Dual Role of Interleukin-10 in Murine Lyme Disease:
Regulation of Arthritis Severity and Host Defense

JEANETTE P. BROWN, JAMES F. ZACHARY, CORY TEUSCHER, JANIS J. WEIS, AND R. MARK WOOTEN*

Division of Cell Biology and Immunology, Department of Pathology, University of Utah School of Medicine, Salt Lake City, Utah 84132, and Department of Veterinary Pathobiology, University of Illinois at Urbana-Champaign, Urbana, Illinois 61802

Received 6 May 1999/Returned for modification 30 June 1999/Accepted 13 July 1999

In the murine model of Lyme disease, C3H/He mice exhibit severe arthritis while C57BL/6N mice exhibit mild lesions when infected with *Borrelia burgdorferi*. Joint tissues from these two strains of mice harbor similar concentrations of *B. burgdorferi*, suggesting that the difference in disease severity reflects differences in the magnitude of the inflammatory response to *B. burgdorferi* lipoproteins. Stimulation of bone marrow macrophages from C3H/HeN mice with the *B. burgdorferi* lipoprotein OspA resulted in high-level production of the inflammatory mediators tumor necrosis factor alpha, nitric oxide, and interleukin-6 (IL-6) than that of macrophages from C57BL/6N mice. In contrast, macrophages from C57BL/6N mice consistently produced larger amounts of the anti-inflammatory cytokine IL-10 than did C3H/HeN macrophages. Addition of recombinant IL-10 suppressed the production of inflammatory mediators by macrophages from both strains. IL-10 was found to modulate *B. burgdorferi*-induced inflammation in vivo, since C57BL/6J mice deficient in IL-10 (IL-10<sup>−/−</sup>) developed more severe arthritis than wild-type C57BL/6J mice. The increase in arthritis severity was associated with a 10-fold decrease in the number of *B. burgdorferi* organisms present in ankle tissues from IL-10<sup>−/−</sup> mice. These findings suggest that in C57BL/6 mice, IL-10-dependent regulation of arthritis severity occurs at the expense of effective control of bacterial numbers.

Lyme disease is a multisystem disorder caused by infection with *Borrelia burgdorferi* (11, 28, 49). The spirochetes are transmitted to a mammalian host via the bite of an infected *Ixodes* tick and subsequently disseminate from the site of inoculation. In the absence of antibiotic therapy, *B. burgdorferi* can infect multiple tissues, but it appears to have some predilection for joints, skin, and heart tissue (48, 49, 62). Lyme arthritis is distinct from other types of arthritis in that a bacterial presence appears to be necessary to elicit lesions and in that arthritis is not dependent on T or B lymphocytes (6, 9, 48, 57, 58, 62, 74). This subacute arthritis appears to be caused by the host inflammatory response to invasion of joints by the spirochete and is characterized by edema, synovial thickening, tendonitis, and a leukocytic infiltration consisting mainly of neutrophils and mononuclear cells (4).

*B. burgdorferi* produces a number of outer membrane lipoproteins which possess potent inflammatory potential and are believed to be responsible for the inherent inflammatory properties attributed to this spirochete (15, 40, 56, 58). These lipoproteins are capable of activating a wide variety of cell types, including macrophages (38, 40, 55, 56, 63), neutrophils (45), and endothelial cells (13, 18, 59, 70), which results in the production of a broad spectrum of pro- and anti-inflammatory mediators that have been linked to inflammatory disease. The receptor responsible for mediating lipoprotein signaling is distinct from that for lipopolysaccharide (LPS)-mediated signaling (40, 50); however, the stimulatory properties of these lipoproteins are potentiated by CD14 (23, 60, 71), the coreceptor for LPS (64, 72), suggesting that these lipoproteins might be directed to receptors on responsive cell types. These and other findings suggest that host responses to these lipoproteins are directly responsible for creating distinctive inflammatory lesions of Lyme disease (25, 51).

