Successful Induction of Adjuvant Arthritis in Mice by Treatment with a Monoclonal Antibody Against IL-4

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Adjuvant arthritis (AA) is an experimental model of autoimmune disease in rats induced by immunization with Mycobacterium tuberculosis (MT). Induction of AA in other species, including mice, has been shown to be difficult. In the present study, we found that AA could be induced in mice if the animals were treated with a mAb (11B11 mAb) against IL-4. Histologically, the joints exhibited synovial edema with infiltration of many neutrophils in the early phase of inflammation. In its late phase, there were proliferation of synovium, cell infiltrate in which mononuclear cells predominated, and destruction of cartilage and subchondral bone. The joint inflammation was passively transferred to normal syngeneic recipient mice with lymphoid cells but not with sera from mice immunized with MT followed by treatment with the anti-IL-4 Ab. Delayed-type hypersensitivity (DTH) and proliferative responses of lymphoid cells to purified protein derivative were markedly augmented in 11B11 mAb-treated mice. Furthermore, the induction of arthritis was associated with a marked decrease in IL-4 secretion but a significant increase in IFN-γ and IL-2 production. Thus, the neutralization of IL-4 by an anti-IL-4 Ab appears to be required for the induction of AA in mice. The Journal of Immunology, 1998, 161: 6904–6908.

A

approximately 40 years ago, Pearson found that a single intradermal injection into rats of heat-killed Mycobacterium tuberculosis (MT) in mineral oils induced arthritis that was known as adjuvant arthritis (AA) (1). Since then AA has been widely used as a model of human rheumatoid arthritis (RA) because this model of arthritis resembles RA in certain clinical and histological aspects (2). However, few studies succeeded in inducing AA in other species, including mice (3). Although the precise mechanism by which AA is induced still remains unclear, the disease has been shown to be mediated by cellular immune responses to MT. For instance, the disease can be passively transferred to naive recipient rats by lymph node and spleen cells from rats primed with MT (4, 5).

IL-4 was originally identified as a mediator that induced the proliferation of murine B lymphocytes (6). Cellular analysis revealed that the source of the cytokine was Th2 cells, a subset of CD4⁺ T cells (7). IL-4 was shown to be crucial in Th2 responses, including IgE Ab production (8). In contrast, the cytokine inhibits Th1 responses, including IFN-γ secretion and DTH (9, 10). More recently, it was demonstrated that the neutralization of IL-4 by Abs against IL-4 suppressed Th2 responses but augmented Th1 responses (11, 12).

The above results indicate that treatment with an anti-IL-4 Ab should increase Th1 responses to MT following immunization with the Ag that is important in the induction of AA in rats. In the present study, we show that mice immunized with MT followed by treatment with a mAb against IL-4 (11B11 mAb) (13) developed chronic erosive arthritis and that this arthritis was passively transferred to normal syngeneic mice with lymphoid cells from the arthritic animals. These findings suggest that AA could be induced in mice in which IL-4 is neutralized with an anti-IL-4 Ab.

Materials and Methods

Animals

Female DBA/1J mice, 8 to 9 wk of age, were used in all experiments. The mice were bred in the animal breeding unit of Saga Medical School, Saga, Japan. They were maintained in a temperature- and light-controlled environment with free access to standard rodent chow and water.

Induction of adjuvant arthritis (AA)

Mice were injected s.c. at the base of the tail with 50 μl of IFA (Difco Laboratories, Detroit, MI) containing 10 mg/ml of finely ground heat-killed M. tuberculosis (MT) (Difco Laboratories). To evaluate the severity of arthritis, the thickness of the right and left footpads was measured using a dial gauge caliper calibrated with 0.01 mm graduations (Oraki MFG, Tokyo, Japan) before and after induction of arthritis, and the mean of the increases in thickness of both footpads was calculated. The lesions of the four paws were also each graded from 0 to 3 as described elsewhere (14).

