Anti-Interleukin-15 Prevents Arthritis in Borrelia-Vaccinated and -Infected Mice

Corey A. Amlong, 1,2 Dean T. Nardelli 1,3 Sara Heil Peterson, 1,2 Thomas F. Warner, 5 Steven M. Callister, 5 and Ronald F. Schell 1,2,3,4,*

Wisconsin State Laboratory of Hygiene 1 and Departments of Bacteriology, 2 Comparative Biomedical Sciences, 3 and Medical Microbiology and Immunology, 4 University of Wisconsin, and Department of Pathology, Veterans Administration Hospital, 5 Madison, and Microbiology Research Laboratory and Section of Infectious Diseases, Gundersen Lutheran Medical Center, La Crosse, 6 Wisconsin

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We showed previously that interleukin-17 (IL-17) plays a significant role in the induction of arthritis associated with Borrelia vaccination and challenge. Little information, however, is available about the chain of immunologic events that leads to the release of IL-17. The production of IL-17 has been linked to stimulation of memory cells by IL-15. Therefore, we hypothesized that IL-15 is involved in the induction of arthritis associated with Borrelia vaccination and infection of mice. Here we present evidence that treatment of Borrelia-vaccinated and -infected mice with anti-IL-15 antibody prevents swelling of the hind paws. More importantly, both anti-IL-15 antibody and recombinant IL-15 receptor alpha-treated Borrelia-vaccinated and -infected mice were free of major histopathologic indications of arthritis, including hyperplasia, hypertrophy, and vilus formation of the synovium. Similarly, the synovial space and perisynovium were free of inflammatory cells. By contrast, the synovium of nontreated Borrelia-vaccinated and -infected mice had overt hyperplasia, hypertrophy, and vilus formation. Moreover, the synovial space and perisynovium were infiltrated with neutrophils, macrophages, and lymphocytes. Finally, we show that recombinant IL-15 stimulates the release of IL-17 from lymph node cells obtained near the arthritic site. These results suggest that IL-15 plays a major role in orchestrating IL-17 induction of arthritis associated with Borrelia-vaccinated and -infected mice.

Arthritis is a major clinical presentation in humans infected with Borrelia burgdorferi (39). Arthritis is also detected in humans following vaccination with Borrelia outer surface protein A (34) and animals following Borrelia infection (5, 6) or Borrelia vaccination and infection (10, 27). The immune mechanisms responsible for this arthritis are poorly understood. We showed previously that treatment of Borrelia-vaccinated and -infected mice with anti-interleukin-17 (anti-IL-17) or anti-IL-17 receptor antibodies prevented the induction of arthritis (8). This finding is important because it defines a major contributor to the pathogenesis of arthritis. Little is known, however, about the immunologic events that lead to the expression of IL-17 and the development of arthritis. Other precursor cytokines may trigger the release of IL-17.

It is known that production of the proinflammatory cytokine IL-17, especially from memory T cells (43), is stimulated by IL-15 (13, 24, 43). IL-15 is a recently discovered cytokine (16) that is produced by synoviocytes (26), monocytes (31), neutrophils (19), and bone marrow stromal cells (33) but not primary T cells (12, 16, 17, 20). In addition, IL-15 is produced by dendritic cells and epithelial cells (36) and influences the local infiltration, activation, and proliferation of antigen-driven T cells at the site of infection or inflammation (28, 42). Clinically, abnormalities of IL-15 expression have been reported for several diseases (1, 19, 25), including rheumatoid arthritis (28). Blocking endogenous IL-15 has been effective in reducing pathology (35). Thus, IL-15 may act as a chemotactic and proliferation factor for the attraction and activation of cells, especially memory T cells capable of releasing IL-17.

In this report, we show that treatment of Borrelia-vaccinated and -challenged mice with anti-IL-15 or its soluble receptor prevents the development of arthritis. In addition, we show that recombinant IL-15 (rIL-15) can stimulate the release of IL-17 from lymph node cells obtained near the arthritic site.

MATERIALS AND METHODS

Mice. Gamma interferon gene-deficient mice were obtained from W. P. Wiedanz (University of Wisconsin) with permission from Genentech (South San Francisco, CA) and housed at the University of Wisconsin Animal Facility. Eight- to 12-week-old male mice weighing 20 to 30 grams were given food and acidified water ad libitum during a light-and-dark cycle of 12 h for the duration of the study. Experimental protocols were approved by the Animal Care and Use Committee of the University of Wisconsin Medical School, Madison.

