Critical Role of Signaling Through IL-1 Receptor for Development of Arthritis and Sepsis During *Staphylococcus aureus* Infection

Olof H. Hultgren, Lena Svensson and Andrej Tarkowski

*J Immunol* 2002; 168:5207-5212; doi: 10.4049/jimmunol.168.10.5207

http://www.jimmunol.org/content/168/10/5207

**References**

This article cites 32 articles, 19 of which you can access for free at:
http://www.jimmunol.org/content/168/10/5207.full#ref-list-1

**Subscription**

Information about subscribing to *The Journal of Immunology* is online at:
http://jimmunol.org/subscription

**Permissions**

Submit copyright permission requests at:
http://www.aai.org/About/Publications/JI/copyright.html

**Email Alerts**

Receive free email-alerts when new articles cite this article. Sign up at:
http://jimmunol.org/alerts
Critical Role of Signaling Through IL-1 Receptor for Development of Arthritis and Sepsis During *Staphylococcus aureus* Infection

Olof H. Hultgren, Lena Svenssson, and Andrej Tarkowski

IL-1R-deficient mice (IL-1R/−/−) and their wild-type controls (IL-1R+/+) were i.v. inoculated with 1 × 10^7 or 10^6 *Staphylococcus aureus* per mouse to mimic bacterial sepsis and septic arthritis. The disease outcome was severely worsened in the IL-1R/−/− mice as compared with IL-1R/+/+ mice. Indeed, 3 days after inoculation of 10^7 *S. aureus* per mouse 84% of IL-1R/−/− mice displayed clinical signs of septicemia as compared with none of the IL-1R+/+ mice. On day 9 after inoculation with 10^6 *S. aureus* per mouse 75% of the IL-1R/−/− mice were dead as compared with none of the IL-1R+/+ mice. Also, the number of staphylococci in circulation was 25- to 30-fold increased in IL-1R/−/− mice as compared with IL-1R+/+ mice. The frequency and severity of septic arthritis were significantly increased in IL-1R/−/− mice, as compared with IL-1R+/+ mice, following i.v. inoculation of staphylococci. This was probably due to an increased accumulation of bacteria in the joints of IL-1R/−/− mice as compared with their wild-type controls. Interestingly, while serum levels of IL-18 in IL-1R/−/− mice were significantly lower than in IL-1R+/+ mice 24 h after inoculation of *S. aureus*, both IL-18 and IL-1β were significantly increased in IL-1R/−/− vs IL-1R+/+ mice 4 days after the bacterial inoculation. In conclusion, IL-1R signaling plays a crucial role in host protection during systemic *S. aureus* infection as seen by the fatal outcome of *S. aureus* sepsis and arthritis in IL-1R-deficient mice. The Journal of Immunology, 2002, 168: 5207–5212.

Septic arthritis is a highly destructive joint disease with high mortality. *Staphylococcus aureus* is the causative organism in ~40% of adult cases and the common route of bacterial spreading is via the bloodstream (1). A mouse model has been established in which staphylococci are i.v. inoculated to trigger sepsis and septic arthritis (2). The pathogenesis of murine *S. aureus* sepsis and septic arthritis involves bacterial as well as host factors. The expression of certain bacterial virulence factors, e.g., capsular carbohydrates, adhesins, and regulatory genes, make the bacteria more resistant to phagocytic functions, and the increased bacterial survival results in an increased joint inflammation as well as increased risk of death (3). The host response must meet the demand of an effective clearance of bacteria.

One of the first steps for the innate immune system in recognizing staphylococci is via the Toll-like receptors (TLRs) (4), e.g., TLR2 and TLR4, recognizing peptidoglycan and lipoteichoic acids, respectively (5). The TLRs share an intracellular (IC) signal pathway with at least two cytokine receptors, IL-1R (6) and IL-18R (7). The receptor signal is conducted in sequence via a myeloid differentiation marker (MyD88), IL-1R-associated kinase, TNFR-associated factor 6, and TGF-β-activated kinase, leading to nuclear translocation of NF-κB (4, 8). Following activation of NF-κB several genes with proinflammatory end products are transcribed. The importance of this IC signal pathway for protection against staphylococcal infection was recently shown using MyD88-deficient mice (9).

