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Bone-Marrow Chimeras Reveal Hemopoietic and Nonhemopoietic Control of Resistance to Experimental Lyme Arthritis

Charles R. Brown and Steven L. Reiner

Both genetic resistance and susceptibility to development of experimental Lyme arthritis are mediated by the innate immune response. To determine whether this process is mainly controlled by hemopoietic or nonhemopoietic cells, we created bone marrow (BM) chimeric mice between arthritis-resistant DBA/2J (DBA) and arthritis-susceptible C3H/HeJ (C3H) mice and infected them with Borrelia burgdorferi. Both sets of BM chimeric mice, C3H donors into DBA recipients (C→D) and DBA donors into C3H recipients (D→C), as well as DBA sham chimeric mice (D→D) were resistant to the development of experimental Lyme arthritis as measured by ankle swelling and arthritis severity scores. Only the C3H sham chimeric mice (C→C) developed severe arthritis. These results indicate that independent and nonoverlapping mechanisms exist in hemopoietic and nonhemopoietic cellular compartments that can provide protection against the arthritis pathology.

Lyme disease is a multisystemic illness caused by tick-transmitted infection with the spirochete Borrelia burgdorferi. In humans the infection causes symptoms in a variety of tissues, with dermatologic, arthritic, cardiac, and neurologic manifestations. If untreated with antibiotics near the time of infection, 60% of patients will go on to develop oligoarticular arthritis of varying severity months after the initial infection. This arthritis is characterized by chronic or intermittent synovitis and tendonitis typically associated with bacterial invasion of joint tissues. Although most patients respond favorably to antibiotic therapy, ~10% will have chronic arthritis, which is refractive to treatment even after the apparent eradication of the spirochete from the joint. The development of treatment-resistant chronic Lyme arthritis has been correlated with the presence of HLA-DR4 and thus may have an autoimmune component. In support of this, T cells responsive to the outer surface protein A (OsPA) of B. burgdorferi have been shown to cross-react with LFA (8). Other possible T cell epitopes and molecular mimics have also been recently described in chronic Lyme disease.

Infection of inbred strains of mice with the spirochete B. burgdorferi recapitulates a portion of the disease spectrum seen in humans with Lyme disease. Susceptible mouse strains generally develop acute arthritis during the second week of infection, involving the joints, tendon sheaths, and bursae. The arthritis peaks during the third or fourth week of infection and then undergoes immune-mediated resolution. Arthritis resolution correlates with Ab-mediated clearance of the spirochetes and B cell activation. Although there is a decrease in the level of pathology with B. burgdorferi-specific Ab responses, sterile immunity is never achieved. Th cell subset phenotypes have been shown to correlate with arthritis development. In vivo modulation of IL-4 or IFN-γ responses, however, tends to alter only the degree of disease severity, rather than bring about a complete reversal of disease phenotype. Recently, we have shown that there is no absolute requirement for the presence of IL-4 or IFN-γ for arthritis resistance or susceptibility, respectively.

The genetic control of development of experimental Lyme arthritis has been linked to both cells of the innate (18) and adaptive (11, 14, 15) immune response. We recently demonstrated that mice made immunodeficient through the targeted disruption of their recombination genes (RAG−/−) and which therefore have no B or T cells retained the arthritis phenotype of their wild-type counterparts. Arthritis-resistant DBA and C57BL/6J mice retained a resistant phenotype, and arthritis-susceptible C3H and BALB/cJ mice retained a susceptible phenotype, even when made immunodeficient by homozygous disruption of their RAGs. To determine whether the genetic control of resistance and susceptibility was mediated by cells of hemopoietic or nonhemopoietic origin, we created radiation bone marrow (BM) chimeras between arthritis-resistant DBA and arthritis-susceptible C3H mice.