The lesions exhibited by *B. burgdorferi*-infected mice are similar to those seen in human disease, making the mouse an excellent model system for studying Lyme disease (4). Infection of different inbred mouse strains with *B. burgdorferi* can result in different but distinct disease outcomes, similar to the variability seen in the human population (5, 37, 49, 74). Infection with a range of inoculum doses of *B. burgdorferi* elicits severe arthritis in C3H/HeN mice but mild to moderate arthritis in C57BL/6N mice at all spirochete concentrations tested (37). When *B. burgdorferi* levels in ankles are quantified by PCR, the two mouse strains possess similar numbers of spirochetes, regardless of the concentration of the infectious dose and the disease severity displayed. One interpretation of these findings is that C57BL/6N mice are better able to regulate inflammation in response to *B. burgdorferi* lipoproteins than C3H/HeN mice, resulting in a less intense inflammatory response and decreased arthritis severity. In the present study, we tested this hypothesis by stimulating macrophages from C3H/HeN and C57BL/6N mice with a prototypic *B. burgdorferi* lipoprotein, OspA, and comparing the levels and scopes of inflammatory mediators produced. Differences in the balance of pro- and anti-inflammatory mediators produced by macrophage cultures from the two mouse strains were observed. The role of one cytokine, interleukin-10 (IL-10), that showed regulatory effects in vitro was assessed by infecting IL-10-deficient (IL-10<sup>−/−</sup>) mice with *B. burgdorferi*. The effect of this gene on disease severity is reported.

**MATERIALS AND METHODS**

**Mice.** Female C3H/HeNCr and C57BL/6NCr mice were obtained from the National Cancer Institute, and female C57BL/6J and C57BL/6-IL-10<sup>−/−</sup>Cr mice were...
was used in all infection studies (5). Passage 4 cultures were stored at 2
passage 3 from the mouse by Steve Barthold (University of California at Davis), laboratory animals.

cording to National Institutes of Health guidelines for the care and use of
in the Animal Resource Center at the University of Utah Medical Center ac-
targeted mutation (34) and backcrossed into C57BL/6J mice. Mice were housed
Purified murine IgG, IgM, and polyclonal HRP-conjugated antibodies specific
IgG2a, IgG2b, and IgG3 were purchased from Zymed (San Francisco, Calif.).
Pharmingen (San Diego, Calif.). Polyclonal goat anti-mouse immunoglobulin
a
rine tumor necrosis factor alpha (TNF-
medium supplemented with L929-conditioned medium for 7 days at 37°C. Mac-
previously described (38). Briefly, bone marrow cells were cultured in RPMI
B. burgdorferi
was a gift from Robert Huebner (Connaught Laboratories, Swiftwa-
burgdorferi
injection. Lipidated recombinant OspA (rOspA) from the B31 strain of
rabbit serum (Sigma Chemical, St. Louis, Mo.) for 3 to 5 days at 32°C prior to
These frozen stocks were subsequently grown in BSK-H medium containing 6%
tissues were harvested from experimental animals sacrificed at 4 weeks postin-
Scores for individual lesions were incorporated into the overall lesion scores
to 5, with 5 representing the most severe lesion and 0 indicating normal tissue.
Histologic analyses were performed on the
the rear ankle joints by the use of a metric caliper. Weekly measurements were
described previously (73) and provided a method of following the course of
DNA preparation.
PCR. Mock-infected animals received 20
B. burgdorferi
DNA in tissues as determined by
PCR. Amplification was performed on 200 ng of sample DNA in a 10-
Idaho Technology, Idaho Falls, Idaho) as previously described (44). Briefly,
aplication was performed on 200 ng of sample DNA in a 10-μl final volume
limiting the cycle-by-cycle accumulation of fluorescently labeled product. The
Statistical analysis. The degrees of statistical significance of the quantitative
differences between sample groups were determined by application of Student's
t test.
RESULTS
Differential production of inflammatory mediators by macro-
phages from C3H/HeN and C57BL/6N mice. Previous studies have shown that C3H (both C3H/HeN and C3H/HeJ) and C57BL/6 mice exhibit different degrees of arthritis severity when infected with equivalent doses of B. burgdorferi and yet their affected tissues contain similar numbers of spirochetes (37). This finding suggests that the differences in arthritis severity between the two mouse strains are related to differences in the intensity of the inflammatory response to B. burgdorferi and its lipoproteins. To address this issue, bone marrow macrophages from C3H/HeN and C57BL/6N mice were cultured in the presence of the B. burgdorferi lipoprotein OspA and supernatants were assayed for the presence of representative inflammatory mediators. Macrophages from C3H/HeN mice were found to produce substantial amounts of IL-6 in response to Ospa, with maximum production elicited in response to 50 to 500 ng of lipoprotein/ml (Fig. 1). Macrophages from C57BL/6N mice secreted significantly less IL-6 in response to Ospa than macrophages from C3H/HeN mice. Similar differences in IL-6 production were seen with macrophages cultured in the presence of LPS, indicating that this distinction is not lipoprotein specific.
Other inflammatory mediators were also produced at higher levels by macrophages from C3H/HeN mice than by macrophages from C57BL/6N mice. C3H/HeN macrophages produced 2- to 10-fold-higher levels of nitric oxide and TNF-α than C57BL/6N mice (Fig. 1). This bias was not specific for lipoproteins, since both nitric oxide and TNF-α levels elicited in response to LPS were also higher in macrophage cultures
obtained from The Jackson Laboratory (Bar Harbor, Maine). The C57BL/6-IL-
lg+/- (mice (10^6-10^7) contain an IL-10 gene that has been inactivated by targeted mutation (34) and backcrossed into C57BL/6J mice. Mice were housed in the animal facility located at the University of Utah Medical Center ac-
according to National Institutes of Health guidelines for the care and use of
Bacteria and lipoproteins. The N40 isolate of B. burgdorferi, provided at
was manufactured by the Urban Animal Center at the University of Utah Medical Center ac-
cording to National Institutes of Health guidelines for the care and use of
laboratory animals.
from C3H/HeN mice than in those from C57BL/6N mice. This disparity was not related to differences in sensitivity to the agonist concentration, since the two macrophage populations responded to similar concentrations of OspA and LPS. Additionally, these differences were not due to production of higher baseline levels of inflammatory mediators by C3H/HeN macrophages, since the two cell types secrete similar quantities of mediators in the absence of an agonist.

