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_J Immunol_ 2005; 175:5591-5595; doi: 10.4049/jimmunol.175.9.5591
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Cutting Edge: CD4⁺CD25⁺ Regulatory T Cells Contribute to Gender Differences in Susceptibility to Experimental Autoimmune Encephalomyelitis

Jay Reddy,* Hanspeter Waldner,* Xingmin Zhang,* Zsolt Illes,* Kai W. Wucherpfennig,† Raymond A. Sobel,‡ and Vijay K. Kuchroo*†

Female B10.S mice are highly resistant to proteolipid protein (PLP) 139–151-induced experimental autoimmune encephalomyelitis (EAE) and depletion of PLP 139–151-reactive CD4⁺CD25⁺ regulatory T (Treg) cells can slightly increase their EAE susceptibility. Although male B10.S mice are moderately susceptible to EAE, we report that depletion of Treg cells in male B10.S mice before immunization with PLP 139–151 renders them highly susceptible to severe EAE with more CNS neutrophil infiltrates than nondepleted controls. Increased susceptibility is associated with an enhanced PLP 139–151-specific T cell response and greater production of IFN-γ, IL-6, and IL-17. Male CD4⁺CD25⁺ effector cells depleted of Treg cells proliferate to a greater degree than those from females in response to either anti-CD3 or PLP 139–151. These data suggest that because of their capacity to regulate potent autoaggressive effector cells, Treg cells partly contribute to the resistance to autoimmunity in the male mice. The Journal of Immunology, 2005, 175:5591–5595.

Autoimmune diseases are more prevalent in females than in males. This disparity also exists in autoimmune disease models (1) and appears to be partly hormone dependent. Sex steroids ameliorate experimental autoimmune encephalomyelitis (EAE) (2–4), but the mechanism(s) by which they alter the disease are unclear. Because immune cells express estrogen and androgen receptors (5, 6), sex hormones may act directly on Ag-specific T cells to alter their functions. Some studies suggest that sex steroids induce immune deviation from a Th1 to a Th2 phenotype (2–4, 7).

A subset of CD4⁺ cells called CD4⁺CD25⁺ regulatory T (Treg) cells that expresses Forkhead box P3 (FoxP3) can control autoimmune responses (8–10). Estrogen modulates the expression of FoxP3 mRNA and middle-aged male mice with EAE have diminished Treg cell activity (11, 12), but it is not known whether Treg cell functions are affected by gender.

Immunization with myelin proteolipid protein (PLP) 139–151 results in EAE in male and female SJL (I-A*) mice with comparable severity, but only female mice show chronic relapsing-remitting disease (13, 14). In contrast, B10.S mice (H-2b congenic with SJL) are relatively resistant to PLP 139–151-induced EAE (15), but it is not known whether gender affects resistance. Using IAα tetramers for PLP 139–151, we found more myelin PLP-specific Treg cells in the naive periphery of female B10.S mice than in SJL mice (15). Depletion of Treg cells in vivo in female B10.S mice predisposed them moderately to EAE.

We report here that although male B10.S mice have fewer PLP 139–151 tetramer⁺ CD4⁺ cells than female mice, depletion of Treg cells in vivo makes them more susceptible to PLP 139–151-induced EAE with increased inflammatory cytokine production and more severe clinical and histological disease than nondepleted mice. Although male and female B10.S mice have comparable Treg cell functions, effector cells expand more in male than in female mice in response to TCR-mediated stimulation. These results indicate that Treg cells partly contribute to gender differences in EAE susceptibility.

Materials and Methods

Mice

B10.S (B10.S-H2b/Sg) wild-type (wt) mice 4–8 wk old were obtained from McLaughlin Research Institute. B10.S/Sg-Tg(TcrPLP)1858Hpw mice (referred to as 5B6 transgenic [tg] B10.S mice) transgenic for the PLP139–151-specific TCR 5B6 were generated and maintained as described previously (16).

Peptide synthesis and immunization procedures

PLP 139–151 (HSLGKWLGHPDKF) and neuraminidase (NASE) 101–120 (EALVRQGLAKVAYYKPNNT) were synthesized on Fmoc chemistry and used for immunizations as described previously (15).

Acknowledgments

This work was supported by National Institutes of Health Grants R01 NS30843, P01 NS38037, and R01 AI44880, NS 046414 (to R.A.S.), P01 AI45757 and R01 NS44914 (to K.W.W.), and National Multiple Sclerosis Society Grant 2571-D9 (to V.K.K.). V.K.K. is the recipient of Javitz Neuroscience Investigator Award.