Materials and Methods

BM chimeras

Female DBA/2J and C3H/HeJ mice between 3 and 4 wk of age were purchased from The Jackson Laboratory (Bar Harbor, ME) and housed in microisolator cages. At least 1 wk before irradiation and BM transfer, the mice were given acidified water ad libitum. On the day of the BM transfer the mice were switched to trimethoprim-sulfamethoxazole in the water. Mice were given lethal total body irradiation (950–1000 rad) from a 137Cs source. Four hours later they were reconstituted with syngeneic or allogeneic BM cells (1 × 107) that had been harvested from the femurs of age-matched mice. Experimental transfers were as follows: C3H donors into C3H recipients (C→C), C3H donors into DBA recipients (C→D), DBA donors into DBA recipients (D→D), and DBA donors into C3H recipients (D→C). In some experiments the BM was depleted of T cells by treatment with anti-Thy1 mAb (PharMingen, San Diego, CA) followed by complement lysis (Cedar Lane, Westbury, NY). Animals were allowed to reconstitute for ~45 days. Before use in experiments all mice were bled from the retro-orbital plexus, and the erythrocytes were removed by hypotonic lysis. PBLs were analyzed by FACScan (Becton Dickinson, Mountain View, CA).
CA) for the expression of H-2Kk or H-2Kd class I molecules to assess the degree of chimerism. Only healthy mice with no obvious signs of graft-vs-host disease were used in experiments. At the time of sacrifice, spleens were harvested and processed into a single-cell suspension. Erythrocytes were removed by ammonium chloride lysis, and the remaining cells were tested by immunofluorescent staining for H-2Kk (AF3-12.1), H-2Kd (SF1-1.1), pan NK cells (DX5: all from PharMingen), and MAC-1 (MI/70.15), B220 (RA3-6B2), CD3 (500-A2), CD4 (CT-CD4), and CD8 (CT-CD8a; all from Caltag, Burlingame, CA). Cells were then analyzed by FACS.

**Bacteria and infections**

The N40 strain of *B. burgdorferi* (gift from Steven Barthold, University of California, Davis, CA) was grown from a low passage frozen aliquot in 7 ml of BSK-H medium (Sigma, St. Louis, MO) for 5 days at 32°C. Before injection *B. burgdorferi* numbers were determined by darkfield microscopy, using a Petroff-Hauser counter. The mice were inoculated in both hind footpads with 5 × 10^9 *B. burgdorferi* organisms in 50 μl of BSK-H medium. Arthritis development was monitored by weekly measurements through the thickest anteroposterior portion of the tibiotalar joint using a metric caliper (Ralmke’s Tool-A-Rama, South Plainfield, NJ). Mice were sacrificed on day 28 following infection. Blood, heart, spleen, urinary bladder, skin (ear punch), and left ankles were aseptically collected and cultured at 32°C for 14 days in BSK-H medium. Cultures were scored for the presence of spirochetes by placing 10 μl of supernatant on a microscope slide under a 22 × 22-mm coverslip and examining 20 high powered fields by dark-field microscopy.

**Histologic assessment of arthritis severity**

Histologic analysis were performed on the right tibiotalar joint from each mouse following their sacrifice 28 days postinfection. The joints were fixed in 10% buffered formalin and embedded in paraffin, and 5-μm sections stained with hematoxylin and eosin. The sections were evaluated in a blinded manner and assessed for arthritis severity on a scale of 0–3 (19). A score of 0 represents normal tissue, 3 represents severe arthritis, and 1 and 2 indicate mild and moderate inflammation, respectively. The pathology present in histologic sections was characterized by edema; neutrophil and monocyte infiltration into the joints, tendons, and ligament sheaths; hyper trophy and hyperplasia of the synovium; and fibrin exudates. The basis for the arthritis severity scores was the extent of the observed inflammatory changes.

**PCR analysis**

To extract DNA from ankles, samples were first incubated in 0.5 ml of 1% collagenase overnight at 37°C. Ankle tissue was then digested by incubation in 0.25 ml of 3% SDS-Tris lysis buffer (0.3 mg/ml proteinase K in 600 mM NaCl, 20 mM Tris-HCl [pH 8.0], 150 mM EDTA, and 0.6% SDS) for 16 h at 55°C. Hearts and ear punches were digested in 1× SDS-Tris lysis buffer only. DNA was extracted using phenol/chloroform and was precipitated with ethanol. The sample DNA was resuspended in 200 μl of Tris-EDTA buffer. DNA from uninfected mice was tested as a negative control. For each PCR run a standard curve was set up consisting of mouse DNA spiked with known numbers of spirochetes. Each PCR reaction contained 10 ng of control or sample DNA. The presence of *B. burgdorferi* ospA in sample DNA was detected using the following primers: ospA 5’ primer, TCTTGAAAGGAACTTTAATCTGCTG; and ospA 3’ primer, CAAGTTTTGTAATTTCAACTGCTGA. PCR reactions were denatured for 60 s at 94°C followed by 35 cycles of denaturation at 94°C for 50 s, annealing at 60°C for 30 s, and extension at 72°C for 60 s. Amplified products were visualized on a 2.5% agarose gel, and the gel were stored as a computer file. The bands were then integrated using National Institutes of Health Image 1.61 software. Quantitative levels of *Borrelia* DNA within each sample was determined comparing the integration levels to those of the standard curve.