Diminished levels or the absence of anti-inflammatory cytokines such as IL-10 has been linked to increased severity of inflammatory disease (32, 36). Analysis of culture supernatants indicated that macrophages from C57BL/6N mice produced up to 10-fold-higher amounts of IL-10 than did macrophages from C3H/HeN mice (Fig. 2); this finding is the opposite of the trend seen with secretion of proinflammatory mediators. These differences were also not lipoprotein specific, since IL-10 levels produced in response to LPS were much higher in macrophage culture supernatants from C57BL/6N mice than in those from C3H/HeN mice. Collectively, the C57BL/6N macrophage cultures that produced small quantities of inflammatory mediators did produce high levels of IL-10 (Fig. 1 and 2 and data not shown), demonstrating that the diminished production of inflammatory mediators was not due to decreased fitness of the C57BL/6N cultures. These data indicate that in response to the B. burgdorferi lipoprotein OspA, macrophages from C3H/HeN mice produce substantially higher levels of inflammatory mediators and smaller amounts of an anti-inflammatory cytokine than macrophages from C57BL/6N mice.

**Exogenous IL-10 reduces the levels of inflammatory mediators produced in response to OspA.** Previous studies have shown that IL-10 can downregulate a wide range of inflammatory mediators produced by macrophages in response to LPS (43). To determine if IL-10 can also suppress the levels of inflammatory mediators produced in response to B. burgdorferi lipoproteins, macrophages from both C3H/HeN and C57BL/6N mice were cultured in the presence of OspA and increasing amounts of rIL-10. In the absence of exogenous IL-10, macrophages from C3H/HeN mice produced two- to threefold more IL-6 than did macrophages from C57BL/6N mice (Fig. 1 and 3). The addition of rIL-10 resulted in a >90% decrease in

![Graphs showing production of inflammatory mediators by macrophages in response to OspA.](http://iai.asm.org/)

**FIG. 1.** Production of inflammatory mediators by macrophages in response to OspA. Bone marrow-derived macrophages from C3H/HeN (circles) and C57BL/6N (squares) mice were stimulated with the indicated doses of OspA or LPS. Supernatants were assayed by ELISA (TNF-α and IL-6) or Griess assay (nitric oxide) at 6 h (TNF-α) or 24 h (nitric oxide and IL-6) after stimulation. Results for nitric oxide reflect supernatants in which agonists were added in the presence of 2 U of gamma interferon/ml. Data points represent duplicate samples, and results are representative of six experiments.
IL-10 REGULATION OF MURINE LYME DISEASE

The higher levels of IL-10 production by macrophages from C3H/HeN mice to drop to levels similar to those produced by C57BL/6N macrophages in response to OspA or LPS in vitro (data not shown). Infected wild-type C57BL/6J displayed mostly mild to moderate arthritis, with one animal displaying severe arthritis (see Fig. 5). Infection was confirmed by culturing the tissue from an ear from each animal at the time of sacrifice: all ear cultures of infected animals produced viable B. burgdorferi after 2 weeks in culture (data not shown). Disease progression was monitored by weekly measurement of rear ankle joints. C3H/HeN mice showed greatly increased ankle swelling within 2 weeks and maximum swelling at 3 to 4 weeks postinfection (Fig. 4). C57BL/6J mice displayed little ankle swelling after infection with B. burgdorferi, consistent with previous reports (37). IL-10−/− C57BL/6J mice showed greater ankle swelling as early as 2 weeks postinfection and maximum swelling at 3 to 4 weeks. Ankle swelling for the infected IL-10−/− mice was not as pronounced as that in C3H/HeN mice but was significantly greater than that of the wild-type C57BL/6J mice (P < 0.01). These findings indicate that in the absence of IL-10, B. burgdorferi-infected C57BL/6J mice display increased ankle swelling.