While IL-18 was previously shown to protect against joint inflammation but aggravate septicemia during *S. aureus* arthritis (10), the importance of IL-1αβ signaling during septic arthritis is hitherto unknown. The results from a model of noninfectious arthritis show that blockade of IL-1β or IL-1R delays disease onset and ameliorates already established collagen-induced arthritis (11). Furthermore, IL-1R antagonist-deficient mice develop spontaneous arthritis resembling rheumatoid arthritis (12), altogether indicating arthritogenic properties of IL-1R signaling in inflammatory joint diseases. IL-1R is responsible for signal transduction of IL-1αβ (13), while the type 2 receptor is lacking a cytoplasmatic tail and is therefore not capable of signal transmission but functions rather as a decoy receptor (14).

Using IL-1R-deficient mice and their wild-type controls, we present evidence for the major importance of IL-1R signaling in *S. aureus* infection in controlling staphylococcal growth and subsequently protecting the host against septic death and septic arthritis.

**Materials and Methods**

**Mice, bacteria, and inoculation procedure**

Age- and sex-matched male or female 6- to 15-wk-old C57BL/6 mice, intact or defective with respect to the IL-1R type I gene, were used throughout the study. Procedure of IL-1R gene disruption has been described in detail elsewhere (15). IL-1R-deficient mice (B6.129S7-Il1r1tm1Imx) as well as their wild-type controls (C57BL/6J) were obtained from The Jackson Laboratory (Bar Harbor, ME). At the time of experiments, IL-1R-deficient mice had undergone five backcrosses to the C57BL/6 background. Mice were kept and bred at the animal facility of the Göteborg University (Göteborg, Sweden). They were kept under standard conditions in a temperature- and humidity-controlled, specific pathogen-free environment with 12-hr light/dark cycles.

conditions of temperature and light and were fed standard laboratory chow and water ad libitum.

_S. aureus_ strain LS-1 was originally isolated from a spontaneously arthritic New Zealand Black/White mouse (16). Before each experiment, bacteria were cultured on blood agar (5% human erythrocytes) for 24 h and then reincubated on blood agar for another 24 h. A bacterial solution was prepared in PBS at a concentration of 5 × 10^8 or 5 × 10^6 bacteria/ml. Two hundred microliters of the solution were injected into one of the tail veins on day 0. Viable counts were used to check the concentration of bacteria injected.

**Evaluation of arthritis and sepsis**

All mice were labeled and monitored individually. Limbs were inspected at regular intervals. Arthritis was defined as visible erythema and/or swelling of at least one joint. To evaluate the severity of arthritis we used a clinical scoring in which macroscopic inspection yields a score of 0–3 for each paw (0, normal; 1, mild swelling and/or erythema; 2, moderate swelling and erythema; 3, marked swelling and occasionally ankylosis), resulting in an arthritis score ranging from 0 to 12 for each mouse. Arthritis index was constructed by a summation of arthritis scores from all mice in the experimental group divided by the number of animals in each group.

The severity of sepsis was judged clinically modified from a previous description (17) where coat appearance (0–1), posture or movements (0–1), and temperature (0–1) yielded a severity score of maximally 3 per mouse. Temperature score was obtained when the mice were severely ill and cold as judged by hand.

Weight was regularly checked with 0.1-g accuracy.

**Determination of staphylococcal load ex vivo**

Bacterial samples from talocrural and radiocarpal joints were obtained using cotton sticks. The bacterial presence was defined if 15 or more CFU per joint were found. Both kidneys were removed aseptically, placed on ice, homogenized, and diluted in 10 ml PBS. Viable counts were done to examine bacterial concentration. To check the staphylococcal load in blood, mice were bled and viable counts were used to titrate the bacterial concentration.

Colonies were tested for catalase (using 18% hydrogen peroxide) and coagulase (using rabbit EDTA-plasma; BD Microbiology Systems, Sparks, MD) reactivity.

**Hematological analyses**

Mice were bled from the tail into heparinized tubes. Total leucocyte counts were determined in a hemocytometer (Sysmex KX-21; TOA Medical Electronics, Kobe, Japan). Blood smears were prepared and stained by the May-Grünwald-Giemsa method for differential counts.

