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Blockade of B-cell activating factor with TACI-IgG effectively reduced Th1 and Th17 cells but not memory T cells in experimental allergic encephalomyelitis mice

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Abstract

B-cell activating factor (BAFF) is regarded as a new therapeutic target in autoimmune diseases such as systemic lupus erythematosus (SLE) and multiple sclerosis (MS). Along with other researchers, we have demonstrated that BAFF inhibitor atacicept (TACI-IgG) suppresses lupus and experimental allergic encephalomyelitis (EAE) by reducing the mature B-cell number but not memory B cells. It is however unclear whether TACI-Ig affects pathogenic T cells and memory T cells. In the present study, we found that blocking BAFF with TACI-IgG effectively reduces the pathogenic Th1 and Th17 cells in EAE mice. However, TACI-IgG did not reduce memory $CD62L^+CD44^{hi}CD4^+$ and $CD62L^+CD44^{hi}CD8^+$ T cells in EAE mice. When interleukin (IL)-15 was neutralized, memory $CD62L^+CD44^{hi}$ T cells were significantly reduced in TACI-IgG-treated EAE mice. These results suggest that TACI-IgG is effective in effective controlling Th1 and Th17 cells, but it also increases IL-15 to upregulate memory T cells in EAE mice. The study provides hints for the clinical application of the combination of BAFF- and IL-15-specific therapeutic agents.

Key words: *TACI-IgG, EAE, BAFF, Th1, Th17, IL-15.*

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Introduction

The pathogenic role of the B-cell activating factor (BAFF) was clearly demonstrated through the development of a lupus-like illness with the production of anti-DNA antibodies and the development of glomerulonephritis in BAFF-transgenic mice [1-3]. This was followed by the observation that BAFF blockage delayed systemic lupus erythematosus (SLE) onset in SLE models [2] and the subsequent discovery that patients with SLE have high serum levels of BAFF and APRIL (a proliferating-inducing ligand). B-cell activating factor level in some studies is correlated with disease activity [4] and as such, BAFF has been regarded as a new therapeutic target in SLE [5].

Belimumab, a fully human anti-BAFF monoclonal antibody, selectively reduces the numbers of $CD20^+$ naïve B cells, activated B cells and plasmablasts. By contrast, belimumab treatment increases memory B-cell numbers [6]. Another BAFF inhibitor atacicept (TACI-IgG) also shows similar clinical results as belimumab by binding a portion of the receptor TACI to block the effect of BAFF and APRIL. It reduces circulating mature B-cell and plasma cell levels in the spleen and bone marrow, inhibits T-cell activation, but not memory B cells [7]. The effect of BAFF on T cells has been reviewed [8]. B-cell activating factor induced $CD4^+$ T cell proliferation [9] and promotes Th17 cells and aggravates experimental autoimmune encephalomyelitis [10] and autoimmune arthritis [11]. TACI-IgG limited collagen-induced arthritis [12] and adjuvant-induced arthritis [13] by regulating T and B lymphocytes.

B-cell activating factor is expressed by astrocytes that are associated closely with BAFF-R-expressing cells [14] and within ectopic lymphoid follicles in the meninges [15] suggesting that BAFF is also a potential target in multiple sclerosis (MS). MOG-induced chronic experimental allergic encephalomyelitis (EAE) in C57BL/6 mice [16] is an animal model for MS. Our previous study has demonstrated that TACI-IgG is effective in reducing B cells, but upregulates IL-15 promoting memory B cells in treated EAE mice [17, 18]. In the present study, our data demonstrated that blockade of BAFF with TACI-IgG reduced pathogenic Th1 and Th17

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cells but not memory $CD62L^{+}CD44^{hi}$ T cells in EAE mice. In addition, neutralizing IL-15 effectively reduced memory T cells in TACI-IgG-treated EAE mice. These results suggest that TACI-IgG is effective in reducing pathogenic T cells but not memory T cells in treating EAE mice. The study provides hints for the clinical application of a combination of BAFF- and IL-15-specific therapeutic agents.

Material and methods

Mice

9-week-old C57BL/6 mice (Chinese Academy of Medical Sciences, Beijing, China) were bred in our animal facilities under specific pathogen-free conditions. Care, use and treatment of mice in this study were in strict agreement with international guidelines for the care and use of laboratory animals and approved by the Animal Ethics Committee of the Beijing Institute of Basic Medical Sciences.