To further assess the effect of IL-10 on arthritis development, one ankle joint from each animal was sectioned and evaluated histopathologically. When the overall lesion scores of the different mouse strains were compared, infected C3H/HeN mice were found to have significantly more lesions than infected C57BL/6J mice (Fig. 5), similar to previous findings with the C57BL/6N strain (37). Again, the arthritis phenotype in the C57BL/6J strain was more variable than previously identified for the C57BL/6N strain (37). IL-10−/− C57BL/6J mice were also significantly lower than those of C3H/HeN ankles (P < 0.01) but were substantially higher than those of wild-type C57BL/6J mice (P = 0.08). When the individual traits that make up the overall lesion scores were compared, no single lesion trait appeared to be linked to the absence of IL-10, but all were somewhat increased. These findings indicate that genetic ablation of IL-10 results in more overall inflammatory lesions; however, the absence of IL-10 alone is not enough to produce arthritis of severity equivalent to that exhibited by infected C3H/HeN mice.

IL-10 deficiency results in decreased numbers of B. burgdorferi in tissues. It has been previously shown that C3H/HeN and C57BL/6N mice exhibit very different levels of arthritis severity when infected with B. burgdorferi yet have quite similar numbers of bacteria in their joint tissues (37). To determine if IL-10 deficiency has any effect on bacterial persistence, DNA from various infected mouse tissues was purified and the numbers of B. burgdorferi organisms present were determined by continuous monitoring of quantitative PCR (46). This technique has been previously shown to allow comparison of various tissues and mouse strains and is based on normalization to the single-copy-number mouse nidogen gene. Ankle tissues from C3H/HeN mice taken 4 weeks postinfection were found to contain an average of 14 B. burgdorferi recA molecules per 1,000 mouse nidogen gene copies (Fig. 6). These numbers were similar to those found in ankles of infected C57BL/6J mice and confirm the trend observed in previous studies using C57BL/6N mice (37). Interestingly, when ankle tissues from infected IL-10−/− mice were examined, every animal contained small numbers of
B. burgdorferi organisms, and the average spirochete numbers were 10-fold lower than that of the wild-type C57BL/6J mice. Also, there was much less variance in B. burgdorferi numbers among infected IL-10−/− mice, with the highest values still being lower than the lowest values of the other mouse strains. When ear tissues were assessed for spirochete numbers, infected C3H ears contained twofold more B. burgdorferi organisms than did ears from C57BL/6J mice (P < 0.05) (Fig. 6). Infected IL-10−/− mouse ear tissues showed a further threefold decrease in B. burgdorferi numbers from that of their wild-type partners (P < 0.05), although the ranges were overlapping. Hearts from infected C3H/HeN mice contained fivefold more B. burgdorferi than did hearts from C57BL/6J (Fig. 6), also consistent with results of previous studies using C57BL/6N mice (37). There was little further decrease in spirochete numbers in IL-10−/− mouse hearts from the already-low levels in wild-type C57BL/6J mice. All tissues isolated from uninfected controls of all three mouse strains contained no detectable B. burgdorferi DNA (data not shown). These findings document that in the absence of IL-10, infected animals

FIG. 3. Effects of exogenous IL-10 on production of inflammatory mediators in response to OspA. Bone marrow-derived macrophages from C3H/HeN and C57BL/6N mice were stimulated with the indicated doses of OspA in the presence of different concentrations of exogenous IL-10. Supernatants were assayed by ELISA at 6 h (TNF-α) or 24 h (IL-6) after stimulation. Data points represent duplicate samples, and results are representative of four experiments.

FIG. 4. Ankle swelling in different mouse strains infected with B. burgdorferi. The indicated mouse strains were infected by intradermal injection of 2,000 B. burgdorferi organisms, and ankles were measured weekly as described in Materials and Methods. Data points represent the averages and standard deviations of values for eight infected animals, and results are representative of two separate experiments. Mock-infected animals showed no increase in ankle swelling at any time point (data not shown).