**In vitro analyses of cytokine production, phagocytosis, and IC killing**

Spleen cells were passed through a nylon mesh, and erythrocytes were depleted by NH_4Cl lysis. Splenocytes were cultured at 2 × 10^6 cells/ml in Iscove’s medium supplemented with 10% FCS, 5 × 10^{-5} M 2-ME, 2 mM t-glutamine, and 50 μg/ml gentamicin and incubated with 1 × 10^6/ml formalin-killed _S. aureus_ LS-1 strain. Supernatants from cell cultures were collected after 24 and 48 h.

Intrapерitoneal macrophages were extracted, adjusted to 2 × 10^6 cells/ml, and incubated in a 24-well plate (Nunc, Roskilde, Denmark) according to a previously detailed procedure (18, 19). Adherent macrophages were incubated with 500 μl of _S. aureus_ at a concentration of 5 × 10^6 bacteria/ml for 50 min and subsequently washed three times in Iscove’s medium. The IC content of live _S. aureus_ was then checked at three time intervals: 0, 4, and 24 h. The content at the 0-h interval is regarded as a measure of the phagocytosis, and the two later time intervals are regarded as a measure of the efficacy of the IC killing capacity contra-IC growth of bacteria (18).

**Cytokine reagents and analyses**

Recombinant murine (rm)IL-1β (R&D Systems, Minneapolis, MN) was reconstituted in accordance with the manufacturer’s instructions, then further diluted in PBS to desired concentration.

IL-6 was measured using the murine hybridoma cell line B13.29, subclone B9, selected for its IL-6 dependency (20). For the assay, B9 cells were harvested by centrifugation, and after one wash in IL-6-free medium they were resuspended at 5 × 10^5 cells/well into microtiter plates (Nunc) in the presence of serum samples and grown for 68 h before adding 3H-thymidine to study proliferative responses to IL-6. After 4 h, the cultures were harvested onto filters and counted in a beta counter. Mouse IL-6 (Genzyme, Cambridge, MA) was used as a standard. The serum samples and standards were all set up in triplicate.

TNF and IL-1β were measured using Quantikine mouse immunoassays (R&D Systems). IL-18 was measured by a quantitative test kit for mouse IL-18 (MBL, Nagoya, Japan). All the assays were performed in accordance with the manufacturer’s instructions.

**Statistics**

Categorical data were analyzed using Fisher’s exact test, and unpaired Student _t_ test was used for statistical analyses of weight changes. All other data were analyzed using the nonparametric Mann-Whitney _U_ test. A value of _p_ ≤ 0.05 was regarded as statistically significant. Results are presented as mean ± SEM (n = number of mice).

**Results**

Severe sepsis and decreased survival in IL-1R-deficient mice during _S. aureus_ infection

IL-1R-deficient mice and their wild-type controls were i.v. inoculated with 1 × 10^7 _S. aureus_ per mouse. The obvious clinical signs of sepsis in IL-1R knockout mice were seen on the third day after inoculation of bacteria, when a majority of the IL-1R-deficient mice displayed sepsis as compared with none of the wild-type mice (Fig. 1). As expected, the severity of sepsis differed significantly between groups (1.2 ± 0.2 vs 0 ± 0; _p_ < 0.0001) at the same time point. The IL-1R-deficient mice started to die at day 4. In a first experiment, three of 15 IL-1R−/− mice were dead at day 4 as compared with none of the controls (0 of 17; NS). The survivors were severely ill and were sacrificed at day 4 to obtain organ samples. The weight was checked daily and, interestingly, 24 h after the inoculation of 1 × 10^7 _S. aureus_ the wild-type mice displayed significantly more weight loss as compared with the IL-1R-deficient animals. This finding was repeated in a second experiment with the 1 × 10^6 dose (data not shown). However, at days 2 and 3 after the inoculation of 1 × 10^7 _S. aureus_ no differences in weight loss were recorded between groups, though the general appearance as measured by sepsis score was highly different at day 3.

These results show that the susceptibility of the IL-1R−/− mice to _S. aureus_ infection is increased. To titrate how high the susceptibility is, IL-1R+/− and IL-1R−/− were inoculated with 1 × 10^6 _S. aureus_ per mouse. As in the case of high dose experiment, wild-type mice responded to infection with an initially more pronounced weight loss as compared with IL-1R knockouts (Fig. 2).

