spleens were removed from mice under aseptic conditions. Single cell suspensions of MNC from individual mice were prepared. The cells were washed 3 times before being resuspended to 2 × 10⁶ MNC/ml in Iscove’s modification of Dulbecco’s medium (Flow Lab., Irvine, UK) supplemented with 1% (v/v) minimum essential medium (MEM) and 2 mM glutamine (both from Flow Lab), 50 IU/ml penicillin, 60 µg/ml streptomycin (both from Gibco, Paisley, UK), and 3% normal human AB± serum without mercaptoethanol.

Lymphocyte Proliferation Assays

MNC suspended in 200 µl aliquots were cultured in triplicates in round-bottomed 96-well poly styrene microtiter plates (Nunc, Copenhagen, Denmark) at a cell density of 2 × 10⁶ cells/ml. For lymphocyte stimulation, 10 µl of either P0 peptide 180–199 or phytohemagglutinin (PHA) (Difco) were added to cultures at a final concentration of 10 µg/ml. After 60 hours (h) of incubation, cells were pulsed with ³H-methylthymidine (1 µCi/well, Amersham, Little Chalfont, UK) and cultured for an additional 2 h. Cells were harvested onto glass fiber filters (Titertek, Skatron, Lierbyen, Norway). ³H-thymidine incorporation was measured in a liquid β-scintillation counter, and results expressed as counts per minute (cpm).

Enumeration of IFN-γ-Secreting Cells

A solid-phase enzyme-linked immunospot assay (ELISpot) was used to detect single cells that secrete IFN-γ upon antigen stimulation (28). Briefly, nitrocellulose-bottomed plates (Micro-titer-HAM, Millipore, Bedford, UK) were coated with 100 µl of a mouse anti-IFN-γ mAb (CLAI) at 20 µg/ml overnight at 4°C. Then 200 µl aliquots containing 4 × 10⁶ MNC were added in duplicate with either medium alone (control cultures without antigen) or 10 µl aliquots of P0 peptide 180–199 (final concentration of 10 µg/ml) or PHA (final concentration of 10 µg/ml). After 48 h in culture, both secreted and bound IFN-γ were visualized by a sequential application of rabbit anti-rat IFN-γ polyclonal antibody (CLAI), biotinylated swine anti-rabbit IgG (Sigma), and avidin-biotin peroxidase complex (ABC Vectastain Elite Kit, Vector). After peroxidase staining, the redbrown immunospots corresponding to the cells that had secreted IFN-γ were counted in a dissection microscope. Results were expressed as numbers of spots per 10⁶ spleen MNC.

ELISA for Measurements of Anti-P0 180–199 IgG Antibodies

Serum was obtained from blood samples at day 24 p.i. Sera from each group of 6 individual mice were pooled. Microtiter plates (Nalge Nunc, Naperville, IL) were coated with 100 µl/well of purified P0 peptide 180–199 (10 µg/ml) at 4°C overnight. Uncoated sites were blocked with 10% fetal calf serum (FCS) for 2 h at room temperature (RT). Serum samples (diluted 1:100) were added and incubated for 2 h at RT. Then plates were incubated for 1 h with biotinylated anti-mouse IgG (Vector), biotinylated rabbit anti-mouse IgG2a, IgG2b (Phar-mingen, San Diego, CA), and avidin-horseradish peroxidase conjugate (Phar-mingen), followed by substrate solution (Phar-mingen) for 30 min. The reaction was stopped with 1M H₂SO₄. Results were expressed as OD at 450 nm.

Statistical Analysis

Differences between groups were evaluated by Student t-test and non-parametric Mann-Whitney U-test, respectively. All tests of significance were 2-sided. The level of significance was set to p < 0.05.

RESULTS

Anti-IL-18 mAb Suppresses the Initiation and Development of Clinical EAN

To explore the role of IL-18 in the development of EAN, C57BL/6 mice were immunized twice with P0 peptide 180–199 in FCA and treated with either anti-IL-18 mAb or control Ab 3 times at either the point when the disease typically begins (treatment group 1) or 3 times afterwards (treatment group 2). All mice acquired EAN. However, anti-IL-18 mAb treatment before onset of disease delayed the appearance of clinical signs, suppressed its severity, and shortened its average duration (Table; Fig. 1A). Treatment with anti-IL-18 mAb after the onset of clinical symptoms did not delay the appearance of clinical signs, although it tended to decrease the maximal clinical scores.