Organisms. Low-passage-number (<10) Borrelia burgdorferi strain 297 (from human spinal fluid) and “Borrelia bissetti” (formerly strain C-1-11, from Microtus pennsylvanicus) were grown at 32°C in modified Barbour-Stoenner-Kelly (BSK) medium until they reached a concentration of approximately 107 spirochetes/ml. Aliquots (500 μl) were then dispensed into 1.5-ml screw-cap tubes (Sarstedt, Newton, NC) containing 500 μl of BSK medium supplemented with 10% glycerol (Sigma Chemical Co., St. Louis, MO). The tubes were sealed and stored at −70°C. When necessary, a frozen suspension of spirochetes was thawed and used to inoculate fresh BSK medium. Spirochetes were viewed and enumerated using dark-field microscopy.

Vaccine preparation. Borrelia burgdorferi strain 297 organisms were grown in 1 liter of BSK medium for 6 days before being pelleted by centrifugation (10,000 × g, 15°C, 10 min) and washed three times with phosphate-buffered saline (PBS, pH 7.4). The washed pellet was resuspended in a 1% formalin solution, incubated at 32°C with periodic mixing for 40 min, and then washed three times by centrifugation with PBS (10,000 × g, 15°C, 10 min). Subsequently, the washed pellet was resuspended in 1 ml PBS, dispensed in aliquots, and frozen at −70°C.

On the day of vaccination, an aliquot was thawed and mixed. The spirochetes

* Corresponding author. Mailing address: University of Wisconsin, Wisconsin State Laboratory of Hygiene, 465 Henry Mall, Madison, WI 53706. Phone: (608) 262-3634. Fax: (608) 265-3451. E-mail: RFSchell@wisc.edu.
were enumerated by using dark-field microscopy and a volume was added to 3% aluminum hydroxide (alum; Reheis, Berkeley Heights, NJ) to yield 5 × 10⁶ spirochetes/mL.

**Vaccination of mice.** Ninety mice were anesthetized with ether contained in a nose-and-mouth cup and injected subcutaneously in the inguinal region with 250 μl of the formalin-inactivated whole-cell *B. burgdorferi* 297 vaccine. Thirty sham-vaccinated mice were also injected with 3% alum. The use of whole cells of *B. burgdorferi* for vaccination is not recommended for humans because of concerns associated with whole-cell vaccines (22). However, the ability of whole cells to consistently induce arthritis in our murine model (8, 10) allowed for the evaluation of the immunological mechanisms that induce arthritis.

**Infection of mice.** Twenty-one days after vaccination, mice were anesthetized with ether contained in a nose-and-mouth cup and injected subcutaneously in the right hind paw with 50 μl of BSK medium containing 10⁶ viable *B. bissettii* organisms. Swelling of the hind paws consistently develops 4 to 6 days after *B. bissettii* infection and peaks on day 8 to 12 (8, 10). Swelling of the hind paws can also be induced by infection with the homologous *B. burgdorferi* strain 297. However, *B. burgdorferi* strain 297-vaccinated mice must be challenged before protective antibodies develop (approximately day 7) or after their decline. Swelling of the hind paws of homologous vaccinated and challenged mice is variable. Therefore, we challenged *B. burgdorferi* strain 297-vaccinated mice with *B. bissettii* to obtain consistent swelling of the hind paws. Vaccination of mice with *B. bissettii* and challenge with *B. burgdorferi* strain 297 also yields consistent swelling of the hind paws, as does challenge with other infectious isolates of *B. burgdorferi* (11, 27, 37). Controls included vaccinated mice injected with alum or BSK medium alone.

**Administration of anti-IL-15 antibody and rIL-15 receptor alpha.** Lyophilized goat anti-mouse immunoglobulin G polycolonal IL-15 antibody (200 μg), normal goat immunoglobulin G (100 μg), and mouse rIL-15 receptor alpha (100 μg) were obtained from R&D Systems (Minneapolis, MN). The antibodies and rIL-15 receptor were resuspended in filter-sterilized (0.2-μm-pore-size filter) (Acrodisk; Gilman Sciences, Ann Arbor, MI) PBS (pH 7.2) or PBS containing 0.1% bovine serum albumin (Fisher Scientific, Pittsburgh, PA), respectively, to yield concentrations of 50 μg/ml. Twenty-one days after vaccination, three groups of eight mice each were injected intraperitoneally with 50 μl of the formalin-inactivated whole-cell *B. bissettii* organisms in the right hind paw. Less than 1 h after infection, the mice were injected subcutaneously in the right hind paw with 50 μl of the anti-IL-15 antibody or rIL-15 receptor alpha preparation. Anti-IL-15 antibody or rIL-15 receptor alpha was injected daily for 6 or 8 days, respectively. In other experiments, anti-IL-15 antibody was injected on day 7 after infection and daily thereafter for 6 days. Control groups received injections with the normal goat isotype antibody or with BSK medium alone.