---

**FIGURE 1.** Septicemia in 25 IL-1R-deficient mice and 25 wild-type mice following i.v. inoculation of 1 × 10^7 _S. aureus_ per mouse. Data are pooled from two experiments. Value of _p_ is calculated using Fisher’s exact test.
type mice (n per mouse) 1 × 10^6 S. aureus.

Mortality in 12 IL-1R-deficient mice was significantly lower than in wild-type mice, whereas no mortality was seen in the wild-type mice (Fig. 3). The experiment was finished 2 days later at day 9. At this time point, only 25% (3 of 12) of the IL-1R−/− mice were alive, whereas no mortality was seen in the wild-type mice (Fig. 3).

IL-1R-deficient mice display increased frequency and severity of S. aureus arthritis

At day 3 after inoculation of 1 × 10^7 S. aureus, 36% of the wild-type mice (n = 25) displayed septic arthritis as compared with 68% of IL-1R-deficient mice (n = 25; p < 0.05). Similarly, the severity of arthritis at day 3 was more pronounced in IL-1R-deficient animals as compared with wild-type mice (Fig. 4). Due to severe septicemia in the IL-1R-deficient group, experiments were finished at days 3–4. To be able to follow the development of arthritis for a longer time, a markedly reduced inoculum size (10^6 per mouse) was given i.v. to 12 IL-1R−/− mice and 15 IL-1R+/+ control animals. Again, at day 3, differences were seen between groups, IL-1R−/− mice displaying somewhat increased frequency of septic arthritis as compared with IL-1R+/+ mice (42 vs 7%; p = 0.06). At day 7, 45% (four of nine) of the IL-1R-deficient mice displayed arthritis as compared with 7% (1 of 15) of wild-type mice (p < 0.05). The severity of arthritis was significantly increased in IL-1R−/− vs IL-1R+/+ mice at days 3 and 7 after inoculation of a lower dose of staphylococci (Fig. 4). The experiment was finished at day 9 after inoculation of 1 × 10^6 S. aureus per mouse, a time point when one of three IL-1R-deficient mice displayed arthritis as compared with 2 of 15 wild-type animals.

The state of IL-1R deficiency is not beneficial to host with regard to survival or septic arthritis. There are at least two hypothetical possibilities for this finding: 1) IL-1R−/− mice accumulate live S. aureus in tissues as compared with wild-type mice, or 2) IL-1R signaling down-regulates inflammation during S. aureus arthritis, directly or indirectly. To check the first possibility we examined the bacterial load in tissues of IL-1R−/− and IL-1R+/+ mice after inoculation of 1 × 10^7 S. aureus per mouse.

High staphylococcal load in IL-1R-deficient mice as compared with wild-type mice

The load of S. aureus was checked in blood, kidneys, and joints after i.v. inoculation of 1 × 10^7 S. aureus per mouse. While very few staphylococci were found in blood 4 h after inoculation of bacteria in both IL-1R−/− and IL-1R+/+ groups, increasingly more S. aureus were found in the blood of IL-1R−/− as compared with wild-type mice 48 and 72 h after bacterial inoculation (Fig. 5A). Indeed, the increase of S. aureus in the circulation of IL-1R−/− mice was ~100-fold between the time points 4 and 72 h. Such an increase was absent in wild-type mice. The bacterial load in kidneys was checked at day 4 after inoculation of bacteria. IL-1R-deficient mice displayed a higher load (3.1 ± 1.1 × 10^8 CFU)
as compared with wild-type mice (4.9 ± 1.2 × 10^7 (NS)). However, at day 4, three IL-1R^-/- mice of 15 had died, probably the most sick ones carrying the highest bacterial load.

The bacterial presence in joints was examined also at day 4 after bacterial inoculation. Staphylococci were significantly more prevalent in IL-1R-deficient mice as compared with their controls (Fig. 5B). Furthermore, five of the seven IL-1R^-/- mice with presence of S. aureus displayed positive culture in two or more of the four joints checked. The only wild-type mouse with presence of staphylococci displayed one positive joint.

Because IL-1β is a potent mediator of neutrophil recruitment from bone marrow into blood (21), we checked whether IL-1R signaling influences the neutrophil counts in circulation in response to S. aureus infection. While no difference in neutrophil counts was recorded between IL-1R intact or IL-1 deficient mice before inoculation of staphylococci, blood of IL-1R-deficient mice displayed significantly fewer neutrophils 4 and 24 h after the inoculation of bacteria (Fig. 6).