**ELISA for Borrelia-specific IgG**

Mice were bled from the retro-orbital plexus, and the serum was collected and stored at 4°C until analyzed. Briefly, 96-well Immulon plates were coated with 40 μl of sonicated *B. burgdorferi* Ag (30 μg/ml) overnight at 4°C. The wells were then blocked with 3% BSA in PBS for 2 h at room temperature. Dilutions of mouse serum (1/1000 in 3% BSA) were added to wells in triplicate and incubated for 2 h at room temperature. Samples were then washed with phosphate-conjugated rat anti-mouse Abs to IgG1, IgG2a, IgG2b, IgG3 (all from PharMingen), or IgM (heavy and light; Jackson ImmunoResearch Laboratories, West Grove, PA) diluted 1/1000 in 3% BSA in PBS and incubated at room temperature for 45 min. Plates were developed with Sigma 104 reagent (Sigma) and read at 405 nm on a spectrophotometer.

**Statistics**

Data were analyzed by Student’s t test for single comparisons or Tukey’s test for multiple comparisons. Critical values for statistical significance were set at α = 0.05.

**Results**

**BM reconstitution of lethally irradiated mice**

To determine whether the genetic control of arthritis development was mediated by cells of hemopoietic or nonhemopoietic origin, we created radiation BM chimeric mice from arthritis-resistant DBA and arthritis-susceptible C3H mice. For proper interpretation of results of experiments using these chimeric mice we must establish their reconstitution by donor cells and the ability of these cells to function in their new environment. To test for the repopulation of chimeric mice by donor BM cells, we stained spleen cells for MHC (C3H H-2Kk, DBA H-2Kd) and cell surface markers for specific cell types and analyzed them by FACS. Fig. 1 shows FACS plots from representative mice from each group for one of three experiments. There was good reconstitution of BM-derived cells regardless of whether they were from syngeneic or allogeneic donors. There was little evidence of graft-vs-host disease even though we did not deplete T cells from the BM in each experiment. Any animal that displayed signs of graft-vs-host disease such as weight loss or skin lesions, was excluded from the study. The mice used in experiments appeared healthy at both the time of infection and the time of sacrifice. Fig. 1A shows the MHC haplotype of spleen cells from the control sham chimeric and chimeric mice. Spleen cells from the C→C and C→D mice show only cells of the H-2Kk C3H donor haplotype, and the D→D and D→C mice show only cells of the H-2Kd haplotype. This indicates repopulation of hemopoietic cells from the BM donors only. We also checked for repopulation of specific cell types: NK cells (Fig. 1B), macrophages (Fig. 1C), B cells (Fig. 1D), and T cells (Fig. 1E). Fig. 1F shows the ratio of CD4+ to CD8+ cells, demonstrating normal percentages of these cell populations. These results indicate proper reconstitution of BM of lethally irradiated mice with hemopoietic cells from donor origin.