Experimental allergic encephalomyelitis induction

At 9 weeks of age C57Bl/6 mice received a subcutaneous injection of 125 μg MOG35-55 peptide (Mimotopes, Australia) emulsified 1 : 1 (vol/vol) in Complete Freund's Adjuvant containing 4 mg/ml of *Mycobacterium tuberculosis* H37Ra (Difco, Detroit, MI), to both flanks and the base of the tail. Pertussis toxin (300 ng in PBS; List Biological, USA) was injected intraperitoneally at the time of induction and a second dose was administered three days later. Animals were weighed, monitored and clinically assessed according to the following grading scale: 0 = no sign; 1 = distal tail weakness; 1.5 = tail weakness and some hindlimb weakness; 2 = complete tail paralysis; 2.5 = complete tail paralysis and partial hindlimb weakness; 3 = complete hindlimb weakness; 3.5 = inability to right when placed on back or significant forelimb weakness; 4 = euthanize or spontaneous death. Mice were euthanized if they lost 20% of their starting weight, displayed a clinical score of 3 for 72 hours or reached a clinical score of 3.5. Mice were examined for up to 21 days post-immunisation.

Treatment of experimental allergic encephalomyelitis mice with TACI-IgG

Experimental allergic encephalomyelitis mice were divided into the following four groups: 1) control CFA mice; 2) PBS-treated; 3) IgG-treated; 4) TACI-IgG-treated. Six EAE mice per group were *i.v.* injected with 2 mg/kg TACI-IgG (Rongchang Bio. Corp, Shandong Province, China) on day 4, 8, 12, 16 (one time per day) after EAE induction.

Treatment of experimental allergic encephalomyelitis mice with TACI-IgG and anti-IL-15 antibody

Experimental allergic encephalomyelitis mice were divided into the following two groups: 1) TACI-IgG + control antibody; 2) TACI-IgG + Anti-IL-15. Six EAE mice per group were *i.v.* injected with 2 mg/kg TACI-IgG and 0.5 mg/kg neutralizing anti-mouse IL-15 antibody (R&D system, CA, USA) or isotype and species-matched IgG (JingMei Bio. Corp, Beijing, China) on day 4, 8, 12, 16 (one time per day) after EAE induction.

Cytometric analysis and intracellular cytokine staining

Cells (1×10^6 cells/sample) were washed with fluorescence-activated cell sorting staining buffer (phosphate-buffered saline, 2% fetal bovine serum or 1% bovine serum albumin, 0.1% sodium azide). All samples were incubated with the 2.4G2 anti-Fc receptors (BD Pharmingen), prior to incubation with other Abs diluted in fluorescence-activated cell sorting buffer supplemented with 2% anti-Fc receptor Ab. Cells were subsequently stained with fluorescence-conjugated anti-mouse CD4, CD8, CD44, and CD62L antibodies (all antibodies from eBioscience). For intracellular cytokine staining, 50 ng/ml PMA and 1 mg/ml Ionomycin (all from Sigma-Aldrich) were added followed by 1 mg/ml brefeldin A and 2 mM monensin three hours later. After another two hours, cells were collected, incubated with the 2.4G2 anti-Fc receptors (BD Pharmingen) and stained with fluorescence-conjugated anti-mouse CD4 antibody (eBioscience). After staining, cells were washed and subsequently fixed for 20 min with 1 ml fixation buffer (Fix and Perm cell permeabilization kit, eBioscience). After washing, the fixed cells were stained with fluorescence-conjugated anti-mouse IFN-γ and IL-17 antibody (all antibodies from eBioscience). Data collection and analysis were performed on a FACS Calibur flow cytometer using CellQuest software.

Statistics

Statistics were generated using *t*-test in GraphPad Prism (version 5.0, GraphPad Software Inc., USA) and values were represented as mean ± standard error of the mean (SEM). Results were considered statistically significant at $p < 0.05$.