Next, we analyzed the phagocytic properties as a function of IL-1R expression. The phagocytosis did not differ between IL-1R^-/- and IL-1R^+/+ macrophages preincubated with or without 100 pg/ml rmIL-1β. However, the addition of rmIL-1β at 1 ng/ml to the cultures significantly increased phagocytosis by wild-type macrophages as compared with IL-1R-deficient macrophages (3973 ± 673 S. aureus per 10^6 cells vs 2257 ± 110; p < 0.05). Expression of IL-1R did not affect the IC killing ability of macrophages.

### IL-1R signaling increases production of TNF and IL-6 in vitro

Next we analyzed the importance of IL-1R signaling for production of cytokines in vivo in response to S. aureus arthritis and in vitro to formalin-killed S. aureus. While TNF and IL-6 are produced in response to S. aureus, the role of IL-1R signaling for production of these cytokines during staphylococcal infection has not been previously analyzed. The serum concentration of these two cytokines was assayed in IL-1R intact/defect mice 4 h, 24 h, and 4 days after inoculation of S. aureus. The importance of IL-1R signaling for the in vivo production of IL-6 was seen already at 4 h after bacterial inoculation. Later, differences in IL-6 production due to functional IL-1R were diminished and overcome (Table I). In contrast, IL-1R deficiency did not affect TNF production during staphylococcal infection (Table I).

Measuring the serum concentration of IL-18 24 h after bacterial inoculation, the IL-1R-deficient mice displayed a decreased production as compared with wild-type mice, indicating that IL-1R signaling is important for optimal production of IL-18. Interestingly, 4 days after inoculation of S. aureus IL-18 production was significantly increased in the IL-1R-deficient mice as compared with wild-type controls (Table I). IL-18 was not detected in vitro in response to formalin-killed S. aureus.
Table I. Serum concentrations of cytokines after i.v. inoculation of S. aureus to IL-1R<sup>+/−</sup> and IL-1R<sup>−/−</sup> mice<sup>a</sup>

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>IL-1R&lt;sup&gt;+/−&lt;/sup&gt;</th>
<th>IL-1R&lt;sup&gt;−/−&lt;/sup&gt;</th>
<th>IL-1R&lt;sup&gt;+/−&lt;/sup&gt;</th>
<th>IL-1R&lt;sup&gt;−/−&lt;/sup&gt;</th>
<th>IL-1R&lt;sup&gt;+/−&lt;/sup&gt;</th>
<th>IL-1R&lt;sup&gt;−/−&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNF</td>
<td>8 ± 3</td>
<td>NS</td>
<td>16 ± 6</td>
<td>NS</td>
<td>16 ± 5</td>
<td>NS</td>
</tr>
<tr>
<td>IL-6</td>
<td>140 ± 23</td>
<td>0.002</td>
<td>30 ± 15</td>
<td>0.06</td>
<td>2800 ± 610</td>
<td>610 ± 2100</td>
</tr>
<tr>
<td>IL-1β</td>
<td>6 ± 2</td>
<td>NA</td>
<td>10 ± 1</td>
<td>NA</td>
<td>17 ± 4</td>
<td>54 ± 9</td>
</tr>
<tr>
<td>IL-18</td>
<td>316 ± 33</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>173 ± 25</td>
<td>190 ± 28</td>
</tr>
</tbody>
</table>

* Mice, intact or defective with respect to IL-1R gene, were inoculated i.v. with 1 × 10<sup>8</sup> S. aureus. Blood samples were obtained from 11 IL-1R<sup>+/−</sup> and 10 IL-1R<sup>−/−</sup> at 4 and 24 h after inoculation of staphylococci. The serum levels of cytokines at 96 h after inoculation of S. aureus were checked in 12 IL-1R-deficient and 16 wild-type mice sacrificed at this time point. Values are expressed as picograms per milliliter (mean ± SEM). Values of <i>p</i> are calculated using the Mann-Whitney U test. NA, Not analyzed.