Treatment with a mAb against IL-4

The cell line of a rat IgG1 mAb that neutralizes murine IL-4 (11B11 mAb) was kindly provided by the Department of Immunology, Saga Medical School. 11B11 mAb was precipitated by ammonium sulfate from ascitic fluid of SCID mice inoculated with the cells and purified using a protein G Sepharose 4FF column (Pharmacia Biotech, Tokyo, Japan), dialyzed with PBS, and filtered. The preparation and characterization of 11B11 mAb have been described previously (13). Two milligrams of 11B11 mAb dissolved in 0.5 ml of PBS was injected i.p. once daily over a period of 10 days, commencing on the day of immunization with MT. As treatment controls, 0.5 ml of PBS only and 0.5 ml of PBS containing 2 mg of normal rat serum IgG purified as described above were given.

Histology

Mice were killed on days 4 and 30 after onset of arthritis. Hind paws were amputated, fixed in 4% formalin, and decalcified in a solution of 3.1% HCl, 5% formic acid, and 7% aluminum chloride. The tissues were embedded in paraffin, sectioned at 4 μm, and stained with hematoxylin and eosin.
Passive transfer of AA

For passive transfer of AA with lymphoid cells from mice treated with 11B11 mAb, the method of Taurog et al. (15) was used. Briefly, mice were immunized with MT followed by the treatment with 11B11 mAb as described above. Twelve days later, lymph nodes and spleens were removed, and single cell suspensions prepared from the lymphoid tissues were cultured in RPMI 1640 medium (Flow Laboratories, McLean, VA) with Con A (3 μg/2 × 10^5 cells/ml). RPMI contained 1 mM glutamine, 100 U/ml penicillin, 100 μg/ml streptomycin, 5 × 10^{-5} M 2-ME, and 1% heat-inactivated autologous mouse serum. After 2 days culture, the cells were washed twice, and 2 × 10^5 cells in 0.5 ml of PBS were injected i.v. into the tail of normal recipient mice. To examine whether arthritis is passively transferred with serum, 1 ml of serum from MT-immunized and 11B11 mAb-treated mice was injected i.v. into normal recipient animals.

DTH measurement

On day 12 after immunization with MT, 50 μl of 0.9% NaCl containing 50 μg/ml of purified protein derivative (PPD, Japan BCG, Tokyo, Japan) was injected s.c. into the right footpad. As a vehicle control, 50 μl of 0.9% NaCl alone was injected into the left footpad. The thickness of the right and left footpad was measured using a dial gauge caliper as described above, immediately before and 48 h after challenge injection. The increase in left thickness was subtracted from the increase in right footpad thickness to give the value due to the specific response to Ag. In unsensitized mice, responses to PPD and 0.9% NaCl were essentially equivalent.

Proliferation assay

Inguinal lymph nodes were removed on day 14 after immunization with MT, and single cell suspensions were prepared. A total of 5 × 10^6 cells in 100 μl of RPMI 1640 were added to each microwell followed by the addition of 100 μl of varying doses of PPD. The cells were cultured for 72 h. Each well was pulsed with 0.5 μCi of tritiated thymidine, and the cells were cultured for another 16 h. The cultures were then harvested onto fiberglass filters using a multiharvester and counted using standard liquid scintillation techniques. Results, expressed in cpm, are average of quadruplicate cultures of cells pooled from four mice.

Cytokine measurement

Single cell suspensions from inguinal lymph nodes were prepared as described above and resuspended at a final concentration of 5 × 10^6 cells/ml and cultured in 1-ml aliquots in 24-well tissue culture plates either in medium alone or with 20 μg/ml PPD. Supernatants were harvested after 48 h and stored at −70°C until assayed. Cytokine production was quantified using sandwich ELISA techniques (16). Briefly, 96-well microtiter plates were coated overnight at 4°C with 100 μl of 0.1% NaHCO 3 buffer containing Abs (4 μg/ml) against IL-2, IL-4, and IFN-γ (PharMingen, San Diego, CA). The plates were blocked by incubation with 100 μl of PBS containing 1% OVA at 37°C for 1 h. After blocking, the plates were washed three times, and samples or standards (recombinant murine IL-2, IL-4, and IFN-γ; PharMingen) were added to each well in a volume of 100 μl and incubated at 37°C for 1 h. The plates were washed three times, and 100 μl/well biotinylated anti-murine IL-2, IL-4, and IFN-γ (2 μg/ml) Abs (PharMingen) diluted in PBS/1% OVA was added. After incubation at 37°C for 1 h, the plates were washed three times, and 100 μl/well of streptavidin-alkaline phosphatase (PharMingen) was added at 2 μg/ml. The plates were washed before 100 μl of p-nitrophenylphosphate was added to each well. The plates were then read at 405 nm using an automatic microplate reader. Cytokine levels were determined with reference to a standard curve constructed using serial dilutions of the standard cytokines, and results are expressed in pg/ml.