FIG. 5. Lesion scores of joints from mice infected with B. burgdorferi. The indicated mouse strains were infected by intradermal injection of 2,000 B. burgdorferi organisms, and rear ankle joints were assessed for lesions. Each open circle represents the overall lesion score for an individual animal, and each black bar indicates the average score for the eight mice in a group. Uninfected controls exhibited normal histology (data not shown). These results are representative of two separate experiments.
are better able to control spirochete numbers in ankle and ear tissues.

Absence of IL-10 results in increased antibody production. One mechanism by which IL-10−/− animals might better control bacterial infection would be through increased production of B. burgdorferi-specific antibodies. When B. burgdorferi-specific antibodies from the serum of infected mice were assessed, C3H/HeN mice were found to possess twofold more antibodies than C57BL/6J mice (Fig. 7). Serum from infected IL-10−/− mice contained larger amounts of B. burgdorferi-specific IgG3 and, especially, IgG2b than serum from the other mouse strains. (We were unable to assess IgG2a levels in IL-10−/− or wild-type C57BL/6 mice because they lack the gene for IgG2a and instead express the novel IgG2c isotype [30, 41, 42]. Commercially available anti-IgG2a sera do not consistently cross-react with IgG2c, and reagents specific for IgG2c are unavailable at this time.) These results indicate that infected animals produce larger quantities of B. burgdorferi-specific Ig in the absence of IL-10 and that this increase is not isotype specific.

C3H/HeN mice were also higher than or similar to those in C57BL/6J serum. Serum from infected IL-10−/− mice contained larger amounts of B. burgdorferi-specific IgG3 and, especially, IgG2b than serum from the other mouse strains. (We were unable to assess IgG2a levels in IL-10−/− or wild-type C57BL/6 mice because they lack the gene for IgG2a and instead express the novel IgG2c isotype [30, 41, 42]. Commercially available anti-IgG2a sera do not consistently cross-react with IgG2c, and reagents specific for IgG2c are unavailable at this time.) These results indicate that infected animals produce larger quantities of B. burgdorferi-specific Ig in the absence of IL-10 and that this increase is not isotype specific.

**DISCUSSION**

The murine model of Lyme disease has proven beneficial in the elucidation of host factors responsible for the development of Lyme arthritis (58). Such studies have indicated that susceptibility to severe subacute arthritis is not linked to genes involved in mediating the acquired immune responses but is more likely due to differences in the inflammatory responses of these strains (1, 6, 31, 68). B. burgdorferi membrane lipoproteins directly activate a number of inflammatory cell types, and differential induction of inflammatory and anti-inflammatory molecules could modulate inflammatory arthritis. In this study, we found that the anti-inflammatory cytokine IL-10 has a ma-

**TABLE 1. Titers of different B. burgdorferi-specific IgG subclasses in sera from infected mice**

<table>
<thead>
<tr>
<th>Mouse strain</th>
<th>IgG subclass titer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IgG1</td>
</tr>
<tr>
<td>C3H/HeN</td>
<td>3,200</td>
</tr>
<tr>
<td>IL-10−/−</td>
<td>3,200</td>
</tr>
<tr>
<td>C57BL/6J</td>
<td>800</td>
</tr>
</tbody>
</table>

*The indicated mouse strains were infected as described in Materials and Methods. Serum was collected 4 weeks postinfection, and B. burgdorferi-specific IgG subclasses were assessed by ELISA. Numbers represent the inverse values for the lowest serum dilutions that produced an optical density of ≥0.1 and reflect the average values for eight infected animals. Values for serum from mock-infected animals at a 1:100 dilution were <0.1 (data not shown). These results are representative of two separate experiments.*
The addition of physiologic amounts of IL-10 to macrophage cultures suppresses the production of OspA-induced TNF, nitric oxide, and IL-6 (Fig. 3). These results suggest the following mechanism for the regulatory influence of IL-10 on arthritis development in B. burgdorferi-infected mice: IL-10 serves to depress the intensity of the inflammatory response to B. burgdorferi lipoproteins that are expressed in vivo. This process results in less-intense inflammatory responses in C57BL/6 mice, since their cells appear to innately produce more IL-10 than those of C3H/HeN mice. The removal of IL-10 from C57BL/63 mice by genetic ablation interrupts the regulation of inflammation and results in an increase in arthritis severity.