Results

TACI-IgG reduced pathogenic Th1 and Th17 cells in experimental allergic encephalomyelitis mice

On day 21 after TACI-IgG was used to treat EAE mice, lymphocytes from the spleen and LN were collected and an-

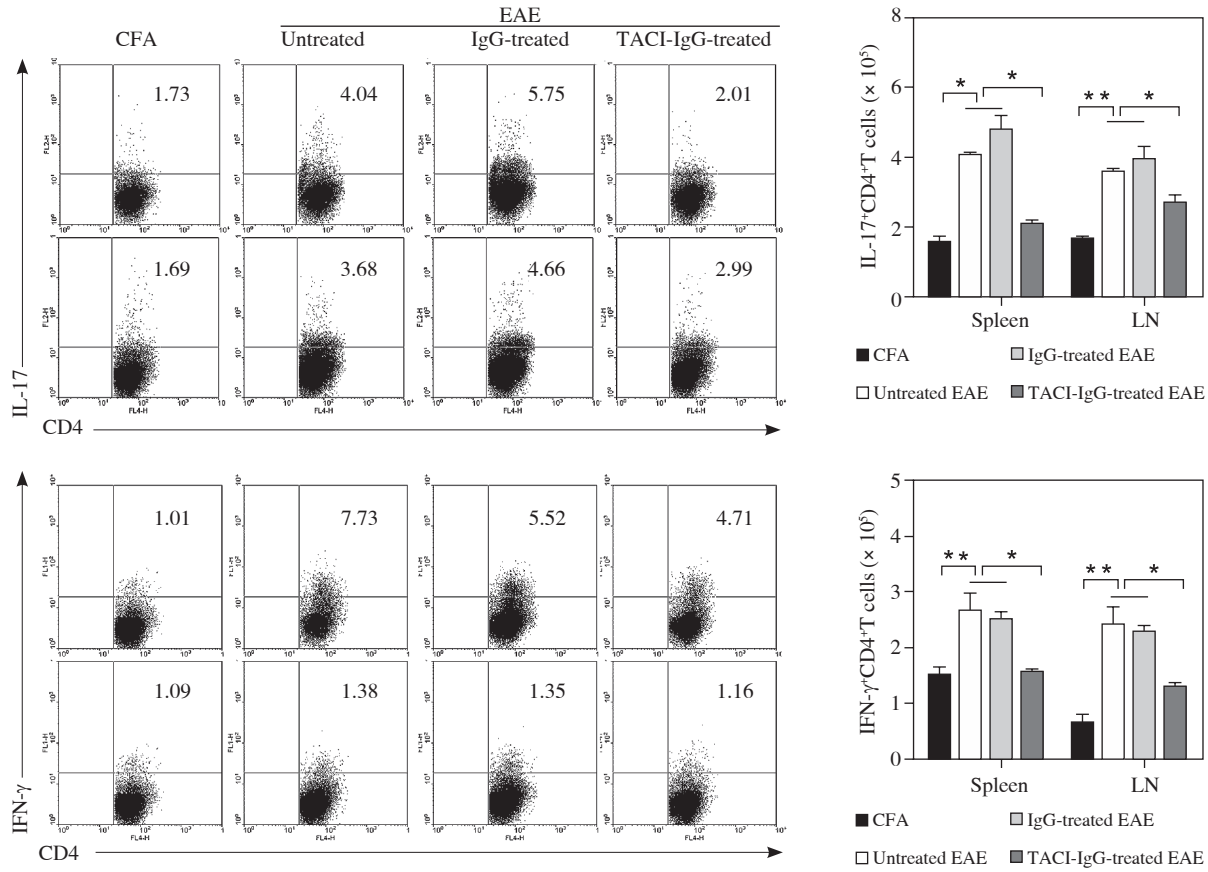

Fig. 1. TACI-IgG treatment reduced Th1 and Th17 cells in EAE mice. Six EAE mice per group were injected *i.v.* with 2 mg/kg TACI-IgG or isotype and species-matched IgG on day 4, 8, 12, 16 (one time per day) after EAE was induced. On day 21 after EAE induction, mice were killed and lymphocytes were collected from the spleen and the lymph node, stained with anti-mouse CD4, IL-17 and IFN-γ antibodies, and analyzed by FACS. The percentage of IL-17$^+$CD4$^+$T, IFN-γ$^+$CD4$^+$T cells was indicated in quadrants. The right panel shows the absolute number of IL-17$^+$CD4$^+$T, IFN-γ$^+$CD4$^+$T cells from the spleen and LN (*$p < 0.05$, **$p < 0.01$). The data represent four independent experiments

alyzed by FACS. The percentage of IL-17$^+$CD4$^+$T cells in the spleen and LN from CFA mice was 1.73 and 1.69, respectively, whereas the percentage increased to 4.04 and 3.68 in the spleens and LN from EAE mice, respectively (Fig. 1). The percentage of IFN-γ$^+$CD4$^+$T cells in the spleens and LN from CFA mice was 1.01 and 1.09, respectively, whereas the percentage increased to 7.73 and 1.38 in the spleens and LN from EAE mice, respectively (Fig. 1). In accordance with the percentage, the absolute number of IL-17$^+$CD4$^+$T and IFN-γ$^+$Th1 cells also increased in EAE mice (Fig. 1). The results suggest that compared with CAF control, EAE mice up-regulated pathogenic Th1 and Th17 cells.

