Genetic Analysis of the Influence of Pertussis Toxin on Experimental Allergic Encephalomyelitis Susceptibility: An Environmental Agent Can Override Genetic Checkpoints

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Genetic Analysis of the Influence of Pertussis Toxin on Experimental Allergic Encephalomyelitis Susceptibility: An Environmental Agent Can Override Genetic Checkpoints


Pertussis toxin (PTX) is a potent ancillary adjuvant used to elicit several different autoimmune diseases, including experimental allergic encephalomyelitis (EAE). To delineate the genetics of PTX effect in EAE, we mapped EAE-modifying (eae-m) loci in cohorts of backcross mice immunized with and without PTX. In this study, we analyzed the genetic basis of EAE susceptibility and severity and the intermediate phenotypes of mononuclear cell infiltration, suppuration, and demyelination. In animals immunized with PTX, one major locus, eae9, controls disease susceptibility and severity. Eae9 also regulates the extent of mononuclear cell infiltration of the spinal cord in male mice. Without PTX, five eae-m loci were noted, including three new loci in intervals on chromosomes 8 (eae14), 10 (eae17), and 18 (eae18). Taken together, these results suggest that eae9 controls the effects of PTX in EAE susceptibility, and is capable of overriding the other genetic checkpoints in the pathogenesis of this disease. The Journal of Immunology, 2000, 164: 3420–3425.

The use of adjuvants is a long-standing and often necessary technique to induce autoimmunity in animals (1). Pertussis toxin (PTX) is an example of a potent ancillary adjuvant used to elicit several different autoimmune diseases, including experimental allergic encephalomyelitis (EAE), experimental allergic orchitis, and experimental autoimmune uveitis (2–4). Numerous theories have been proposed to explain the action of PTX in the development of organ-specific autoimmune disease (5). The prevailing hypothesis is that PTX “opens” blood-tissue barriers, allowing enhanced infiltration of the T cells and macrophages that are responsible for inflammation (5). This proposed role for PTX is supported by EAE studies in which PTX injection leads to breakdown of the blood-brain barrier (BBB) as revealed by the influx of radioactive tracers into the brain parenchyma (6–8). In a transgenic mouse model, pathogenic T cells accumulate in the CNS only when PTX is administered (9). However, other well-known activities of PTX, including its immunomodulatory, lymphocytosis-promoting, thymolytic, and lymphostatic effects, may also contribute to disease pathogenesis (5, 10, 11).

As an initial step in understanding the genetic control of PTX effects in regulating EAE susceptibility, we mapped the locus (Bphs) controlling PTX-induced hypersensitivity to histamine (12). This phenotype has been reported to be associated with susceptibility to EAE (13) and to experimental allergic orchitis (14). Bphs is on chromosome 6 (12) and has been physically located within a yeast artificial chromosome contig encoding Eno2, Tnfrsf7 (Cd27), Lbhr, Tnfrsf1a (Tnfr1), and Vwf (15). However, Bphs does not determine EAE susceptibility in all PTX-dependent strains of mice, and some strains of mice differ in EAE susceptibility but do not differ in histamine sensitivity or Bphs alleles. Therefore, additional loci controlling PTX effects must exist. The purpose of the present study was to examine the genetic control of PTX effects in EAE by using strains of mice that are concordant for both Bphs and H2. Examination of EAE in (B10.S/DvTe × SJL/J) × B10.S/DvTe backcross (BC1) mice conditioned with PTX allows the determination of whether PTX elicits more frequent and/or more severe clinical signs of EAE and the identification of additional loci mediating its effects. We report here that the use of PTX significantly increases the proportion of backcross mice with clinical signs of EAE. One major locus on chromosome 9 controlling PTX effects in EAE susceptibility was found, in contrast to the multiple eae-m loci that are involved in EAE in the absence of PTX. Our results support the hypothesis that PTX is capable of circumventing or overriding many of the genetically determined checkpoints associated with EAE in this strain combination.