**Measurement of IL-17 produced by immune lymph node cells.** Twenty-one days after vaccination, six mice were euthanized with ether contained in a nose-and-mouth cup and the inguinal lymph nodes were removed. The nodes were teased apart with a forceps, and single-cell suspensions were obtained by passing the cells through a sterile Falcon 100-μm-pore-size m-pore-size filter) (Acrodisk; Gilman Sciences, Ann Arbor, MI) PBS (pH 7.2) or PBS containing 0.1% bovine serum albumin (Fisher Scientific, Pittsburgh, PA), respectively, to yield concentrations of 50 μg/ml. Twenty-one days after vaccination, three groups of eight mice each were injected intraperitoneally with 50 μl of the formalin-inactivated whole-cell *B. bissettii* organisms in the right hind paw. Less than 1 h after infection, the mice were injected subcutaneously in the right hind paw with 50 μl of the anti-IL-15 antibody or rIL-15 receptor alpha preparation. Anti-IL-15 antibody or rIL-15 receptor alpha was injected daily for 6 or 8 days, respectively. In other experiments, anti-IL-15 antibody was injected on day 7 after infection and daily thereafter for 6 days. Control groups received injections with the normal goat isotype antibody or with BSK medium alone.

**Histopathologic confirmation that anti-IL-15 antibody treatment inhibited development of arthritis.** Vaccinated mice challenged with *B. bissettii* showed severe inflammation and edematous changes throughout the paw, including the synovial space, synovium, perisinovium, and the small bones of the paw 9 days after infection (Fig. 2). Moreover, the synovium had significant hyperplasia and hypertrophy along with villus formation. However, no evidence of histopathologic changes, except edema and minor infiltration of neutrophils, macrophages, and lymphocytes in the synovium, was detected in vaccinated mice infected with *B. bissettii* and treated with anti-IL-15 antibody (Fig. 2). The controls, including vaccinated mice and vaccinated mice treated with anti-IL-15 antibody, were also free of significant histopathology (Fig. 3). Nonvaccinated but infected mice developed only marginal pathology of the synovial space, synovium, and perisinovium (Fig. 3).

Fourteen days after challenge, considerable infiltration of neutrophils, macrophages, and lymphocytes was observed in the synovial space, synovium, and perisinovium of *Borrelia*-vaccinated and -infected mice with or without prior treatment with anti-IL-15 antibody (Fig. 4). Hyperplasia and villus formation were also detected in the synovium of *Borrelia*-vaccinated and -infected mice treated with anti-IL-15. Treatment with anti-IL-15 antibody, however, was terminated in this group of mice 8 days previously. No significant histopathologic changes were detected in the remaining controls, including vaccinated mice with or without treatment with anti-IL-15 antibody, or in mice challenged with *B. bissettii* alone.
In a separate set of experiments, *Borrelia*-vaccinated and -infected mice were administered anti-IL-15 antibody 7 days after infection and daily thereafter for 6 days. Significant pathology was detected in the tibiotarsal joints of these mice. In fact, no differences in the swelling of the hind paw or histopathologic changes, compared to non-anti-IL-15 antibody-treated vaccinated and infected mice, were detected.

**Effects of rIL-15 receptor alpha on arthritis.** Two groups of five vaccinated mice each were infected with $10^8$ *B. bissettii* organisms. One of these two groups was administered rIL-15 receptor alpha at the time of infection and daily thereafter for 8 days. Controls included vaccinated mice injected with rIL-15 receptor alpha. Hind-paw swelling was detected in vaccinated mice challenged with *B. bissettii* on day 4 after infection, peaked on day 9, and gradually decreased. Treatment of vaccinated and challenged mice with rIL-15 receptor alpha delayed the onset of swelling of the hind paw and significantly ($P < 0.05$) decreased its severity at all intervals until day 8 after infection. No swelling of the hind paw was detected in vaccinated, but not infected, mice treated with rIL-15 receptor alpha. Histopathologic examination of the paws from each group of five mice confirmed that rIL-15 receptor alpha prevented severe inflammation of the hind paw.