The percentage and absolute number of IL-17$^+$CD4$^+$T and IFN-γ$^+$Th1 cells was comparable in untreated or IgG-treated EAE mice. The percentage of IL-17$^+$CD4$^+$ T cells in the spleens and LN from IgG-treated EAE mice was 5.8 and 4.7, whereas the percentage reduced to 2.0 and 3.0 in the spleens and LN from TACI-IgG-treated EAE mice, respectively (Fig. 1). The percentage of IFN-γ$^+$CD4$^+$T cells in the spleens and LN from IgG-treated EAE mice was 5.5 and 1.4, respectively, whereas the percentage reduced to 4.7 and 1.2 in the spleens and lymph nodes (LN) from TACI-IgG-treated EAE mice, respectively (Fig. 1). In accordance with the percentage, the absolute number of IL-17$^+$CD4$^+$T and IFN-γ$^+$Th1 cells also reduced in TACI-IgG-treated EAE mice (Fig. 1). The results suggest that compared with IgG, TACI-IgG reduced Th1 and Th17 cells in EAE mice.

TACI-IgG could not reduce memory T cells in experimental allergic encephalomyelitis mice

Previous studies have shown that belimumab or TACI-IgG treatment increases memory B-cell numbers in

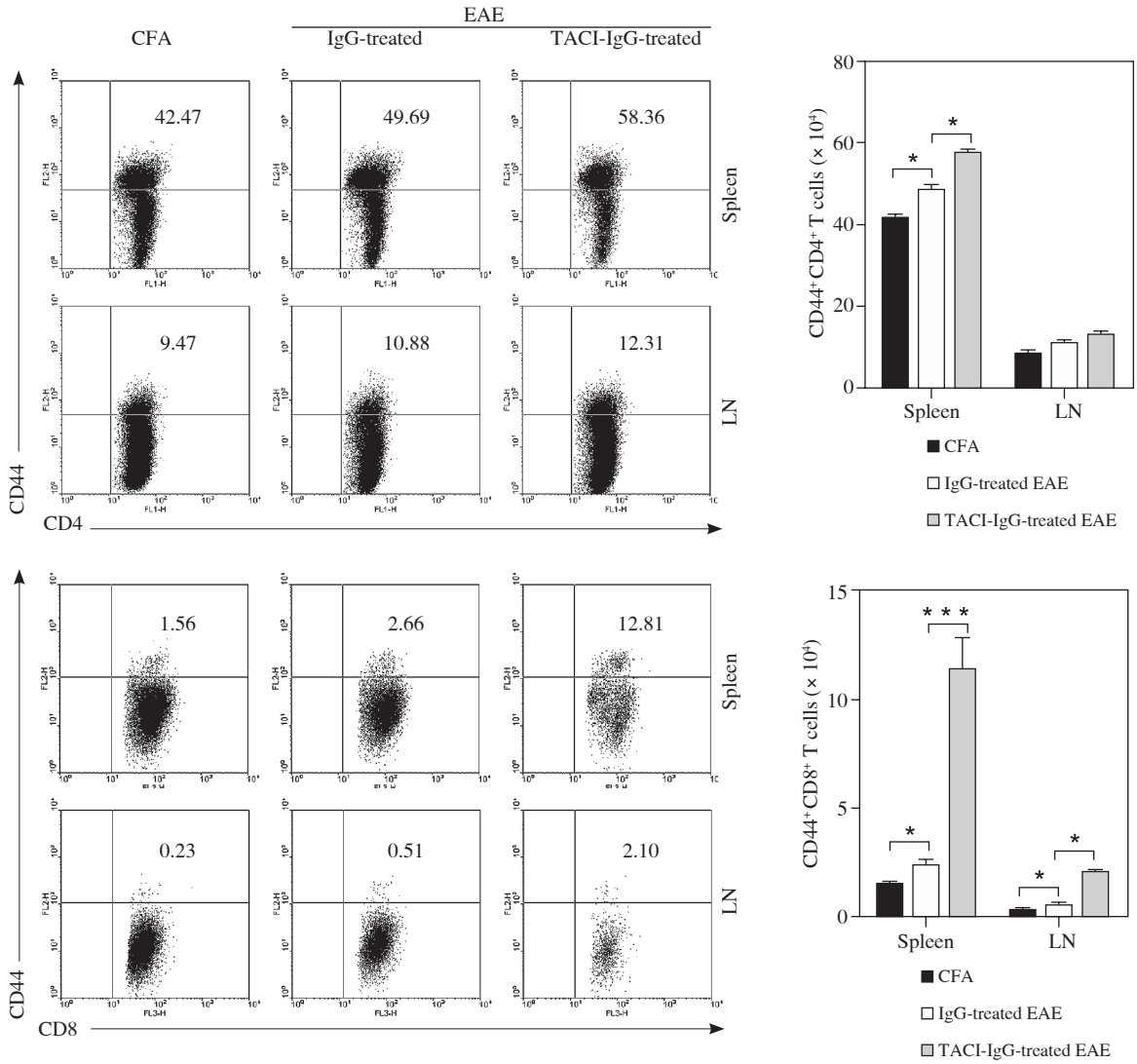

Fig. 2. TACI-IgG up-regulated CD44^{hi} memory T cells in EAE mice. Six EAE mice per group were injected *i.v.* with 2 mg/kg TACI-IgG or isotype and species-matched IgG on day 4, 8, 12, 16 (one time per day) after EAE was induced. On day 21 after EAE induction, lymphocytes in the spleen and lymph nodes were collected from CFA mice, IgG or TACI-IgG-treated EAE mice. Cells were stained with anti-mouse