Materials and Methods

Animals and immunizations

(B10.S/DvTe × SJL/J) × B10.S/DvTe backcross mice (BC1) were generated continuously over 12 mo from the same pool of B10.S/DvTe and (B10.S/DvTe × SJL/J) F1, hybrid breeding stock. Inoculation of groups of mice, ranging in age from 6 to 12 wk, was staggered over the same period. Mice were injected s.c. at two sites on the posterior flank (0.15 ml/injection site) with 1.0 mg of SJL/J spinal cord homogenate (SCH), in 0.15 ml PBS, emulsified with an equal volume of CFA (16). A booster injection of SJL/J...
SCH + CFA, prepared in the same manner as the primary inoculum, was given on day 7. PTX-treated mice received 10 μg of crude PTX (17) i.p. at the time of inoculation and 5 μg 24–48 h later. Ninety-two mice were immunized using SCH, CFA, and PTX (PTX1) and 122 mice were immunized with SCH and CFA alone (PTX2). Mice were monitored daily for symptoms and graded from 0 to 4 as follows: 0, no clinical expression of disease; 1, floppy tail without hind limb weakness; 2, hind limb weakness with or without flaccid tail; 3, hind leg paralysis and floppy tail; and 4, hind leg paralysis accompanied by a floppy tail and urinary or fecal incontinence. Animals progressing to a score of 4 were euthanized. Animals were observed for 30 or 60 days, at which time they were sacrificed and their brains and spinal cord (SC) were retrieved for histological analysis. Severity of disease among affected animals was analyzed using a severity index generated by averaging the clinical scores for each animal over the number of days that it exhibited clinical symptoms. Liver tissue was collected for DNA isolation.

Histological evaluation

Brain and SC samples were dissected from calvaria and vertebral columns, respectively, and fixed by immersion in 10% phosphate-buffered Formalin (pH 7.2) at 4°C. Following adequate fixation, brain and SC were trimmed and representative transverse sections embedded in paraffin, sectioned at 5 μm, and mounted on glass slides. Sections were stained with hematoxylin and eosin for routine evaluation and luxol fast blue-periodic acid Schiff reagent for demyelination. Representative areas of the brain and SC, selected for histological evaluation, were chosen based on previous studies (18, 19). These included brain stem, cerebrum, and the cervical, thoracic, and lumbar segments of the SC. Scoring was based on a semiquantitative assessment for the following individual variables: 1) severity of the lesion as represented by each component of the histological assessment; 2) extent and degree of myelin loss and tissue injury (swollen axon sheaths, swollen axons, and reactive glialosis); 3) number of neutrophils/eosinophils comprising the inflammatory exudate; and 4) number of lymphocytes/macrophages comprising the inflammatory exudate. A score was assigned to the entire brain and to the entire SC based on a subjective numerical scale ranging from 0 to 5. A score of zero indicates no lesion, myelin loss, or inflammatory response was present in the tissue evaluated. The remaining scores were as follows: 1, minimal; 2, mild; 3, moderate; 4, marked; and 5, severe lesions, myelin loss, or inflammatory response present in the tissue.

Genetic analysis

Genomic DNA was isolated from liver tissue by standard techniques and used as template for PCR amplification using radiolabeled primers as described previously (16). Primers for microsatellite markers were purchased from Research Genetics (Huntsville, AL). Alleles at these markers were resolved on denaturing polyacrylamide gels and read from autoradiographic films directly into a MapManager QT database (20). Linkage maps were generated to provide a sampling distribution of the maximum test statistic from each of the 1000 permutations used to set experimentwise significance thresholds. Linkages were reported if the test statistic for a particular marker locus was greater than the experimentwise critical value calculated for α = 0.10 (suggestive) or α = 0.05 (significant) for that trait. Significant linkages, or suggestive linkages that replicate the findings of a previous study, were given eae locus designations.

Interaction between marker loci

To test the hypothesis that significant QTL interact, we used a regression model containing significant marker loci and two-locus interaction variables between significant marker loci. Regression models with dummy coding for marker loci were analyzed in SAS using PROC REG (23). Significance of the overall model was assessed using an F statistic, and significance of interaction variables was assessed using a T statistic (24).

Results

Incidence of EAE in the two treatment groups

Signs of EAE were more frequent, and the latency to onset was significantly shorter, in both males and females in the PTX+ group (69% affected) compared with the PTX− group (43% affected) (Table I). Although the incidence of disease was higher in PTX+ mice, there was no difference in susceptibility between males and females within either group. However, disease as measured by average peak score (or by a severity index, data not shown) was less severe in the PTX+ group, especially in females (Table I). A substantial cohort of mice in the PTX− group developed neuropathology in the absence of detectable clinical signs. We have recently termed this type of disease benign EAE (25). Benign EAE was prominent in PTX− mice: 40% clinically unaffected PTX− mice showed monocytes and lymphocytes in their SCs without any outward signs of EAE, whereas only 16% of unaffected PTX+ mice had this phenotype. This was not influenced by sex.