**rIL-15 induces IL-17 production from mouse immune cells.** Inguinal lymph nodes were obtained from *Borrelia*-vaccinated mice at day 21 after vaccination. The lymph node cells were cocultured with or without $5 \times 10^6$ viable *B. bissettii* organisms for 48 h in the presence or absence of rIL-15. Figure 5 shows that immune lymph node cells incubated with 0.5 pg/ml of rIL-15 in the presence or absence of *B. bissettii* induced the production of 18 or more pg/ml of IL-17. Likewise, lower concentrations, 0.1 and 0.2 pg/ml, of rIL-15 in the presence of spirochetes also stimulated immune lymph node cells to release 14 and 13 pg/ml of IL-17, respectively. Immune lymph node cells cultured in RPMI medium alone or RPMI medium with BSK medium released less than 7 pg/ml of IL-17 (similar to background levels in RPMI medium alone), as did cells cultured with PBS containing 0.1% bovine serum albumin. When these experiments were repeated, comparable findings were obtained. Similar experiments conducted using the lymph nodes of nonvaccinated mice yielded no detectable IL-17 (data not shown).

**DISCUSSION**

In the present study, we hypothesized that IL-15 is a primary mediator involved in the induction of arthritis associated with *Borrelia* vaccination and infection of mice. In support of this hypothesis, we showed that treatment of *Borrelia*-vaccinated and -challenged mice with anti-IL-15 antibody prevented swelling of the hind paws. In addition, treatment of *Borrelia*-vaccinated and -infected mice with rIL-15 receptor alpha also prevented hind-paw swelling. More importantly, both anti-IL-15 antibody and rIL-15 receptor alpha-treated *Borrelia*-vaccinated and -challenged mice were free of major histopathologic indications of arthritis, including hyperplasia, hypertrophy, and villus formation of the synovium. Similarly, the synovial space and perisynovium were free of inflammatory cells. By contrast, the synovium of non-anti-IL-15-treated *Borrelia*-vaccinated and -infected mice had overt hyperplasia, hypertrophy, and villus formation. Moreover, the synovial space and perisynovium were infiltrated with neutrophils, macrophages, and lymphocytes. These results suggest that IL-15 plays a major role in the induction of arthritis associated with *Borrelia*-vaccinated and -infected mice.

Although IL-15 is involved in the induction of arthritis associated with *Borrelia* vaccination and infection, we showed previously that IL-17 is also a major participant in the induction of this arthritis (8). When *Borrelia*-vaccinated and -infected mice were administered anti-IL-17 antibody, development of arthritis was prevented (8, 32). Likewise, treatment of *Borrelia*-vaccinated and -infected mice with anti-IL-17 receptor
FIG. 2. Histopathology of the tibiotarsal joints of three *Borrelia*-vaccinated and -infected mice (day 9 after infection) with (panels A, B, and C) and without (panels D, E, and F) treatment with anti-IL-15 antibody. No histopathology was found in the three *Borrelia*-vaccinated and -infected mice (panels A, B, and C) treated with anti-IL-15 antibody. In the absence of anti-IL-15 antibody treatment, the three vaccinated and challenged mice (panels D, E, and F) showed substantial inflammation at the tibiotarsal joint. Arrows indicate inflammation. Magnification, ×40.
antibody prevented arthritis, including cartilage and bone destruction (8). Taken together, these results show that both IL-15 and IL-17 play a significant role in arthritis induced by *Borrelia* vaccination and infection of mice.

What is the mechanism by which IL-15 and IL-17 drive the arthritis? Presumably, at the time of infection, some spirochetes are processed by neutrophils (14, 30, 41) and macrophages (15, 29), leading to the release of IL-15 from these cells (19, 31). Since IL-15 is rarely detected in culture supernatants or tissues (4, 31), it probably binds rapidly to the IL-15 receptor alpha, the IL-2 receptor beta, and the common gamma-chain located especially on memory T cells (4, 16, 17, 20). The memory cells, or *Borrelia*-vaccinated T lymphocytes, then release IL-17 that triggers the production of other proinflammatory cytokines, such as IL-1, IL-6, and IL-8 (3, 9, 21), that contribute to the development of arthritis. In support of this theory, we showed that rIL-15 caused the release of IL-17 in ex vivo cultures of immune lymph node cells isolated from a site adjacent to the hind paws. Ziolkowska et al. (43) and Kim et al. (24) also showed that IL-15 triggers the release of IL-17. Our results, as well as those of Ziolkowska et al. (43) and Kim et al. (24), show a definite connection between IL-15 and IL-17. Additional studies are needed to determine if IL-15 directly causes IL-17 production. This linkage is important for the potential therapy of *Borrelia*-induced arthritis as well as other inflammatory diseases (1, 9, 25). Clearly, therapy with anti-IL-15 or anti-IL-17 (8) antibody benefits vaccinated mice when it is started at the time of challenge with *Borrelia* organisms.