| Clinical variables | Clinical samples | Statistical Analysis
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<td>Maximal clinical scores</td>
<td>T1 1.4 ± 0.1**</td>
<td>C1 2.3 ± 0.3</td>
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<td>Days of onset</td>
<td>15.3 ± 1.5**</td>
<td>11.3 ± 1.0</td>
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<td>Days of disease</td>
<td>56.3 ± 2.1**</td>
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*Mice were immunized with P0 peptide 180–199 in FCA and monitored for development of EAN (n = 56). In addition, mice of treatment group 1 (T1) and control group 1 (C1) received either anti-IL-18 mAb or normal control antibodies i.p. close to the day of immunization (days −1, 0, and 3 p.i.). Mice of treatment group 2 (T2) and control group 2 (C2) received either anti-IL-18 mAb or control antibody i.p. after the onset of the disease. The results are presented as mean values ± SD. The treatment and control groups were compared to evaluate statistical significance. ** p < 0.01.

Fig. 1A. Treatment with anti-IL-18 mAb after the onset of clinical symptoms did not delay the appearance of clinical signs, although it tended to decrease the maximal clinical scores.
of diseases (treatment group 2) reduced the severity of disease to the same extent as in the treatment group 1 (Table; Fig. 1B).

**Anti-IL-18 mAb Treatment Inhibits Inflammatory Cell Infiltration and Demyelination of PNS**

To examine the influence of anti-IL-18 mAb on the recruitment of inflammatory cells to the PNS, we performed histopathological and immunohistochemical studies at the height of the clinical course of EAN (day 24 p.i.). Histopathological evaluation revealed that both anti-IL-18 mAb treatment groups markedly decreased the numbers of macrophages, lymphocytes, and granulocytes (Figs. 2A, 3A) and also reduced the extent of regional demyelination (Fig. 2C) in sciatic nerve sections when compared to 2 control groups (Figs. 2B, D, 3A) (both comparisons p < 0.01). However, there was no difference between treatment with anti-IL-18 mAb before and after the onset of disease. Immunohistochemical studies showed that extensive CD4⁺ T cell and macrophage infiltration was regularly detected in sciatic nerve sections from control antibody-treated EAN mice (Fig. 3B, C). In contrast, only a few CD4⁺ cells and macrophages were seen in sciatic nerve sections from anti-IL-18 mAb-treated mice (Fig. 3B, D). For infiltration of CD8⁺ T cells, there were no differences between mice receiving either anti-IL-18 mAb or control antibody.

**Anti-IL-18 mAb Treatment Suppresses Spleen Cell Proliferation**

Since disease suppression by anti-IL-18 mAb could stem from insufficient differentiation of T cells into Th1 effector cells in the periphery, we examined draining spleen cells from mice at the height of the disease on day 24 p.i. and tested them for proliferation and numbers of IFN-γ-secreting cells in response to re-stimulation with P0
peptide 180–199 and PHA in vitro. When compared to mice treated with control antibodies, the anti-IL-18 mAb-treated mice of both groups showed impaired proliferation of splenic MNC (Fig. 4A) and a reduced number of IFN-γ-secreting cells (Fig. 4B). Upon mitogenic stimulation with PHA, treatment with anti-IL-18 mAb also decreased MNC proliferation and reduced the number of IFN-γ-secreting cells. These results demonstrate that the CD4+ T cells had been inadequately primed for a Th1 cell response in vivo, as measured by IFN-γ production in anti-IL-18 mAb-treated mice.

We also measured the IL-4 concentration in serum. However, neither the anti-IL-18 mAb-treated mice nor control antibody-treated mice showed detectable levels of IL-4 (data not shown).

**Anti-IL-18 mAb Treatment Alters the Th1/Th2 Balance of Infiltrating Cells in the PNS**

IL-18 in vivo can enhance both Th1 and Th2 cytokine production by autoreactive T cells (26, 29, 30). To assess how IL-18 regulates P0 peptide-induced cytokine responses, we used an immunohistochemical technique to examine IFN-γ-, IL-12-, IL-4-, and TNF-α-positive cells in sciatic nerve sections (Fig. 5). At the height of the disease on day 24 p.i., the number of IFN-γ- and TNF-α-positive cells in sciatic nerve sections from anti-IL-18