Neuropathology in the two treatment groups

SC and brain samples were obtained from and scored for the occurrence and degree of mononuclear infiltration, suppuration, and demyelination. The character and distribution of CNS histopathological lesions observed in this study were consistent with those reported in previous studies (18, 19, 25). Inflammatory responses in susceptible animals ranged from those with a predominantly neutrophilic response admixed with a smaller monocytic/lymphocytic component to those with a predominantly monocytic/lymphocytic response. CNS tissue response ranged from mice with no tissue injury to those with loss of myelin, reactive glialosis, swollen axon sheaths, and swollen axons. In all mice with histopathology, the inflammatory response had a perivascular distribution that was predominantly observed in the meninges and in the white matter.
In the SC, predilection for the nerve root entry zone was observed, as reported previously (19).

When mice from the two treatment groups were examined for the presence of histopathology in the CNS (brain or SC), the PTX+ group again had a higher incidence of affected mice than the PTX− group for either CNS site (data not shown). Differences between males and females were not observed for histopathological traits in the brain or SC of PTX+ mice. In contrast, female mice in the PTX− group had significantly greater brain involvement than males (Table II). Because animals were not all euthanized at the same time points subsequent to the manifestation of their disease, overall between-group comparisons could not be made for histopathology. For PTX+ mice, linkage to the binary trait of susceptibility was found in an interval that is marked by D9Mit105 (χ² = 17.0). A QTL designated eae9 has previously been identified in the same interval in an F2 intercross with the same parental strains (16). In the PTX− cohort, linkage to susceptibility was found to markers on chromosome 8, peaking at D8Mit190 (χ² = 18.6, α = 0.1).

Loci that showed evidence of linkage to severity or histopathological signs of EAE are given in Table III. In the PTX+ cohort, we again found linkage to a single major QTL (eaem) between D9Mit22 and D9Mit12. The SJL-derived allele at eaem is associated with increased severity. Stratification by sex revealed that one phenotype of eae9 is to increase monocyte/lymphocyte infiltration in the SC in males. No linkage to any other locus, including previously identified eaem loci, was seen in PTX− mice. In contrast,

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**Table II. CNS histopathology in male and female PTX+ or PTX− BC1 mice**

<table>
<thead>
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<th>Trait</th>
<th>PTX+</th>
<th>PTX−</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
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</tr>
<tr>
<td>Demyelination</td>
<td>1.04</td>
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<td>Suppuration</td>
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<tr>
<td>Monocytic/lymphocytic infiltration</td>
<td>1.44</td>
<td>1.42</td>
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**Brain**

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<th>PTX−</th>
</tr>
</thead>
<tbody>
<tr>
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<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Demyelination</td>
<td>0.15</td>
<td>0.09</td>
</tr>
<tr>
<td>Suppuration</td>
<td>0.47</td>
<td>0.33</td>
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<tr>
<td>Monocytic/lymphocytic infiltration</td>
<td>1.16</td>
<td>1.51</td>
</tr>
</tbody>
</table>

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* Mean value for the specified trait.

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**Table III. Quantitative trait loci linked to EAE susceptibility in PTX-treated vs untreated backcross mice**