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Received for publication June 10, 2005. Accepted for publication September 1, 2005.

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3 Abbreviations used in this paper: EAE, experimental autoimmune encephalomyelitis; Treg, regulatory T; PLP, proteolipid protein; wt, wild type; tg, transgenic; TMBV, Theiler’s murine encephalomyelitis virus; 7-AAD, 7-aminoactinomycin D; PMN, polymorphonuclear leukocyte.
Proliferation assays
To assess inhibitory effects of Treg cells, PLP 139–151-specific 5B6 tg T cells were fractionated into CD4⁺CD25⁻ and CD4⁺CD25⁺ cells by magnetic separation (Miltenyi Biotec). They were plated at a density of 1 × 10⁶ cells/ml in the presence of APCs and PLP 139–151 (20 μg/ml) for 2 days in complete DMEM. After pulsing with 1 μCi of [³H] thymidine (1 Ci = 37 GBq) for 16 h, proliferation was measured as counts per minute. CD3⁺ T cells enriched by negative selection (R & D Systems) from immunized B10.S wt mice were stimulated with PLP 139–151 in the presence of APCs. Response of CD4⁺CD25⁻ T cells to anti-CD3 (1 μg/ml, clone, 145-2C11; BD Pharmingen) was tested with CD11c⁺ cells as APCs.

Flow cytometry
To study cellular subsets in lymph nodes, various mAbs procured from BD Pharmingen. After staining, cells were analyzed by flow cytometry (FACSCalibur; BD Biosciences); data were analyzed using FlowJo software (Tree Star).

IA⁺ tetramer staining
Frequencies of Ag-specific T cells were determined by flow cytometry using IA⁺/PLP 139–151 and Thicler’s murine encephalomyelitis virus (TMEV) 70–86 tetramers (negative control) as described previously (15). Four-color analysis included anti-CD25/FITC (clone, 7D4), IA⁺ tetramers (PE), and 7-amino-70–86 tetramers (negative control) as described (15). Frequencies of IA⁺ tetramer cells in the live (7-AAD⁻) CD4⁺ population were determined.

Cytokine analysis
CD3⁺ T cells were enriched from anti-CD25- and control Ig-treated B10.S mice 10 days after immunization with PLP 139–151. They were stimulated with APCs loaded with PLP 139–151 (50 μg/ml) for 4–6 days. Supernatants on day 2 were tested for cytokines by ELISAs, and frequencies of cytokine-secreting cells were determined on day 4 by intracellular staining, as described previously (15).

Real-time (TaqMan) RT-PCR
Total RNA was extracted from CD4⁺CD25⁻ and CD4⁺CD25⁺ cells from a group of B10.S mice followed by treatment with DNase 1 (REneasy kit; Qiagen), CDNA was synthesized using TaqMan RT reagents (Applied Biosystems). Foxp3 and GAPDH mRNA was measured by PCR in separate tubes in duplicates using probes labeled with FAM and VIC and with TAMRA as a quencher (Applied Biosystems). Primers and probe for GAPDH were purchased using TaqMan universal mix and the ABI Prism 7700 sequence detection system (Applied Biosystems). Foxp3 sequences were as described previously (17). A comparative threshold cycle (Ct) was used to determine mRNA expression of Foxp3 and GAPDH relative to no-template control (calibrator). CT value was normalized for each sample using the formula: ΔCt = Ct (Foxp3) − Ct (GAPDH), and the relative expression of Foxp3 was then calculated using the formula 2⁻ΔCT.

Histopathology
Following induction of EAE, the mice were monitored for clinical signs of disease for 4 wk and scored as described previously (13). Mice were killed when their score reached ≥4 or when they began to recover. Brains and spinal cords were fractionated into CD4⁺ and CD8⁺ cells by magnetic separation (Miltenyi Biotec). They were plated at a density of 1 × 10⁶ cells/ml in 10% phosphate-buffered formalin. Histologic disease was evaluated as previously described (13) and polymorphonuclear leukocyte (PMN) infiltration as described in Table 1 legend.

Statistics
Student’s t test was used to determine significance of data except for rank correlations between inflammatory foci and PMN scores, which were determined by Wilcoxon signed rank test. A value of p ≤ 0.05 was considered significant.

