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LETTERS

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Reply to letter by Nardelli and Schell commenting on the pathogenesis of Lyme arthritis

AQ: 1

To the Editor:

In a recent letter to the editor (1) about our article on the pathogenesis of Lyme arthritis and the role that cytokines play in the process (2), Drs. Nardelli and Schell make important points that are largely consistent with our own findings. In particular, the authors stress that Th1 cells, producing high levels of interferon-γ [IFNγ], are not solely responsible for the induction of Lyme arthritis (3,4), since experimental Lyme arthritis can occur and propagate even in IFNγ-deficient mice (5,6). The possible involvement of interleukin-17 (IL-17) in the genesis of Lyme arthritis is suggested by the observations that IL-17 inhibition prevents the development of arthritis in vaccinated mice challenged with *Borrelia burgdorferi* (7), and that T cell priming with peptides in the presence of *B burgdorferi* induces IL-17 production in Th cells (8). In our study, we demonstrated that T cells from the synovial fluid of patients with Lyme arthritis produce IL-17 in response to the neutrophil-activating protein A (NapA) of *B burgdorferi* (2).

Second, Nardelli and Schell state their support for the hypothesis that Th17-associated cytokines, such as IL-23, transforming growth factor β (TGFβ), and IL-6, are also involved in the *Borrelia*-mediated arthritic processes in mice (9). We are strongly in favor of this hypothesis. Our findings in human subjects revealed that *B burgdorferi* NapA is able to induce the expression of IL-6, IL-1β, and TGFβ in monocytes, and IL-23 in neutrophils and monocytes (2).

AQ: 2

Third, the authors suggest that Treg cells might also influence the development of Lyme arthritis, since neutralization of IL-17 in *Borrelia*-vaccinated and -infected mice is associated with both an increased number of CD4+CD25+ T cells in the local lymph nodes and the prevention of severe destructive arthritis (10). Furthermore, it has been demonstrated that TGFβ activates Treg cell responses regardless of the combination of TGFβ, IL-23, and IL-6 that is driving Th17 responses (11). Thus, on the basis of the results obtained so far in humans (2) and in mice (7), it can be speculated that the relative amount of the different cytokines (TGFβ, or TGFβ plus IL-23, IL-6, and IL-1β) present in the local synovium might dictate the progression of the disease toward more severe destructive arthritis.

AQ: 3

Overall, considering the results obtained in humans (2) and in studies of *Borrelia*-vaccinated and -challenged mice by Drs. Nardelli and Schell (7) and others, we conclude that in *B burgdorferi* infection, a synovial Th17 response (Figure 1) plays an important role in the genesis of Lyme arthritis, and that further exploration of the mechanisms regulating the Th17 pathway may prove helpful in the design of novel tools for the prevention and treatment of the disease.

F1

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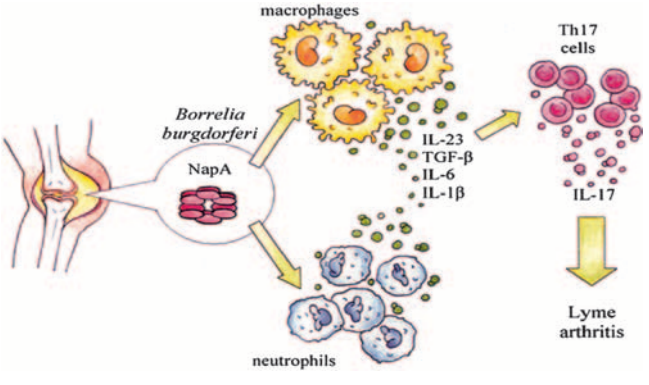

Figure 1. The synovial Th17 response in *Borrelia burgdorferi* infection. NapA = neutrophil-activating protein A; IL-23 = interleukin-23; TGFβ = transforming growth factor β.

COLOR

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AUTHOR QUERIES

AUTHOR PLEASE ANSWER ALL QUERIES 1

1—**Author: I was the staff member who copyedited your article. If you have any questions or comments about the editing, or if you would like to discuss specific aspects of your responses to any of the queries, please write your comments on the proofs or contact me by e-mail (jbauermeister@rheumatology.org), phone (404-633-3777, ext 836), or fax (404-329-7335).** ***Josh Bauermeister, Manuscript Editor.***

2—**Author: I changed this sentence from "**. . . **considering that in humans, we provided evidence that** *B burgdorferi* **NapA is able to induce the expression of IL-23 in neutrophils and monocytes, IL-6, IL-1**β**, and TGF-**β **in monocytes" to "Our findings in human subjects revealed that** *B burgdorferi* **NapA is able to induce the expression of IL-6, IL-1**β**, and TGF**β **in monocytes, and IL-23 in neutrophils and monocytes (2)." Okay? If not, clarify the meaning of your original sentence.**

3—**Author: I changed this sentence from "Furthermore, it has been demonstrated that TGF-**β **activates Treg responses whether the combination of TGF-**β**, IL-23, and IL-6 drive Th17 responses" to "Furthermore, it has been demonstrated that TGF**β **activates Treg cell responses regardless of the combination of TGF**β**, IL-23, and IL-6 that is driving Th17 responses." Okay? If not, please clarify the meaning of your original sentence.**