Results

Induction of AA in mice treated with 11B11 mAb

None of 12 mice immunized with MT followed by treatment with either PBS or normal rat IgG developed arthritis at least up to day 120 (Table I). On the other hand, 2 of 12 mice (17%) treated once daily with 11B11 mAb over a period of 10 days, commencing on the day of immunization with MT, showed signs of arthritis on day 19. The incidences of arthritis in these animals on days 22, 25, and 28 (to 120) were 58, 75, and 83%, respectively. The joint inflammation reached a peak on day 28 and thereafter decreased gradually, as shown in Fig. 1, A and B. On day 40, ankylosis of the ankle joints was observed. The average number of limbs affected per mouse was 2.3. Treatment with 11B11 mAb by itself without immunization with MT induced no joint inflammation (data not shown).

Histologic changes in tarsal joints of mice with AA

Histologic changes in tarsal joints of mice with AA were examined. On 4 days after onset of arthritis, there was a marked edema of synovial tissues with infiltration of many inflammatory cells, including neutrophils (Fig. 2B), that was absent before onset of joint inflammation (Fig. 2A). On day 30, proliferation of synovium, cell infiltration in which mononuclear cells predominated, and destruction of cartilage and subchondral bone were observed (Fig. 2C).

Passive transfer of AA with lymphoid cells

Next, we investigated whether AA was passively transferred to normal recipient mice with lymphoid cells from mice with the disease. When normal recipients were injected i.v. with spleen and

<table>
<thead>
<tr>
<th>Days After Immunization</th>
<th>PBS</th>
<th>11B11</th>
<th>Rat IgG</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>0/12 (0)*</td>
<td>0/12 (0)</td>
<td>0/12 (0)</td>
</tr>
<tr>
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<td>22</td>
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<td>0/12 (0)</td>
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<tr>
<td>25</td>
<td>0/12 (0)</td>
<td>9/12 (75)</td>
<td>0/12 (0)</td>
</tr>
<tr>
<td>28</td>
<td>0/12 (0)</td>
<td>10/12 (83)</td>
<td>0/12 (0)</td>
</tr>
<tr>
<td>32</td>
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</tr>
<tr>
<td>120</td>
<td>0/12 (0)</td>
<td>10/12 (83)</td>
<td>0/12 (0)</td>
</tr>
</tbody>
</table>

* Mice were immunized s.c. with MT at the base of the tail on day 0. Two milligrams of 11B11 mAb was injected i.p. once daily from day 0 to day 10. PBS and 2 mg of normal rat IgG were injected as controls. The incidence of arthritis was examined on the days indicated above. * Percentage of incidence in parentheses. Data are representative of three experiments.

FIGURE 1. Treatment with 11B11 mAb induces AA in mice. Mice were immunized with MT at the base of the tail on day 0. Two milligrams of 11B11 mAb was injected i.p. once daily from day 0 to day 10. PBS and 2 mg of normal rat IgG were given as controls. The severity of arthritis was determined by measuring footpad swelling (A) as well as by giving joint scores (B) on days 16, 18, 19, 22, 25, 28, 32, 36, and 40. Closed circle, 11B11 mAb. Open circle, PBS. Open triangle, normal rat IgG. Vertical bars show SEM of 10 mice with arthritis. Data are representative of three experiments.
lymph node cells from mice immunized with MT followed by treatment with 11B11 mAb, 7 of 8 mice (88%) showed signs of arthritis on day 6 after the injection, and the joint inflammation reached a peak on day 10 (Fig. 3). The average number of limbs affected per mouse was 1.8. Injection into normal recipient mice of lymphoid cells from mice immunized with MT and treated with PBS failed to induce arthritis throughout the experiment. No joint inflammation was observed in recipient mice injected i.v. with sera from mice immunized with MT and treated with the anti-IL-4 mAb.