Results and Discussion
We report here that Treg cells partly contribute to gender differences in susceptibility to EAE. We previously showed that PLP 139–151-reactive Treg cells exist in the naive periphery of EAE-resistant B10.S female mice and that depletion of these in vivo before immunization with PLP 139–151 resulted in expansion of IFN-γ-producing cells and induction of EAE in ~30% of mice (15). Because autoimmune diseases are more common in females than males, we hypothesized that there may

Table 1. Clinical and histologic EAE in B10.S mice treated with anti-CD25 or control Ab

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Incidence (%)</th>
<th>Mean day of onset</th>
<th>Mean maximum score</th>
<th>Meninges</th>
<th>Parenchyma</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>Rat IgG control</td>
<td>3/12 (25)</td>
<td>14.3 ± 1.9</td>
<td>10.3 ± 4.1</td>
<td>0.25 ± 0.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anti-CD25</td>
<td>12/14 (85.7)</td>
<td>17.3 ± 1.3</td>
<td>64.3 ± 11.8</td>
<td>0.0002</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anti-CD25</td>
<td>9/11 (81.8)</td>
<td>1.2 ± 0.6</td>
<td>12.0 ± 0.6</td>
<td>0.00004</td>
<td></td>
</tr>
</tbody>
</table>

Numbers are mean ± SEM. Rat IgG control = 0/8 (0); anti-CD25 = 0/10 (0).

*P values 0.001 0.0002 0.0008 0.0003 0.0004

Rat IgG control = 0/8 (0); anti-CD25 = 0/10 (0).

Students t test was used to determine significance of data except for rank correlations between inflammatory foci and PMN scores, which were determined by Wilcoxon signed rank test. A value of p ≤ 0.05 was considered significant.

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be gender differences in the function of the naturally occurring CD4^+CD25^- Treg cell subset. When we depleted Treg cells in vivo by administration of anti-CD25 Ab in male B10.S mice before immunization, 85% of the mice (12 of 14) developed moderate to severe EAE, whereas only 3 of 12 control mice (25%) developed mild EAE, i.e., loss of tail tonicity (p ≤ 0.001) (Table I). In agreement with our previous results (15), a small number of female B10.S mice (three of nine, 33%) depleted of Treg cells but no control Ab-treated mice developed disease, suggesting that genetic resistance to EAE in female B10.S mice does not lie entirely in the Treg population. In female B10.S mice, multiple factors may contribute to EAE resistance, i.e., Ag-specific defects in Th1 cytokine secretion and II.12-Rb2 expression (18, 19), a tendency to produce elevated amounts of Th2 cytokines (20), APCs (16) and the presence of a high proportion of Treg cells (17). This study suggests either that Treg cells from female mice are more efficient in their suppressive function than those in males or that the effector cells expanded to a greater extent (Fig. 2). In male mice as ratios of Treg cells to effectors were lowered, the percentage of effector cells in males are capable of responding to autoantigens CD4^+CD25^- Treg cell subset.

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We then confirmed that Treg cells in male and female B10.S mice, but the percentage of Treg cells is lower in male mice than in anti-CD25-treated females (mean total inflammatory foci = 124.9 vs 44.8) (p ≤ 0.05). The disease severity in females was enhanced when compared with control mice but inflammatory foci contained fewer neutrophils (Table I, Fig. 1b).

To determine the mechanisms for greater incidence and severity of EAE in Treg-depleted male B10.S mice, we tested whether there are any differences in Treg cell function between male and female B10.S mice in vitro.

We first determined that male B10.S mice have a higher percentage of CD3^+ cells in their lymph nodes than age-matched female B10.S mice, but the percentage of Treg cells is lower in males (Table II). We then confirmed that Treg cells in male and female B10.S mice are equally effective in inhibiting expansion of effector cells using anti-CD3 as a stimulus (data not shown). FoxP3 mRNA, a marker for Treg cells, was also expressed in comparable amounts (Fig. 2a). Therefore, we could identify no major differences in Treg populations between male and female B10.S mice. We next tested whether Treg cells from male and female B10.S mice have any defect in their suppressive function in response to self-Ags using TCR tg mice specific to PLP 139–151 (16). We found that Treg cells from male and female tg B10.S mice did not proliferate to PLP 139–151, whereas male and female effector cells responded equally well to PLP 139–151. Treg cells inhibited the proliferative response of effector cells but there were differences; the inhibition of CD4^+CD25^- cells mediated by Treg cells in female B10.S mice was maintained even at low ratios of regulatory:effector cells. However, in male mice as ratios of Treg cells to effectors were lowered, the effector cells expanded to a greater extent (Fig. 2b). This suggests that Treg cells from female mice are more efficient in their suppressive function than those in males or that the effector cells in males are capable of responding to autoantigens.