CD62L, CD4 or CD8, CD44 antibodies. Cells were gated on CD62L^{+}CD4^{+} or CD62L^{+}CD8^{+} with numbers in quadrants indicating the percentage of CD44^{hi} – expressing CD4^{+} or CD8^{+} T cells. The right panel shows the absolute number of CD44^{hi} – expressing CD4^{+} or CD8^{+} T cells from the spleen and LN (*$p < 0.05$, ***$p < 0.001$). The data represent three independent experiments

SLE patients [6, 7, 17, 18]. Thus, we examine whether TACI-IgG treatment could control memory T cells in EAE mice. The percentage of CD44^{hi}CD62L^{+}CD4^{+}T cells in the spleens and LN from IgG-treated EAE mice was 49.7 and 10.9, respectively, whereas the percentage increased to 58.4 and 12.3 in the spleens and LN from TACI-IgG-treated EAE mice, respectively (Fig. 2). In accordance with the percentage, the absolute number of CD44^{hi}CD62L^{+}CD4^{+}T cells was also upregulated in TACI-IgG-treated EAE mice (Fig. 2). The results suggest that compared with IgG, TACI-IgG expanded CD44^{hi}CD62L^{+}CD4^{+}T memory cells in the spleen of EAE mice.

The percentage of CD44^{hi}CD62L^{+}CD8^{+}T cells in the spleens and LN from IgG-treated EAE mice was 2.7 and 0.5, respectively, whereas the percentage increased to 12.8 and 2.1 in the spleens and LN from TACI-IgG-treated EAE mice, respectively (Fig. 2). In accordance with the percentage, the absolute number of CD44^{hi}CD62L^{+}CD8^{+}T cells was also upregulated in TACI-IgG-treated EAE mice (Fig. 2). The results suggest that compared with IgG,