Footpad DTH reactions to PPD

DTH reactions to PPD were measured to learn whether treatment with 11B11 mAb affected this type of Th1 responses. As shown in Fig. 4, mice treated with the anti-IL-4 mAb showed significantly increased DTH responses to PPD in the footpad, compared with those injected with either PBS or normal rat IgG.

Proliferative responses to PPD

To examine whether proliferative responses to PPD are modulated by treatment with 11B11 mAb, lymph node cells from mice immunized with MT and injected with the anti-IL-4 Ab were cultured with PPD. As shown in Table II, the proliferation to PPD of lymphoid cells from 11B11 mAb-treated mice was much greater than that from PBS- or rat IgG-treated animals.

Secretion of cytokines in mice treated with 11B11 mAb

The effects of 11B11 mAb on secretion of the Th2 cytokine IL-4 and the Th1 cytokines IFN-γ and IL-2 were examined. The results showed that secretion of IL-4 by lymph node cells in mice treated with 11B11 mAb was markedly reduced compared with that in those treated with PBS or rat IgG (Table III). In contrast, there was greater production of IFN-γ and IL-2 in mice treated with the anti-IL-4 Ab than in those injected with PBS or rat IgG.

Induction of AA in other strains of mice treated with 11B11 mAb

To investigate whether other strains of mice also develop arthritis following treatment with 11B11 mAb, BALB/c and C57BL/6 mice were used. As shown in Table IV, both strains of mice treated with the mAb but not with PBS developed arthritis. The incidence and the severity of joint inflammation were similar to those in DBA/1J mice.

FIGURE 2. Histologic changes in tarsal joints of mice with AA. Tarsal joints of mice were histologically examined before onset (A) and day 4 (B) and day 30 (C) after onset of AA. Hematoxylin and eosin stained, ×200. Scale bar = 100 μm.

FIGURE 3. Passive transfer of AA with lymphoid cells from mice treated with 11B11 mAb. Mice were immunized with MT at the base of the tail on day 0. Two milligrams of 11B11 mAb was injected i.p. once daily from day 0 to day 10 (11B11). PBS was given as a control (PBS). On day 12, 2 × 10⁸ lymphoid cells from the 11B11 mAb- or PBS-treated animals were prepared as described in Materials and Methods and injected i.v. into the tail of normal recipient mice (Lymphoid cells). One milliliter of serum from 11B11 mAb-treated mice was also given to recipient animals (Serum). Closed circle, 11B11/Lymphoid cells. Open circle, PBS/Lymphoid cells. Open triangle, 11B11/Serum. Vertical bars show SEM of seven mice. Data are representative of two experiments.

FIGURE 4. Treatment with 11B11 mAb augments footpad DTH responses to PPD. Mice were immunized s.c. with MT at the base of the tail on day 0. Two milligrams of 11B11 mAb was injected i.p. once daily from day 0 to day 10. PBS and 2 mg of normal rat IgG were injected as controls. On day 12 after immunization, footpad DTH responses to PPD were measured as described in Materials and Methods. Horizontal bars show SEM of 8 mice. *, p < 0.05 vs PBS-treated mice, by Student’s t test. Data are representative of two experiments.
Discussion

The present study demonstrates that immunization with MT induced AA in mice treated daily with an anti-IL-4 mAb (11B11 mAb) over a period of 10 days from the time of immunization. Treatment with 11B11 mAb alone or immunization with MT followed by treatment with either PBS or normal rat IgG failed to induce arthritis. Therefore, the neutralization of IL-4 with the anti-IL-4 mAb appeared to be required for the induction of AA in mice. Pearson (1) and Glenn et al. (3) previously showed that a single intradermal injection of MT without additional treatment induced AA in rats, but not in other species of animals including mice. However, in those studies, there were no attempts to induce AA in mice by treating them with an anti-IL-4 Ab.