**Reconstituted BM chimeric mice make Borrelia-specific Ab responses**

After ~45 days of BM reconstitution the mice were infected in both hind footpads with 5 × 10^3 *B. burgdorferi* of the N40 strain. The mice were injected in the hind footpads to deliver the spirochetes to a site just adjacent to the joint of interest. This obviates the need for the spirochetes to disseminate and traverse to this site and minimizes differences in dissemination patterns that have been shown to occur between mice of different strains and immunological status (10, 19, 20). Sham inoculations of BSK-H medium alone into the footpads does not result in pathological changes in the joint itself (C. Brown, unpublished observation). To demonstrate that the reconstituted BM cells were capable of making a proper specific immune response to challenge we examined the ability of these mice to activate B cells and produce *Borrelia*-specific Abs. BM chimeric and wild-type mice infected for 28 days were bled from the retro-orbital plexus, and the levels of *Borrelia*-specific IgG in the serum were measured by ELISA. As shown in Fig. 2A, all mouse strains were able to produce Ab to *B. burgdorferi*. The chimeric mice and control sham chimeric mice made *B. burgdorferi*-specific IgG in amounts very similar to those in the wild-type control mice. Thus, the repopulation by donor BM cells resulted in recovery of the functional ability to produce specific immune responses similar to those of wild-type mice.
The production of specific IgG isotypes has been correlated with susceptibility to Lyme arthritis development (15, 21). We measured *B. burgdorferi*-specific IgG isotype production in the chimeric mice to determine whether their arthritis phenotypes could be correlated with Ab production (Fig. 2B). The C→C chimeric mice made significantly higher levels of IgG1 than did the other BM chimeric mouse strains. These mice, however, also had higher total IgG levels (Fig. 2A). While the arthritis-susceptible C→C mice also tended to have higher levels of IgG2b, they were not statistically different from the levels found in the arthritis-resistant D→D or D→C mice. There were no differences in the production of IgG2a or IgG3 Ab isotypes between any of the BM chimeric mice.

**Experimental arthritis development in BM chimeric mice**

We infected the BM chimeric mice and monitored arthritis development for 28 days by weekly measurement of tibiotarsal joints (Fig. 3). Only the arthritis-susceptible control sham chimeric mice, C→C (C3H donors into C3H recipients), developed any ankle swelling. This swelling became evident during the second week of infection and peaked around the third week of infection. All other mice were resistant to ankle swelling and had significantly smaller ankle diameters than the C→C mice at 3 and 4 wk of infection (p < 0.001). To determine whether ankle swelling correlated with underlying development of arthritis, one ankle from each mouse was sectioned and evaluated histologically. Ankle sections were stained with hematoxylin and eosin and were given an arthritis severity score in a blinded manner. The results of these analysis are given in Table I. In correlation with the ankle swelling results, only the sham chimeric C→C mice had significantly higher arthritis severity scores than the other mouse strains (p < 0.001). Sham chimeric C→C mice had moderate to severe arthritis severity scores, while the other strains had only mild inflammation. These results indicate that resistance to arthritis development is dominant over susceptibility and that this resistance can be mediated by non-overlapping mechanisms of hemopoietic or nonhemopoietic cells.
Relative *B. burgdorferi* loads in tissues of BM chimeric mice

We have previously shown that arthritis-resistant DBA and arthritis-susceptible C3H mice can harbor relatively equal numbers of *B. burgdorferi* in their tissues and yet retain their distinct phenotypic outcomes (22). To determine whether the BM chimeric mice also harbored similar levels of *B. burgdorferi* within their tissues, we measured the presence of spirochetes in various tissues by culture and measured the relative levels of spirochetes in selected tissues by PCR. Spirochete dissemination and presence in tissues were similar in all mouse strains tested (Table I). The presence of spirochetes was highest in urinary bladder and skin (ear punches) and lowest in spleen, which is a common pattern seen using this experimental model. PCR detection of *Borrelia ospA* DNA in individual mice and tissues shows a wide variation of spirochetal loads (Fig. 4). In ankles, mice from the C3H recipients appear to contain less spirochetal DNA than the mice from the DBA recipients (Fig. 4A). Thus, even though the C3H mouse ankles contained the fewest spirochetes, they were the only mice to develop arthritis. The D→C mice, which had similar levels of spirochetes in their ankles, and the D→D and C→D mice, which had higher levels of spirochetes in their ankles, were resistant to arthritis development. These results confirm previous reports that showed no correlation between spirochete loads in tissues and arthritis development (22, 23), although at distant sites (skin and hearts; Fig. 4, B and C, respectively), while the C→C mice still have low levels of *ospA* DNA, the D→C and C→D mice appear to harbor higher *ospA* DNA levels than the mice that received syngeneic BM cells. This may indicate a failure of the immune system of the D→C and C→D chimeric mice to effectively clear the spirochetes, even though they made adequate levels of *Borrelia*-specific IgG (see Fig. 2). It is possible that the epitopes recognized by the Abs from these mice are not as efficient as those from the control sham chimeric mice at spirochetal clearance.