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Marker</th>
<th>cM</th>
<th>eae</th>
<th>Trait</th>
<th>Trait</th>
<th>LRT</th>
<th>Allele</th>
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</thead>
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<tr>
<td>PTX+ Total</td>
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<td>35</td>
<td>eae9</td>
<td>High score</td>
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<td>151*</td>
<td>SJL</td>
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<td></td>
<td>D9Mit105</td>
<td>35</td>
<td>eae9</td>
<td>Severity index</td>
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<td></td>
<td>SJL</td>
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<tr>
<td>Females</td>
<td>None</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>D9Mit105</td>
<td>35</td>
<td>eae9</td>
<td>Mono/lymph SC</td>
<td>12.8*</td>
<td></td>
<td>SJL</td>
</tr>
<tr>
<td>PTX Total</td>
<td>D8Mit190</td>
<td>21</td>
<td>eae14</td>
<td>High score</td>
<td>22.9*</td>
<td>B10.S</td>
<td>SJL</td>
</tr>
<tr>
<td></td>
<td>D8Mit190</td>
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<td>eae14</td>
<td>Severity index</td>
<td>25.9*</td>
<td>B10.S</td>
<td>SJL</td>
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<td>SJL</td>
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<td>eae7</td>
<td>Severity index</td>
<td>13.7*</td>
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<td>SJL</td>
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<tr>
<td>Males</td>
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<td>eae14</td>
<td>High score</td>
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<td>B10.S</td>
<td>SJL</td>
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<td>eae14</td>
<td>Demyelination in SC</td>
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<td>B10.S</td>
<td>SJL</td>
</tr>
<tr>
<td></td>
<td>D10Mit131</td>
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<td>eae17</td>
<td>High score</td>
<td>16.2*</td>
<td></td>
<td>SJL</td>
</tr>
<tr>
<td></td>
<td>D10Mit131</td>
<td>36</td>
<td>eae17</td>
<td>Severity index</td>
<td>15.8*</td>
<td></td>
<td>SJL</td>
</tr>
<tr>
<td></td>
<td>D16Mit12</td>
<td>27</td>
<td>eae11</td>
<td>Mono/lymph SC</td>
<td>13.1*</td>
<td></td>
<td>SJL</td>
</tr>
<tr>
<td>Males</td>
<td>D18Mit3</td>
<td>54</td>
<td>eae18</td>
<td>Mono/lymph SC</td>
<td>17.8*</td>
<td></td>
<td>SJL</td>
</tr>
<tr>
<td></td>
<td>D18Mit3</td>
<td>54</td>
<td>eae18</td>
<td>Demyelination in SC</td>
<td>20.4*</td>
<td></td>
<td>SJL</td>
</tr>
</tbody>
</table>

* LRT is significant for experimentwise threshold of α < 0.05. Cutoffs for the α = 0.05 level of significance range from LRT 12.9 to 15.6. The level of significance indicated by an LRT > 15.6 was not established in this experiment.

**Genetic control of EAE**

Genome scanning was performed on both the PTX+ and PTX− cohorts. We analyzed both the binary trait of EAE incidence (or susceptibility) and the quantitative traits of severity and histopathology. For PTX+ mice, linkage to the binary trait of susceptibility was found in an interval that is marked by D9Mit105 (χ² values were 11.7 and 9.3, indicating probability of linkage at α = 0.05 and α = 0.1, respectively). This effect came largely from male mice (χ² = 17.0). A QTL designated eae9 has previously been identified in the same interval in an F2 intercross with the same parental strains (16). In the PTX− cohort, linkage to susceptibility was found to markers on chromosome 8, peaking at D8Mit190 (χ² = 18.6, α = 0.1).

Loci that showed evidence of linkage to severity or histopathological signs of EAE are given in Table III. In the PTX+ cohort, we again found linkage to a single major QTL (eaem) between D9Mit22 and D9Mit12. The SJL-derived allele at eaem is associated with increased severity. Stratification by sex revealed that one phenotype of eae9 is to increase monocyte/lymphocyte infiltration in the SC in males. No linkage to any other locus, including previously identified eaem loci, was seen in PTX− mice. In contrast,
five linkages were seen in the PTX− cohort, including two QTL previously shown to play a role in this strain combination (16, 25). The most significant QTL in the PTX− cohort is on chromosome 8 between D8 Mit3 and D8 Mit31. Susceptibility, severity, and SC demyelination are associated with the B10.S-derived allele at this locus, which we have designated eae14. In addition to eae14, a locus on chromosome 11 that colocalizes with eae7 (16) contributed to severity in this cohort. As in the F2 intercross between these same strains, sex-specific linkages were seen in the PTX− mice. Females from the PTX− group showed linkage to chromosome 10 for severity of clinical signs in an interval between D10 Mit126 and D10 Mit10. We have designated this locus as eae17. A QTL controlling severity of mononuclear infiltrates in the SC was mapped to a broad region of chromosome 16. Increased severity of inflammation was associated with inheritance of the SJL allele at this locus, which was previously designated as eae11 (25). In PTX− males, a strong QTL was mapped to chromosome 18. The SJL-derived allele at this locus (eae18) resulted in greater infiltration and demyelination in the SC. No QTL for brain histopathology met experimentwise cutoffs for suggestive (α = 0.10) or significant (α = 0.05) linkage in either cohort.