![FIGURE 1](link) Effect of anti-CD25 treatment on CNS inflammatory infiltrates in PLP 139–151-immunized male and female B10.S mice. a, An inflammatory focus in an anti-CD25-treated male mouse with EAE contains a predominance of neutrophils intermixed with mononuclear cells (PMN score = 3+; see legend to Table I). b, Typical mononuclear infiltrates in an anti-CD25-treated female mouse (PMN score = 0). c, A small subpial mononuclear cell infiltrate in a control lg-treated male mouse. d, No inflammatory cell infiltrates in a control lg-treated female mouse. Each panel is from the spinal cord with a spinal nerve root on the left side of the field. Luxol fast blue-H&E stain. Original magnification, ×240. Bar in a = 25 µm.

![FIGURE 2](link) PLP 139–151-specific Treg cells are functional in both male and female B10.S mice. a, FoxP3 and GAPDH mRNA expression in Treg and CD4^+CD25^- cells. Each bar represents relative FoxP3 mRNA mean ± SEM values. n = 5 (four to five mice per sample). b, Treg and CD4^+CD25^- cells isolated from PLP 139–151-specific tg B10.S mice of either sex were stimulated with PLP 139–151 together at indicated ratios or separately and proliferation was measured as described in Materials and Methods. A representative experiment is shown.

<table>
<thead>
<tr>
<th>Marker</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD3^+</td>
<td>51.06 ± 0.99</td>
<td>44.68 ± 1.84</td>
</tr>
<tr>
<td>CD4</td>
<td>49.36 ± 0.77</td>
<td>50.52 ± 1.33</td>
</tr>
<tr>
<td>CD8</td>
<td>42.82 ± 0.43</td>
<td>40.52 ± 1.43</td>
</tr>
<tr>
<td>CD25^-</td>
<td>7.70 ± 0.26</td>
<td>9.71 ± 0.29</td>
</tr>
</tbody>
</table>

Table II. Lymphocyte subsets in male and female B10.S mice

* Lymph node cells from male and female B10.S mice were stained with the indicated markers. The percentages of individual subsets were then determined by flow cytometry. n = 5/group. p ≤ 0.007. p ≤ 0.00047.
more vigorously than those in females. We quantified the precursor frequency of PLP 139–151 tetramer+ cells in male mice to be 0.04% of CD4 cells (8 in 20,000). By contrast, the precursor frequency in female B10.S mice is 40 in 20,000 CD4 cells (15). We did not observe any significant shift in PLP 139–151 tetramer reactivity in effector vs Treg cells, as previously reported in female B10.S mice (15) (data not shown). Therefore, the higher incidence and greater severity of EAE in male B10.S mice are unlikely to be due to an increased frequency or function of PLP 139–151-specific Treg cells.

We next compared T cell proliferation to PLP 139–151 between anti-CD25 and rat IgG-treated male mice. The PLP 139–151-specific responses, but not NASE responses, were significantly higher in the anti-CD25 Ab-treated than in the control group (Fig. 3a). Consistent with this, percentages of PLP 139–151 tetramer+ CD4 cells were increased by ~3-fold more in the anti-CD25 Ab-treated males compared with controls (Fig. 3b). This response was specific because there was negligible reactivity to TMEV 70–86 tetramers. These data suggest that the expansion of PLP 139–151-reactive cells in mice depleted of Treg cells contributed to the more severe disease. This expansion appeared to have resulted from the loss of regulation mediated by Treg cells, which can prevent the expansion of effector cells in an Ag nonspecific manner (21).