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**Fig. 3.** Sciatic nerve sections from EAN mice receiving anti-IL-18 mAb or control IgG were examined on day 24 p.i. Histopathological appearance of infiltrating cells per mm² (A) and immunohistochemical assessment of numbers of CD4+ T cells, CD8+ T cells, and macrophage-positive cells per mm² (B). The results are expressed as mean values ± SD (6 mice per group). Groups are defined as described in Figure 1. Statistical evaluation compared the different treatment and control groups. **p < 0.01. Immunohistochemical studies showed extensive macrophage infiltration in sciatic nerve sections from control antibody-treated EAN mice (C). A few macrophages were seen in sciatic nerve sections from anti-IL-18 mAb-treated mice (D). Magnification: ×100.
Anti-IL-18 mAb Treatment Ameliorates EAN

Fig. 4. Anti-IL-18 mAb treatment suppresses P0 peptide 180–199-specific spleen cell proliferation and IFN-γ production in vitro. Mice were immunized and antibody-treated as described in Figure 1. Draining spleen cells were harvested on day 24 p.i. and tested for their proliferation (A) and the numbers of IFN-γ secreting cells (B) in response to in vitro re-stimulation with P0 peptide 180–199 and PHA. The results are expressed as the mean valves ±SD (6 mice per group). Groups are defined as described in Figure 1. Statistical evaluation compared the different treatment and control groups. *p < 0.05; **p < 0.01.

mAb-treated mice was significantly lower than in sections from the control antibody-treated mice of both groups. This result demonstrates that the Th1 cell response was impaired in vivo after anti-IL-18 mAb treatment. Although IL-12 is known to induce IFN-γ, the number of IL-12-positive cells in sciatic nerve sections from anti-IL-18 mAb-treated mice was almost the same as in control antibody-treated mice. This result suggests that the reduced IFN-γ production was not secondary to low induction of IL-12. In contrast, significantly increased numbers of IL-4-positive cells were found in sciatic nerve sections from anti-IL-18 mAb-treated mice as compared to control antibody-treated mice in both groups. These results demonstrate that, in vivo, anti-IL-18 mAb treatment alters the Th1/Th2 balance in favor of Th2 selection during EAN.

Anti-IL-18 mAb Treatment Reduces Anti-P0 Peptide 180–199 IgG Autoantibody Responses

To address how anti-P0 peptide antibody responses were influenced by anti-IL-18 mAb treatment, we measured anti-P0 peptide 180–199 antibodies in sera from both anti-IL-18 mAb-treated and control mice (Fig. 6). Levels of P0 peptide 180–199-specific IgG, IgG2a, IgG2b antibodies in sera from the anti-IL-18 mAb-treated animals of both groups were significantly lower than in mice treated with control antibody.

DISCUSSION

The present study shows that IL-18 is a pivotal agent in the initiation and development of EAN and that anti-IL-18 treatment can act effectively to attenuate EAN. Mice
injected with the P0 peptide 180–199 that received control antibody developed the typical symptoms of severe EAN. However, mice given anti-IL-18 mAb before the onset of disease, i.e. at the immunization stage, had a delay in the clinical signs of EAN, a reduction in the severity of ongoing EAN, as well as a shortened duration of disease. Even after the onset of EAN, anti-IL-18 mAb treatment decreased the intensity of related clinical signs. These data show that 2 anti-IL-18 regimens are beneficial for resolving EAN. However, complete suppression of EAN was not achieved by these treatments, suggesting that other pro-inflammatory mechanisms have to be addressed. It is possible that the pro-inflammatory cytokine, IL-12, compensates for IL-18 in anti-IL-18-treated mice, since IL-12 is known to work synergistically with IL-18 and shares apparent biological functions with IL-18 (31, 32).

Several findings indicate that an appropriate combination of cytokines and immunocompetent cells is required to mount a successful immune response. Since EAN is a CD4⁺ T cell-mediated autoimmune disease of the PNS, the presence of CD4⁺ T cells and T cell-activation by antigen-presenting cells is necessary and sufficient for the initiation and development of EAN. The pathological lesions in EAN are characterized by the perivascular infiltration of autoreactive T cells, the presence of macrophages, and demyelination of tissues in the PNS. IL-18 seems to play an important role in this process, since it exerts pro-inflammatory activity via induction of inflammatory cytokines such as IFN-γ and chemokines like MIP-1, which in turn activate macrophages (33). Our results showed that reduced inflammatory cell infiltration into the PNS and decreased demyelination in anti-IL-18 mAb-treated mice was achieved, since anti-IL-18 mAb strongly inhibits the differentiated effector T cells from migrating into the PNS where they would produce inflammation. IL-18-deficient mice are resistant to MOG35–55 peptide-induced autoimmune encephalomyelitis (EAE), a disease of the central nervous system that closely resembles EAN and involves a defect in autoreactive Th1 and autoantibody responses (34).