Some histologic features of AA in mice resembled those in rats. They include marked edema of synovial tissues with infiltration of many inflammatory cells, including polymorphonuclear cells in the early phase of joint inflammation. In the chronic inflammatory phase, synovial hyperplasia and destruction of cartilage and bone were observed. However, AA in mice was obviously different in its severity from that in rats. In the rat AA, markedly pronounced proliferation of synovium that often leads to granuloma formation and almost complete destruction of cartilage and bone were observed (17–20), while such severely inflamed joint inflammation was not seen in the mouse AA. Furthermore, in the rats, inflamatory lesions are not restricted to the joints but spread throughout the body (17, 18). For instance, ears and tails are also often inflamed in rats with AA, while these appeared to be intact in mice with AA.

AA in mice was passively transferred to normal syngeneic recipient animals with lymph node and spleen cells from mice immunized with MT and treated with 11B11 mAb, suggesting that cellular immune responses appear to be involved in the progression of the joint disease. The role of T cells in AA in rats was also previously demonstrated by the experiment of the successful passive transfer of arthritis to normal recipients with MT-immunized lymphoid cells (4, 5). The direct role of humoral responses in the progression of AA in mice appears to be unlikely since the attempt to transfer AA to normal syngeneic animals with sera from MT-immunized and 11B11 mAb-treated mice was unsuccessful. Similarly, it was previously shown that normal recipient rats injected with sera from MT-immunized rats developed no joint inflammation (21).

As mentioned above, induction of AA in mice has been shown to be difficult. However, there is one report by Knight et al. demonstrating that BALB/c, SJL, CBA/C, or C57BL/10 mice developed arthritis approximately 2 mo after injection of CFA containing MT, although they did not show whether the joint inflammation was passively transferred with T cells from the arthritic animals (22). Since AA in rats normally develops 10 to 15 days after immunization with MT, they concluded that the lack of success in the induction of AA in mice shown previously by Pearson (1) and Glenn et al. (3) was due to the failure to wait for longer time periods following immunization with MT and that the induction of AA was not restricted to rats. In our studies, immunization with MT itself induced no arthritis in DBA/1J mice up to 120 days after the immunization. The neutralization of IL-4 with the anti-IL-4 Ab was required for the induction of AA in the animals. In addition, mice immunized with MT followed by treatment with 11B11 mAb showed signs of arthritis on day 19, and the joint inflammation reached a peak on day 28. Furthermore, the present study, as well as the studies by Knight et al. (22) showing the induction of AA in different strains of mice, suggests that the MHC restriction to AA susceptibility appears to be broad. AA in the rat was also shown to be induced in the different strains (23).

The precise mechanism by which AA developed in mice following treatment with 11B11 mAb remains unclear at present. However, IL-4 is known to play a role in Th2 responses, including IgE production, while the cytokine inhibits Th1 responses, including IFN-γ secretion and DTH (8–10). Conversely, IFN-γ enhances Th1 responses but suppresses Th2 responses (24, 25). An anti-IL-4 Ab has been shown to inhibit Th2 responses (11, 12) while the Abs augment Th1 responses that play a critical role in DTH (26, 27). In our experiments, treatment with 11B11 mAb also inhibited IL-4 secretion while the mAb enhanced IFN-γ production and footpad DTH to PPD. Secretion of IL-2 and proliferative responses to PPD were also increased by the anti-IL-4 mAb treatment. These results appear to indicate that the neutralization of IL-4 by 11B11 mAb resulted in a marked increase in Th1 responses to MT that was important in the induction of AA. Therefore, AA in mice may be due to the shift toward Th1 responses to MT following the anti-IL-4 mAb treatment.