**Discussion**

This is the first report presenting the central role of IL-1R signaling in systemic S. aureus infection. Mice lacking IL-1R type I, the receptor responsible for transmission of IL-1α signals into cells, develop severe septic arthritis and septicemia and eventually die in response to i.v. inoculation with S. aureus. One of the obvious reasons for the severe clinical outcome of septic arthritis in IL-1R-deicient mice is the accumulation and proliferation of live staphylococci in various tissues. Such a defective control of S. aureus growth in vivo could be due to, e.g., a nonoptimal recruitment of neutrophils and a diminished phagocytosis. Furthermore, we show a major importance of the IL-1R signaling pathway in controlling production of proinflammatory cytokines such as TNF, IL-6, IL-1β, and IL-18 in response to S. aureus.

Weight loss the first 24 h after inoculation of staphylococci depends on IL-1R signaling. This is clearly shown in response to both doses of staphylococci used in the present study. While IL-1β exerts directly a down-regulatory effect on food intake (22), indirect effects of IL-1R signaling are also possible. Indeed, TNF is also involved in regulation of weight (23) and, as shown in this study, its production is regulated by IL-1R expression. It is well known that IL-6 production is triggered by IL-1 (24). Both in vitro and in vivo, the IL-6 levels in response to S. aureus were highly decreased in the absence of IL-1R signaling. IL-6 induces fever and in vivo, the IL-6 levels in response to S. aureus infection concern development of septicemia. The severe condition of IL-1R knockout mice might be caused directly via staphylococcal products or indirectly via host mediators, e.g., cytokines, highly induced by high staphylococcal load. IL-18 was previously shown to be a detrimental mediator in S. aureus infection concerning development of septicemia (10). The high serum levels of IL-18 found in IL-1R-deficient mice as compared with wild-type controls could thus contribute to the severe septicemia of IL-1R<sup>−/−</sup> mice.

The protective effects mediated by IL-1R signaling with respect to development of septicemia and septic death are greater as compared with protection mediated by TNF/lymphotoxin α (29). Indeed, we have previously demonstrated that, while being susceptible to S. aureus infection, TNF/lymphotoxin α double-mutant mice or TNF single-deficient mice were protected against septic arthritis. This is not the case for IL-1R-deficient mice. The increased frequency and severity of septic arthritides in IL-1R<sup>−/−</sup> mice also increases IC killing of S. aureus (26).

Table II. Supernatant concentrations of cytokines following in vitro stimulation with formalin-killed S. aureus<sup>a</sup>

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>IL-1R&lt;sup&gt;+/−&lt;/sup&gt;</th>
<th>IL-1R&lt;sup&gt;−/−&lt;/sup&gt;</th>
<th>IL-1R&lt;sup&gt;+/−&lt;/sup&gt;</th>
<th>IL-1R&lt;sup&gt;−/−&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNF</td>
<td>182 ± 20</td>
<td>&lt;0.05</td>
<td>84 ± 12</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>IL-6</td>
<td>NA</td>
<td>NA</td>
<td>2100 ± 750</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>IL-1β</td>
<td>7 ± 1</td>
<td>NS</td>
<td>9 ± 2</td>
<td>NS</td>
</tr>
<tr>
<td>IL-18</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

* Spleen cells from noninfected mice, intact or defective with respect to IL-1R gene, were stimulated in vitro using 1 × 10<sup>8</sup> formalin-killed S. aureus. Detection limit is 25 pg/ml. Values are obtained from three mice in each group and expressed as picograms per milliliter (mean ± SEM). Values of <i>p</i> are calculated using the Mann-Whitney U test. NA, Not analyzed; ND, not detected.
mice, as compared with IL-1R−/− mice, is most probably explained by staphylococci being densely expressed in the joints of the former group. The high staphylococcal load in joints is explained by staphylococci being densely expressed in the joints of mice, as compared with IL-1R−/− mice only a few days following bacterial inoculation. It is possible that the high IL-18 production in IL-1R-deficient mice, compared with the controls, increases the joint manifestations via recruitment of inflammatory cells and their production of reactive oxygen intermediates.

The regulation of IL-18 production was recently reviewed (8). Because its promoter region contains a NF-κB recognition sequence that is downstream of IL-1R signaling, it is not very surprising that IL-18 production is influenced by an IL-1R knockout situation. However, the impact of IL-1R signaling on IL-18 production has not been previously described. Evidently, IL-18 production is directly or indirectly dependent on a functional IL-1R, as seen by higher serum levels of this cytokine 24 h after the inoculation of bacteria in wild-type mice as compared with IL-1R−/− mice.


References