The balance between Th1 and Th2 cytokines may determine the outcome of an autoimmune disease (35). By virtue of their differing cytokine production, CD4⁺ Th cells are divided into the 2 populations, Th1 and Th2, with contrasting and cross-regulating profiles. Only a few cytokines, such as IFN-γ, IL-12, and IL-18, participate in the commitment of undifferentiated Th0 cells to becoming Th1 cells (6). CD4⁺ Th1 cells function in the pathogenesis of EAN by releasing inflammatory cytokines, such as IL-2 and IFN-γ, which can activate macrophages that directly attack the myelin sheath through phagocytosis and release of injurious factors and other pro-inflammatory cytokines (36–38). Convincing evidence asserts that the level of IFN-γ producing cells in the blood, lymph nodes, and PNS tissue roughly parallels the clinical severity of EAN, consistent with an inflammatory role of Th1-promoting cytokines in the pathogenesis of EAN (21, 39). In addition, shifting the Th1/Th2 balance towards Th2 cells by the administration of IL-4 (2) or IL-10 (40) in vivo markedly suppresses EAN. Spontaneous recovery from EAN in rats correlates with an expansion of Th2-like cells and Th2 cytokines (21). IL-18 has been shown to enhance Th1 development and is a potent inducer of IFN-γ production by the lymphocytes and natural killer lymphocytes (7). IL-18 also induces the production of TNF-α (18), an important pro-inflammatory cytokine in driving T cell-mediated autoimmunity. Also, high levels of IFN-γ positively select for TNF-α-secreting Th1 cells (41). IL-18 can enhance proliferation of activated T cells (6, 7). We show here that treatment with anti-IL-18 mAb impairs MNC proliferation and reduced the number of IFN-γ-secreting cells in the spleen, but elevated the numbers of IL-4 expressing cells and decreased IFN-γ and TNF-α expressing cells in sciatic nerves. This outcome suggests that EAN suppression by anti-IL-18 mAb results from an insufficiency of antigen-specific T cells available to differentiate into Th1 effector cells in the periphery, thereby altering the Th1/Th2 balance in favor of Th2 selection in vivo.

Optimal activation of B lymphocytes and differentiation into Ig-secreting cells depends on the helper effects of CD4⁺ Th cells and are mediated via both direct Th-B cell interaction and the elaboration of antigen-non-specific cytokines (42). Although EAN is predominantly a T cell-mediated disease, evidence indicates that intraneuronal injection of serum from animals with EAN may cause demyelination in the nerve of naive mice (43). Systemic injection of antibodies to galactocerebroside and reactive T cells into recipient Lewis rats produces more severe demyelination than the transfer of reactive T cells alone (44). Clearly, specific autoreactive cells and antibodies act synergistically in the demyelination process (45). Presumably, T cells increase the endothelial permeability, permitting antibody access to myelinated fibers and inducing demyelination in the PNS (37, 46). Previous studies revealed that production of IgG2b antibodies is associated with the Th1 response (47) and that IL-18 enhances IgG2a, which are typically produced during Th1 response (16). The significant reduction of serum anti-P0 peptide 180–199 IgG, IgG2a, and IgG2b antibody levels seen in the present study may result from suppression of Th1 cells. The helper function of B cells and/or the direct effects of anti-IL-18 mAb on the B cells themselves. In either case, the reduced autoantibody response seen here was a factor that contributed to the suppression of EAN in anti-IL-18 mAb-treated mice.

In summary, the current study demonstrates that anti-IL-18 mAb can effectively attenuate EAN. Alteration of
the Th1/Th2 balance toward Th2 cells and reduced autoantibody responses are the main mechanisms underlying EAN blockade by anti-IL-18 mAb immunotherapy. We conclude that IL-18 may play a decisive role in the pathogenesis of this model of autoimmune diseases and that IL-18 antagonists may offer a promising new and potentially powerful strategy for treatment of autoimmune demyelinating diseases of the PNS.

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