**Discussion**

Despite much effort, the mechanism(s) responsible for genetic resistance and susceptibility to development of experimental Lyme arthritis remains elusive. We recently reported that immunodeficient RAG−/− mice, which have no functional B or T cells, on either arthritis-resistant or -susceptible genetic backgrounds retained the arthritis phenotype of their wild-type counterparts. These results confirmed and extended work by others (24) and demonstrated innate immunity control of Lyme arthritis pathology. In the current study we sought to extend these results further by localizing the controlling cells to either the hemopoietic or non-hemopoietic compartments. Our hypothesis was that polymorphisms contained within nonhemopoietic cells (e.g., fibroblasts, synoviocytes, etc.) might control the development of pathology.

![Figure 2](http://www.jimmunol.org/)

**FIGURE 2.** Total *Borrelia*-specific IgG responses from wild-type and BM chimeric mice. Bars represent the mean ± SD of total *B. burgdorferi*-specific IgG levels (A) and IgG isotype levels (B) in serum of infected animals. Data are representative of two experiments.

![Figure 3](http://www.jimmunol.org/)

**FIGURE 3.** Ankle swelling following infection of BM chimeric mice with *B. burgdorferi*. Data are representative of three separate experiments. Open symbols, syngeneic BM transfer; closed symbols, allogeneic BM transfer. Squares, C3H recipient mice; circles, DBA recipient mice. Error bars show the SD. Asterisks indicate significant differences in ankle swelling between C→C mice and other mouse strains (p < 0.001).

### Table I. Arthritis development and isolation of *B. burgdorferi* from selected tissues of BM chimera mice

<table>
<thead>
<tr>
<th>Strain</th>
<th>Arthritis Severity</th>
<th>Culture Results</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Joint</td>
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<tr>
<td>C → C</td>
<td>2.5 ± 0.5*</td>
<td>2/6</td>
</tr>
<tr>
<td>D → C</td>
<td>1.2 ± 0.8</td>
<td>1/2</td>
</tr>
<tr>
<td>D → D</td>
<td>1.2 ± 0.7</td>
<td>8/8</td>
</tr>
<tr>
<td>C → D</td>
<td>1.3 ± 0.5</td>
<td>7/8</td>
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* Mice were infected with 5 × 10⁷ *B. burgdorferi* and sacrificed at 28 days. Tibiotal arthritis severity was scored on a scale from 0 to 3 (mean ± SD). Asterisks indicate C → C severity scores were significantly higher than all other mice (p < 0.001).

Culture results are presented as number of cultures positive for *B. burgdorferi*/number cultured.
possibility through the differential recruitment and activation of hemopoietic cells, or, conversely, that polymorphisms contained within the hemopoietic cells responding to the site of infection might drive differences in pathology. Another possibility not addressed in this study, however, is that phenotypic changes that occur within spirochete populations as they adapt in the face of the host immune response may influence the development of arthritis in different mouse strains.

We thus created radiation BM chimeras between arthritis-resistant DBA and arthritis-susceptible C3H mouse strains. Following reconstitution of each mouse strain with BM from syngeneic or allogeneic donors, the animals were infected in the hind footpads with the N40 strain of B. burgdorferi. Surprisingly, only the sham transfer of BM from a genetically susceptible mouse into a genetically resistant mouse into a genetically susceptible mouse (D → C) resulted in resistance to arthritis development. Transfer of bone marrow from a genetically resistant mouse into a genetically susceptible mouse (D → C) resulted in resistance to arthritis development. Similarly, transfer of BM from a genetically susceptible mouse into a genetically resistant mouse (C → D) also resulted in resistance to arthritis development. That the transferred BM cells were active was shown by their ability to make Borrelia-specific Ab responses similar to those of wild-type animals. There was no correlation between Borrelia-specific Ab isotype production and arthritis development in the chimeric mice. These results suggest that at least two mechanisms are likely to provide protection against arthritis development in Lyme disease: one of hemopoietic origin and one of nonhemopoietic origin. This is in contrast to streptococcal cell wall-induced arthritis and adjuvant-induced arthritis in which only hemopoietic cells mediated susceptibility to chronic joint inflammation (25).