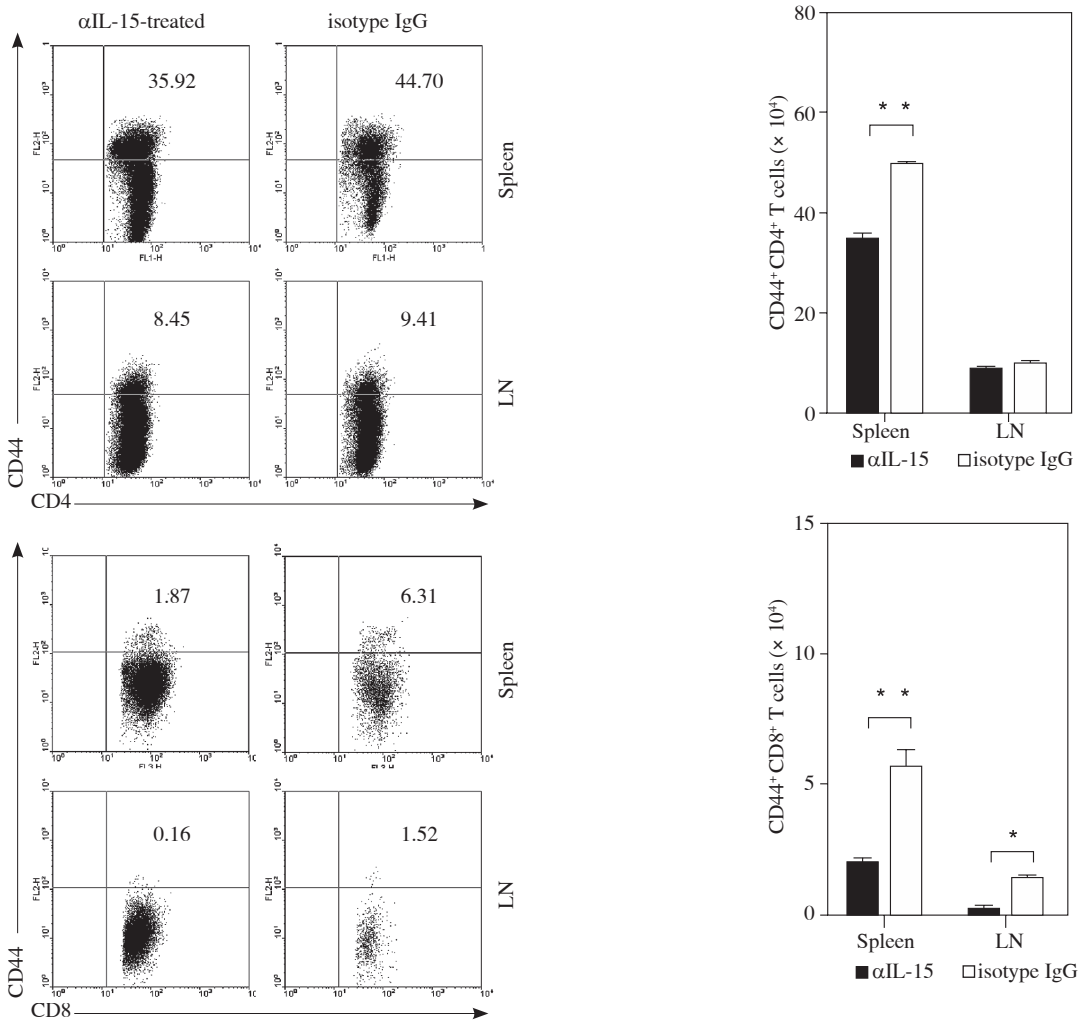

Fig. 3. Blockage of IL-15 efficiently reduced CD44^{hi} memory T cells in TACI-IgG-treated EAE mice. Six EAE mice per group were injected *i.v.* with 2 mg/kg TACI-IgG plus 0.5 mg/kg neutralizing anti-mouse IL-15 antibody or isotype and species-matched IgG on day 4, 8, 12, 16 (one time per day) after EAE was induced. On day 21, mice were killed and lymphocytes were collected from the spleen and lymph node. Cells were stained with anti-mouse CD62L, CD4 or CD8, CD44 antibodies. Cells were gated on CD62L$^+$CD4$^+$ or CD62L$^+$CD8$^+$ with numbers in quadrants indicating the percentage of CD44^{hi} – expressing CD4$^+$ or CD8$^+$ T cells. The right panel shows the absolute number of CD44^{hi} – expressing CD4$^+$ or CD8$^+$ T cells from the spleen and LN (*$p < 0.05$, **$p < 0.01$). The data represent three independent experiments

TACI-IgG expanded CD44^{hi}CD62L$^+$CD8$^+$T memory cells in the spleen of EAE mice.