The arthritic mechanism, however, may be more complex than the simple linear stimulation of IL-17 production by IL-15. Histopathologic examination showed that treatment of *Borrelia*-vaccinated and -infected mice with anti-IL-15 antibody or rIL-15 receptor alpha dramatically decreased the infiltration of inflammatory cells at the tibiotarsal joint, especially neutrophils. In contrast, neutrophils dominated the cell infiltrate in non-anti-IL-15-treated *Borrelia*-vaccinated and -infected mice. It is known that resting neutrophils, along with infiltrating monocytes, express IL-2 receptor beta and IL-2 receptor gamma, which can readily bind high concentrations of IL-15 (43). We speculate that initially resting neutrophils exposed to the infectious challenge release IL-15. Subsequently, IL-15 binds to these IL-2 receptors as well as the high-affinity IL-15 receptor alpha (23). Interactions between IL-15 and its receptor complex lead to increased signaling and activation of neutrophils (19). Further activation of these neutrophils by IL-15 also increases their phagocytic ability (19). Therefore, IL-15 may have a dual role in the response to infection. It promotes the proinflammatory cytokine cascade via IL-17 production and may oversee the elimination of the initial spirochete challenge. In support of this theory, termination of anti-IL-15 treatment 6 days after challenge was followed immediately by

![FIG. 3. Histopathology of the tibiotarsal joints of vaccinated mice (A), vaccinated mice treated with anti-IL-15 antibody (B), and nonvaccinated mice infected with *B. bissettii* (C). No histopathologic changes were detected in the vaccinated mice or vaccinated mice treated with anti-IL-15 antibody. Only minor inflammation (day 9) was observed in nonvaccinated infected mice. The arrow indicates an area of inflammation. Magnification, ×40.](image-url)
an increase in hind-paw swelling in *Borrelia*-vaccinated and -challenged mice. Histological samples from these animals taken 14 days after challenge (8 days after treatment cessation) revealed dramatic infiltration of immune cells as well as vilus formation and destruction of the synovial lining. In addition, others (18) have shown that IL-15 can affect the migration and phagocytosis of neutrophils in patients with Lyme disease.

Although we showed that treatment of *Borrelia*-vaccinated mice at the time of challenge with anti-IL-15 antibody prevented arthritis, treatment with anti-IL-15 antibody failed to ameliorate the arthritis once it was established. Specifically, no resolution of arthritis was detected when *Borrelia*-vaccinated and -challenged mice were administered anti-IL-15 antibody 7 days after infection, as opposed to the case for controls. This was disappointing, and it suggests that anti-IL-15 therapy is not suitable for the treatment of established arthritis associated with *Borrelia* vaccination and infection. In contrast, Baslund et al. (7) have recently shown that treatment of humans with an antibody targeting IL-15 benefited patients with longstanding rheumatoid arthritis. This discrepancy may be related to differences in immune responses that maintain chronic arthritis in rheumatoid arthritis and arthritis induced by *Borrelia burgdorferi*. Additional studies are under way to determine which mediators could be neutralized to hasten the resolution of Lyme arthritis.

The failure of anti-IL-15 antibody to ameliorate established

![FIG. 4. Histopathology of the tibiotarsal joint of *Borrelia*-vaccinated and -infected mice (day 14 after infection) with (A) and without (B) treatment with anti-IL-15 antibody. (A) Anti-IL-15 antibody treatment was discontinued 8 days previously or 6 days after infection. Inflammation of the tibiotarsal joint is present in both mice. Arrows indicate areas of inflammation. Magnification, ×28 (original magnification, ×40).](image)

![FIG. 5. The effects of rIL-15 (0.1, 0.2, or 0.5 pg) on production of IL-17 from lymph node cells obtained from *Borrelia*-vaccinated mice in the presence or absence of 4 × 10^6 viable *B. bissetti* organisms (B.b.). Control groups included supernatants from wells containing only RPMI medium or wells in which immune cells (IC) were cultured with RPMI medium, RPMI medium with BSK medium, or RPMI medium with BSK medium containing 4 × 10^6 viable *B. bissetti* organisms. Data are the means ± standard errors for the experiment.](image)
arthritus does not lessen the cytokine’s clinical importance. A major concern with development of a Lyme disease vaccine is the induction of adverse effects, such as arthritis. Once a Lyme disease vaccine has been shown to be protective, it could also trigger the induction of adverse effects, such as arthritis. Once a Lyme vaccine has been shown to be protective, it could also trigger the induction of arthritis. Although rIL-15 treatment of immune cells led to increased production of IL-17 from these cells, additional studies are needed to determine if IL-17 solely promotes this production. Other studies are also needed to determine mediators that could be neutralized to enhance the resolution of established arthritis.

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