One possible mechanism by which nonhemopoietic cells might influence the development of experimental Lyme arthritis is through their regulation of inflammation. It had been speculated that the mechanism of genetic resistance and susceptibility to arthritis development in inbred mouse strains might be due to different patterns of cytokines produced by first-line defense cells such as fibroblasts and endothelial cells early in infection, which would then determine the further course of pathogenesis and infection (24). Fibroblasts can be activated by substances released during tissue injury or derived from infectious organisms, such as the lipid moiety of B. burgdorferi OspA to produce chemokines and other compounds to recruit and activate hemopoietic cells (26–29). Chemokines have been implicated in many disease processes, including collagen-induced arthritis, rheumatoid arthritis, lung fibrosis, granuloma formation, atherosclerosis, and septic shock (30–35). The up-regulation of adhesion molecules and IL-8 production promotes the transendothelial migration of neutrophils (36, 37) and monocytes (38), which constitute a large portion of the inflammatory infiltrate seen in the joints of experimental animals (39) and Lyme patients with active disease (40). Similarly, fibroblasts, even those from a single tissue, are composed of cellular subsets, much like lymphocytes (43, 44), and those from different anatomic regions display distinct phenotypic characteristics (45). Thus, it is possible that these differences among fibroblasts may not only control genetic resistance and susceptibility to pathology, but may even be the basis for its tissue specificity. These studies demonstrate the ability of B. burgdorferi to stimulate the nonhemopoietic first-line defense of cells to recruit and regulate an inflammatory response. Polymorphisms contained within these nonhemopoietic cell types could account for the genetic predisposition of inbred mouse strains to resistance or susceptibility to experimental Lyme arthritis.

Various hemopoietic cell types or their products have been implicated in mediating the development of experimental Lyme arthritis. We and others have demonstrated that both genetic resistance and susceptibility to arthritis development are mediated by cells of the innate immune response (18, 25). We have also shown that NK cells were activated in arthritis-susceptible, but not resistant, mouse strains during early Lyme infection. This suggested that an early overexuberant inflammatory response or perhaps the activation of macrophages via IFN-γ may lead to excess inflammation and arthritis pathology (46). Depletion of NK cells (46, 47), however, or the infection of susceptible C3H mice deficient in IFN-γ production (17), had no effect on arthritis development. Human monocytes can be activated by B. burgdorferi or its lipoproteins to produce pro- and anti-inflammatory cytokines and chemokines (48, 49) through the activation of NF-κB (50). Manipulation of the levels of pro- or anti-inflammatory cytokines produced by macrophages, including IL-6 (51), IL-10 (52), and IL-12 (53), can modulate the severity of arthritis development in mouse models, but does not induce an overall change in arthritis phenotype. Only C57BL/6 (B6) mice with the beige mutation appear to undergo a phenotype switch from arthritis-resistant to susceptible following infection with B. burgdorferi (47). Mice with the beige mutation and patients with Chediak-Higashi syndrome have defective vesicular transport to and from the lysosome and late endosome (54). B6 mice are normally resistant to arthritis development when infected with B. burgdorferi; however, B6 beige mice developed severe arthritis similar to that in C3H control animals. Although the authors of that study failed to identify the cell type responsible for resistance in the B6 animals, they speculated that granulocytes were the most likely mediators of the protection (47). Thus differences in a single gene can alter genetic resistance or susceptibility in inbred mouse strains. Perhaps polymorphisms in granulocytes between C3H and DBA mice can explain the hemopoietic component of the genetic control of Lyme pathology.

Recently, Weis et al. (55) reported correlations between genetic loci and susceptibility to experimental Lyme arthritis. They linked three distinct chromosomal regions with arthritis severity. Regions associated with ankle swelling were mapped to chromosomes 4
and 5, regions associated with arthritis severity were mapped to chromosomes 5 and 11, thus indicating several possible control points for determining the type of host response made. More inbred strains of mice are either resistant or susceptible to arthritis development and retain this phenotype even when challenged with high or low numbers of spirochetes (56). BALB/c mice, however, have a resistant phenotype when challenged with low numbers of spirochetes, but a susceptible phenotype when challenged with high numbers (23). Thus, there appears to be one resistance mechanism that is sensitive to overall bacterial load and one that is not. Whether these mechanisms correlate with the hemopoietically and nonhemopoietically mediated resistance mechanisms we describe in this report is unknown. Further studies to identify these control mechanisms are currently underway.

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References