**Multiple linear regression analysis**

Multiple linear regression was used to test the hypothesis that significant QTL interact. Significant marker loci for disease severity (D8 Mit190, D11 Mit98, and D10 Mit42), SC demyelination (D8 Mit190 and D18 Mit3), and SC monocytic/lymphocytic infiltration (D8 Mit190, D16 Mit50, and D18 Mit3) were analyzed as independent variables in multiple linear regression analyses with the appropriate phenotype as the dependent variable. To investigate possible interactions between significant marker loci, two-locus interaction terms were added to the regression models as independent variables. None of the interaction terms was significant (p > 0.05). Without interaction variables, statistical significance was achieved for disease severity (F = 13.59, p < 0.0001), SC demyelination (F = 10.54, p < 0.0001), and SC monocytic/lymphocytic infiltration (F = 6.31, p = 0.0005).

**Discussion**

In our study, EAE was more frequent in PTX-treated backcross mice. However, disease symptoms were milder. These findings are consistent with previous studies demonstrating that PTX can “convert” some EAE-resistant rodent strains to susceptible ones, indicating that autoimmune resistance is environmentally sensitive (26). The ability to convert otherwise resistant mice implies that some checkpoints in autoimmunity may be controlled by environmentally sensitive loci (27). For example, if a particular locus maintains the integrity of the BBB, administration of PTX might overcome that mechanism of EAE resistance. Thus, the activity of any EAE resistance alleles at that locus could be bypassed by PTX in a genetic cross where those alleles were segregating, and thus linkage to that locus would be minimized. Characterization of the loci controlling the activity of PTX in EAE will be helpful in understanding the action of environmentally sensitive loci in susceptibility to autoimmune disease.

PTX has many effects on the immune system, aside from its vasoactive amine-sensitizing activity (6, 7). Because our animals were not segregating for the Bphs phenotype, which is believed to be associated with BBB permeability changes, we expect that other genetically regulated PTX-mediated phenotypes will be present in our cross. The mechanism by which PTX affects EAE in this backcross could therefore be related to one of its other known activities (5). For example, PTX causes a generalized lymphocytosis that is accompanied by a depletion of lymphocytes in the spleen, lymph node, and thymus due to the failure of cells to migrate back to the peripheral lymphoid tissue (28, 29). PTX is also reported to be preferentially mitogenic for T cells (30), and it has been reported to enhance delayed-type hypersensitivity responses in an Ag-specific manner (31, 32). The enhanced delayed-type hypersensitivity due to PTX correlates with elevated Ag-specific production of IFN-γ by these cells (33). Additionally, PTX can induce both Th1 and Th2 immune responses (34, 35) and can increase expression of the costimulatory molecules B7-1 and B7-2 on macrophages and B cells, and CD28 on T cells (35). In this regard, PTX is capable of preventing the induction of peripheral T cell anergy to murine encephalitogenic peptides, again in an Ag-specific manner (36); central mechanisms of tolerance may also be affected by PTX (37). Any of these or other known roles of PTX might be critical to the development of clinical signs or neuropathology.

In the genetic analysis of the PTX− group, only one locus (eae9) shows evidence of linkage to disease susceptibility in comparison to five loci in the PTX+ group. Our results therefore suggest that PTX overcomes these critical genetic checkpoints in the etiology of autoimmune disease. Eae9 was associated with the extent of mononuclear infiltration in the SC and severity of EAE clinical signs. This QTL is located in an interval encoding Blr1/CXCR5, Il10ra α-chain, and Il18 (IFN-γ-inducing factor). Any of these candidate genes could be responsible for the eae9-mediated phenotypes mentioned above. Given that PTX can induce increased IFN-γ production by T cells, it is interesting to consider the possibility that eae9 is Il18. Another possibility is that lymphocytosis could be affected by the differential action of the chemokine receptor Blr1/CXCR5 alleles. This is particularly intriguing given that the chemokines Scy1 (T cell activation 3), Scy2 (monocyte chemoattractant protein (MCP)-1), and Scy12 (MCP-5) are candidates for eae7 on chromosome 11 (38), which was also identified in the PTX− backcross (Table III). In three separate crosses, therefore, we observed linkage to either chemokines or their receptors (eae9 and eae7 in the BC PTX+ and PTX−, and eae7 in the F2 in Ref. 38), and thus allelic differences in the chemokine-signaling pathways may control susceptibility to EAE by regulating the migration of inflammatory cells and their access into the CNS.