A striking finding from this study was that infected IL-10⁻/⁻ mice, which displayed larger ankle lesions, contained 10- and 3-fold-fewer spirochetes in ankle and ear tissues, respectively than infected C57BL/6J mice. This was surprising, since previous studies of arthritis-resistant BALB/c mice demonstrated that arthritis resistance could be overcome by a high inoculum dose and that this dose was associated with an increase in the number of spirochetes in ankle tissues (37). Similarly, Pennington et al. showed that a serotype of Borrelia turicatae that caused severe arthritis was present at sevenfold-higher levels in affected tissues than a serotype that caused less-severe disease (53). In this study, the increase in arthritis severity in IL-10⁻/⁻ mice was correlated with decreased numbers of B. burgdorferi spirochetes in ankle tissues. These results indicate that IL-10-dependent regulation of the inflammatory response coordinately reduces the effectiveness of the host defense against B. burgdorferi. Whether the reduction in B. burgdorferi numbers is mediated at the level of inhibiting spirochete dissemination to affected tissues or increased clearance of the spirochetes after they reach these tissues has yet to be determined. Therefore, understanding the mechanism of action of IL-10 in this infectious process will provide insight into the normal host defense against B. burgdorferi.

There have been several reported cases in which IL-10 has been shown to reduce the antimicrobial activities of immune cells. Studies of infected IL-10⁻/⁻ or mice in which IL-10 has been neutralized with antibodies have generally indicated that the elimination of pathogens is more effective when IL-10 is absent (14, 21, 47, 65, 75). In some cases, the effect of IL-10 has been at the level of CD4⁺ T-cell responses, with IL-10 modulating the type of help for antibody production. In this study, IL-10⁻/⁻ mice produced higher levels of B. burgdorferi-specific IgG1, IgG2b, and IgG3 than wild-type mice at 4 weeks postinfection. However, increases in the levels of these Ig isotypes have not been directly linked to decreased bacterial numbers. Additionally, B. burgdorferi numbers were already reduced at 2 weeks postinfection, a time at which no obvious differences in B. burgdorferi-specific IgG or IgM levels were seen between mouse strains (data not shown). It has increasingly been recognized that a major target of IL-10 is the phagocytic cell and that suppression leads to an inhibition of the innate ability of this cell type to combat microbial infections (14, 21, 24, 65, 75). We hypothesize that the activity of neutrophils, monocytes, and/or other cell types involved in innate defenses may be suppressed by IL-10 in C57BL/6 mice and that in the absence of this cytokine there is more-efficient killing of the bacteria. Burns and Furie have shown that IL-10 treatment of endothelial monolayers causes a decrease in migration of monocytes in response to B. burgdorferi (12), suggesting that the anti-inflammatory effects of IL-10 may be mediated through the recruitment of inflammatory cells.

As previously mentioned, while the severity of arthritis in IL-10⁻/⁻ mice was greater than that in wild-type C57BL/6J mice, it was not as great as that observed for the C3H/HeN mice. This finding suggests that genes within other regulatory
pathways also contribute to arthritis severity. This hypothesis is consistent with published results from our mapping study, in which the IL-10 structural gene and its receptor map to regions distinct from those identified in our quantitative trait loci analysis, we expect that the arthritis-regulatory genes within these loci are involved in other pathways that regulate disease severity and that these other pathways are involved in the disease phenotype or polymorphism seen in C3H/HeN and C57BL/6 mice.

In summary, increased production of IL-10 by C57BL/6 mice appears to be related to decreased arthritis severity. The anti-inflammatory effect of IL-10 appears to allow C57BL/6 mice to minimize inflammation produced in response to B. burgdorferi lipoproteins in infected joint tissues. However, this decreased inflammation does have a cost to the animal, since the numbers of persisting spirochetes in these tissues are large. This expense to the animal is documented by the fact that an IL-10-deficient mouse harbors significantly fewer spirochetes 4 weeks postinfection than does a wild-type C57BL/6 mouse. Therefore, it appears that C57BL/6 mice have established a balance in their innate responses to B. burgdorferi: the magnitude of inflammation in joints is regulated at the expense of persistence of large numbers of spirochetes in joint tissues.

ACKNOWLEDGMENTS

This work was supported by National Institutes of Health grants AI-32223 (J.J.W) and AR-43521 (J.J.W and C.T.), an Arthritis Foundation postdoctoral fellowship (R.M.W.), and grant 5F30-CA-42014 from the University of Utah.

We thank Robert Huebner for recombinant OspA and Kathy Seiler, Tom Morrison, and John Weis for guidance.

REFERENCES