Memory T-cell-associated interleukin 15 level increased in TACI-IgG-treated experimental allergic encephalomyelitis mice

Interleukin 15 is an important cytokine maintaining T memory cell survival and expansion. Our previous study demonstrated that TACI-IgG expanded memory B cells by upregulating IL-15 in lupus-like mice and EAE mice [17, 18]. Thus, we examined whether blocking IL-15 could reduce the T memory cell number in TACI-IgG-treated EAE mice. The percentage of CD44^{hi}CD62L$^+$CD4$^+$T cells in the spleens and LN from TACI-IgG plus isotype IgG-treated EAE mice was 44.7 and 9.4, respectively, whereas the percentage reduced to 35.9 and 8.5 in the spleens and LN from TACI-IgG plus anti-IL-15-treated EAE mice, respectively (Fig. 3). In accordance with the percentage, the absolute number of CD44^{hi}CD62L$^+$CD4$^+$T cells was also reduced in TACI-IgG plus anti-IL-15-treated EAE mice

(Fig. 3). The results suggest that blockage of IL-15 reduced $CD44^{hi}CD62L^{+}CD4^{+}$T memory cells in TACI-IgG-treated EAE mice.

The percentage of $CD44^{hi}CD62L^{+}CD8^{+}$T cells in the spleens and LN from TACI-IgG plus isotype IgG-treated EAE mice was 6.3 and 1.5, respectively, whereas the percentage increased to 1.9 and 0.2 in the spleens and LN from ACI-IgG plus anti-IL-15-treated EAE mice, respectively (Fig. 3). In accordance with the percentage, the absolute number of $CD44^{hi}CD62L^{+}CD8^{+}$T cells was also reduced in TACI-IgG plus anti-IL-15-treated-treated EAE mice (Fig. 3). The results suggest that blockade of IL-15 reduced $CD44^{hi}CD62L^{+}CD8^{+}$T memory cells in TACI-IgG-treated EAE mice.

Discussion

B cell activating factor demonstrates specific activity toward B cells, and supports B-cell proliferation, differentiation, and survival [19]. B cell activating factor-transgenic mice harbor increased $B220^{+}$ B cells and plasma cells in the spleen and lymph nodes, and develop antidouble-stranded DNA antibodies, proteinuria, and glomerulonephritis consistent with a systemic lupus erythematosus-like autoimmunity as they age [20]. In contrast, BAFF knockout mice have a markedly reduced mature B-cell population and decreased serum Ig levels [21].

Many trials have been done to study the effect of BAFF inhibition on SLE such as belimumab (anti-BAFF antibody), and atacicept (TACI-IgG). Our previous studies [7] have shown that TACI-IgG reduce circulating mature B-cell levels. In the present study, TACI-IgG was effective in suppressing T cells-mediated inflammatory response such as Th1 and Th17 expansion (Fig. 1). These studies suggest that treatment of BAFF inhibitor TACI-IgG on MS may be an efficient way of suppressing effective T and B cells.

We and other researchers have demonstrated that agents designed to target BAFF failed to effectively control memory B cells [7, 17, 18]. Here, we used EAE mice to understand whether TACI-IgG control memory T cells. Our data demonstrated that TACI-IgG treatment upregulated memory T cells (Fig. 2). These studies suggest that TACI-IgG could not efficiently control immune memory. As long as the reactive memory is maintained, this is probably acceptable, as autoimmune diseases can in principle be restored from it [22].

Our previous study has demonstrated that IL-15 was upregulated in TACI-IgG-treated EAE mice and when IL-15 was neutralized, memory B cells decreased in EAE [17, 18]. Previous studies have shown that survival signals that maintain memory T cells in the absence of antigen are provided by IL-15 [23, 24]. Thus, we blocked IL-15 in TACI-IgG-treated EAE mice. We found that effective blocking of IL-15 reduced $CD44^{hi}CD62L^{+}$ T memory cells in TACI-IgG-treated EAE mice.

Interleukin 15 is a dangerous inflammatory cytokine and inhibits self-tolerance by IL-2 mediated activation-induced cell death and facilitates maintenance of memory cells. Disordered IL-15 expression has been reported in patients with an array of inflammatory autoimmune diseases [25-27] including aggravated EAE disease in IL-15 knockout mice [28]. Two recent studies have shown that B cell-derived IL-15 [29] and astrocyte-derived IL-15 enhance $CD8^{+}$T cell cytotoxicity in MS patients [30]. Thus, a combination of BAFF- and IL-15-specific blocking agents will be an effective way to treat autoimmune diseases.

In conclusion, TACI-IgG was effective in reducing effective T cells but not memory T cells in EAE mice. In addition, blockage of IL-15 could reduce memory T cells. The study provides hints for the clinical application of a combination of BAFF- and IL-15-specific therapeutic agents for the treatment of autoimmune diseases.

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The authors declare no conflict of interest.

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