Previously, male SJL mice immunized with myelin basic protein or PLP were found to produce IL-4 and IL-10, while females produced more IFN-γ (2, 22). We tested whether a similar bias exists in immunized male B10.S mice, with or without Treg cell depletion. By ELISA, the production of both IL-2 (p = 0.01) and IFN-γ (p = 0.006) was significantly elevated, with a marginal increase in IL-17 production (p = 0.08) on day 2 in the cultures derived from CD25+ cell-depleted male mice compared with controls (Fig. 3c). As previously noted in female B10.S mice (15), IL-10 secretion was reduced in the anti-CD25 Ab-treated group (p = 0.02), suggesting that Treg cells may directly or indirectly regulate IL-10 production. However, by intracellular staining, the frequencies of cells secreting all of the cytokines tested (IL-2, IL-4, IL-6, IL-10, IL-17, and IFN-γ) were elevated in anti-CD25 Ab-treated vs control mice. The number of TNF-α-secreting cells did not vary between groups (data not shown). Recently, it was reported that

FIGURE 3. Depletion of Treg cells before immunization with PLP 139–151 enhances Ag-specific T cell proliferation and inflammatory cytokines in male B10.S mice. a, Male B10.S mice pretreated with anti-CD25 or isotype control on day −5 and day −3 were immunized with PLP 139–151. Ten days later, CD3+ cells were stimulated with PLP 139–151 and proliferation was measured as described in Materials and Methods. A representative experiment is shown. b, Viable lymphoblasts harvested from the cultures stimulated with PLP 139–151 were stained with PLP 139–151 or TMEV 70–86 tetramers. These data suggest that the expansion of PLP 139–151-reactive cells in mice depleted of Treg cells contributed to the more severe disease. This expansion appeared to have resulted from the loss of regulation mediated by Treg cells, which can prevent the expansion of effector cells in an Ag nonspecific manner (21).

![Image](http://www.jimmunol.org/DownloadedFrom/5594.png)

![Image](http://www.jimmunol.org/DownloadedFrom/5594.png)

FIGURE 4. Ag-specific, CD4+ CD25− effector cells from male B10.S mice expand more vigorously than those derived from female mice. a, CD4+ CD25− cells isolated by magnetic separation from male and female B10.S mice were stimulated with anti-CD3 Ab (1 μg/ml) and CD11c+ cells as APCs, and proliferation was measured as described in Materials and Methods. A representative experiment of three is shown. b, CD3+ cells were enriched from male and female B10.S mice pretreated with anti-CD25 or IgG Ab and immunized with PLP 139–151. The cells were stimulated with PLP 139–151 and proliferation was measured as above. Mean ± SEM values are shown. (a) Male (n = 8, females, n = 7). (1.5 μg/ml, p ≤ 0.08; 15 μg/ml, p ≤ 0.09).
IL-23-dependent production of inflammatory cytokines (IL-17, IL-17F, IL-6, and TNF-α) is essential for the development of CNS inflammation (23). In anti-CD25 Ab-treated mice, the numbers of cells that secrete IFN-γ, IL-6, and IL-17 was increased, implying that Treg cells regulate the expression of these cytokines. In the absence of Treg cells, the effector cells producing inflammatory cytokines may expand resulting in altered chemokines and increased proportions of PMNs in inflammatory foci (24).

We then sought to detect any fundamental difference in the expansion of effector cells between male and female B10.S wt mice. Using anti-CD3 as a stimulus, we observed that the effector cells from male B10.S mice expanded to a greater extent than those from female mice (Fig. 4a). To verify that a similar differential response occurs to PLP 139–151, we immunized groups of male and female B10.S mice with PLP 139–151 after treating them with anti-CD25 or control Ab. We measured the PLP 139–151-specific response by [3H]thymidine incorporation. As expected, mice depleted of CD25+ cells responded to PLP 139–151 significantly more strongly than controls of either sex (Fig. 4b). However, the T cell response to PLP 139–151 in the male B10.S mice tended to be higher than in the female mice treated with anti-CD25 Ab, especially at lower Ag concentrations (Fig. 4b). Similar trends were confirmed by using 5B6 tg T cells specific to PLP 139–151 (data not shown). These data suggest that the autoreactive effector cells in male B10.S mice can respond to autoantigens vigorously, but they are kept in check by Treg cells.

In summary, in male B10.S mice treated with anti-CD25 Ab, the incidence of PLP 139–151-induced EAE was enhanced significantly when compared with female B10.S mice, suggesting that Treg cells do not play as large a role in mediating genetic resistance to EAE in female compared with male mice. Although there was no fundamental difference in Treg cell function between male and female mice, the effector cells from male B10.S mice in the absence of Treg cells tended to proliferate to a higher degree than those from females. This suggests that male Treg cells control the expansion of pathogenic autoreactive cells more effectively and that this contributes to their greater disease resistance.

Disclosures
The authors have no financial conflict of interest.

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