The five QTL in the PTX− cohort include a novel eae-m locus we have named eae14. eae14 demonstrates significant linkage to disease incidence and severity and to the extent of SC demyelination. This QTL maps to an interval containing several genes of possible relevance to EAE, two of which are glutathione reductase (Gr1) and caspase-3 (Casp3). Glutathione reductase (EC 1.6.4.2) is an enzyme in the cytosol that maintains high levels of reduced glutathione in the cell, which provides significant antioxidant activity. It is expressed in macrophages and in brain. A deficiency in glutathione reductase in either of these tissues could render them susceptible to the toxic effects of free oxygen radicals in the inflammatory site (39). C57BL strains have the Gr1 alleles. It is known to have lower enzyme activity, whereas SJL/J mice have the Gr1b allele and higher enzymatic activity (40). This difference in enzyme activity could explain why B/B homoygotes for eae14 develop more severe disease in the PTX− group. The second candidate gene in this interval is caspase-3, a downstream effector molecule of cellular apoptosis. The active form of caspase-3 is highly expressed in the spleen and less so in the brain (41). It has been hypothesized that apoptosis of T cells might play a role in the resolution of EAE (42–44).

The PTX− cohort displayed sexual dimorphism. One linkage to EAE severity was found on chromosome 10 only in PTX− females. This interval contains several interesting candidate genes, including matrix metalloproteinase 11 (Mmp11 at 41 cM), tissue...
inhibitor of metalloproteinase 3 (Timp3 at 49 cM), insulin-like growth factor 1 (Igf1 at 48 cM), migration inhibitory factor (Mif at 41 cM), and the aire locus (Ref. 4 and R. Roper et al., manuscript in preparation). AIRE is a known autoimmune susceptibility gene in the human autoimmune polyendocrineopathy candidiasis ectodermal dystrophy (45). In addition, PTX™ females showed linkage to a QTL on chromosome 16, which colocalizes with eae11 seen in an F2 cross between these same parental strains (25).

The apparent female specificity of eae11 in the backcross for one of the SC traits is not the same as in the F2 cross, where only males displayed linkage markers in the eae11-defining region (D16 Mit110-D16 Mit140 at ~20–40 cM). This could be due to one of several reasons: the genetic environment for the F2 and backcross are different, and we would not expect all of the genetic effects to be replicated between the experiments. If so, a significant interaction in the F2 between eae11 and some other locus/loci (a combination not present in the BC1) could account for the difference. Alternatively, the larger population studied for the F2 provides more statistical power to detect any QTL, particularly one with small effects, and perhaps the effects of eae11 in the backcross males are not observed due to less power. These are not necessarily the same QTL, because the eae11 interval is quite broad.

In males from the PTX™ cross, the strongest QTL, located on distal chromosome 18, is associated with significant inflammation and demyelination in the SC. This QTL, eae18, resides in an interval that contains the melanocortin receptor (Mcr2 at 37 cM) and the myelin basic protein gene (Mbpr, at 55 cM). In an earlier report, Baker et al. (46) found an eae-m locus in this region in an (ABH × NOD)F1 × NOD backcross. It is noteworthy that B10.S and SJL/J are also the type strains for Theiler’s murine encephalomyelitis virus-mediated demyelination and loci that control viral persistence have been mapped on both chromosomes 10 and 18 in similar intervals to eae17 and eae18, respectively (47). The chromosome 18 QTL did not predict viral persistene in subsequent testing of congenic lines (48), although the myelin basic protein gene itself contributes to viral persistence in mice segregating for the shiverer mutation (49).

In summary, we have identified two new EAE-modifying loci, one of which is a new locus controlling the effects of PTX in EAE pathogenesis. The precise mechanism of action of this gene remains unknown, but presumably reflects an intermediate phenotype other than PTX-induced vascular permeability changes. The molecular characterization of this QTL will potentially aid in the understanding of environment–gene interactions in autoimmune disease.

Acknowledgments

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References