Table II. Proliferative responses to PPD in mice treated with 11B11 mAb (cpm)*

<table>
<thead>
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<th>Treatment</th>
<th>2</th>
<th>10</th>
<th>50</th>
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</thead>
<tbody>
<tr>
<td>PBS</td>
<td>12,890 ± 1,644</td>
<td>28,396 ± 3,054</td>
<td>36,286 ± 3,086</td>
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<tr>
<td>11B11</td>
<td>38,252 ± 4,452</td>
<td>71,063 ± 6,237</td>
<td>89,257 ± 6,755</td>
</tr>
<tr>
<td>Rat IgG</td>
<td>14,216 ± 1,633</td>
<td>24,860 ± 2,118</td>
<td>38,280 ± 2,364</td>
</tr>
</tbody>
</table>

* Mice were immunized s.c. with MT at the base of the tail on day 0. Two milligrams of 11B11 mAb was injected i.p. once daily from day 0 to day 10. PBS and 2 mg of normal rat IgG were injected as controls. On day 14 after immunization, proliferative responses to PPD of lymphoid cells were measured as described in Materials and Methods. The background counts of the cell proliferation without PPD were between 1500 and 2500 cpm. Values are the mean ± SEM of quadruplicate cultures of cells pooled from four mice. Data are representative of three experiments.

Table III. Secretion of cytokines in mice treated with 11B11 mAb*

<table>
<thead>
<tr>
<th>Cytokine (pg/ml)</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IL-4</td>
</tr>
<tr>
<td>PBS</td>
<td>364 ± 28</td>
</tr>
<tr>
<td>11B11</td>
<td>26 ± 3</td>
</tr>
<tr>
<td>Rat IgG</td>
<td>402 ± 56</td>
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</table>

* Mice were immunized s.c. with MT at the base of the tail on day 0. Two milligrams of 11B11 mAb was injected i.p. once daily from day 0 to day 10. PBS and 2 mg of normal rat IgG were injected as controls. On day 14 after immunization, lymph nodes were removed, and the secretion of IL-4, IFN-γ, and IL-2 from the lymphoid cells were examined by sandwich ELISA as described in Materials and Methods. Values are the mean ± SEM of quadruplicate samples from culture supernatants of cells pooled from four mice. Data are representative of three experiments.

Table IV. Effects of 11B11 mAb on the incidence and the severity of AA in different strains of mice*

<table>
<thead>
<tr>
<th>Strain</th>
<th>Treatment</th>
<th>Incidence</th>
<th>Mean Joint Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>DBA/1J</td>
<td>PBS</td>
<td>0/12 (0)*</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>11B11</td>
<td>9/12 (75)</td>
<td>4.9 ± 1.16†</td>
</tr>
<tr>
<td>BALB/c</td>
<td>PBS</td>
<td>0/12 (0)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>11B11</td>
<td>10/12 (83)</td>
<td>5.6 ± 1.42</td>
</tr>
<tr>
<td>C57BL/6</td>
<td>PBS</td>
<td>0/12 (0)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>11B11</td>
<td>8/12 (67)</td>
<td>4.3 ± 1.27</td>
</tr>
</tbody>
</table>

* The indicated strains of mice were immunized with MT at the base of the tail on day 0. Two milligrams of 11B11 mAb was injected i.p. once daily from day 0 to day 10. PBS was given as a control. The incidence and the severity of arthritis was determined on day 30. † Percentage of incidence in parentheses. ‡ Mean ± SEM of mice with arthritis. Data are representative of two experiments.
Although the etiology of human RA is still obscure, it was previously shown that patients with RA had elevated serum levels of antitymococcal Abs (28, 29). There were also studies demonstrating that T cells from RA patients responded to an MT Ag fraction (30, 31) that contained an epitope recognized by rat arthritisogenic T cell clones (32). Although these results suggest that immune responses to MT may at least in part contribute to the progression of RA, it appears to be unlikely that mycobacterial Ags are directly involved in the pathogenesis of the disease. For instance, it is not common that patients recovered from tuberculosis develop chronic erosive joint inflammation as seen in RA, although it was previously reported that 0.5 to 1% of patients with bladder cancer treated with bacille Calmette-Guérin (BCG) developed arthritis that was resolved spontaneously within 14 days (33, 34). Thus, humans appear to be resistant rather than susceptible to the development of chronic arthritis following sensitization with mycobacteria. However, it may not be denied that a shift toward Th1 responses to MT might lead to the development of arthritis in humans, as seen in mice. It is of note that RA has been shown to be a Th1-dominant disease since there is a significant increase in humans, as seen in mice. It is of note that RA has been shown to

References