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LETTERS

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

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).

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.

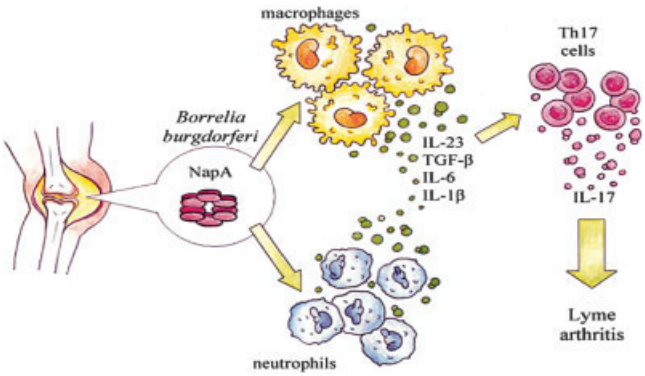

Figure 1. The synovial Th17 response in *Borrelia burgdorferi* infection. NapA = neutrophil-activating protein A; IL-23 = interleukin-23; TGFβ = transforming growth factor β.

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.

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1. Nardelli DT, Schell RF. Expanded role for interleukin-17 in Lyme arthritis: comment on the article by Codolo et al [letter]. Arthritis Rheum 2009;60:1202.
2. Codolo G, Amedei A, Steere AC, Papinutto E, Cappon A, Polenghi A, et al. Borrelia burgdorferi NapA–driven Th17 cell inflammation in Lyme arthritis. Arthritis Rheum 2008;58:3609–17.
3. Yssel H, Shanafelt MC, Soderberg C, Schneider PV, Anzola J, Peltz G. Borrelia burgdorferi activates a T helper type 1-like T cell subset in Lyme arthritis. J Exp Med 1991;174:593–601.
4. Gross DM, Steere AC, Huber BT. T helper 1 response is dominant and localized to the synovial fluid in patients with Lyme arthritis. J Immunol 1998;1602:1022–8.
5. Brown CR, Reiner SL. Experimental Lyme arthritis in the absence of interleukin-4 or γ interferon. Infect Immun 1999;67:3329–33.
6. Christopherson JA, Munson EL, England DM, Croke CL, Remington MC, Molitor ML, et al. Destructive arthritis in vaccinated interferon γ-deficient mice challenged with Borrelia burgdorferi: modulation by tumor necrosis factor α. Clin Diagn Lab Immunol 2003;10:44–52.
7. Burchill MA, Nardelli DT, England DM, DeCoster DJ, Christopherson JA, Callister SM, et al. Inhibition of interleukin-17 prevents the development of arthritis in vaccinated mice challenged with Borrelia burgdorferi. Infect Immun 2003;71:3437–42.
8. Infante-Duarte C, Horton HF, Byrne MC, Kamradt T. Microbial lipopeptides induce the production of IL-17 in Th cells. J Immunol 2000;165:6107–15.
9. Nardelli DT, Luk KH, Kotloski NJ, Warner TF, Torrealba JR, Callister SM, et al. Role of IL-17, transforming growth factor-β, and IL-6 in the development of arthritis and production of anti-outer surface protein A borreliacidal antibodies in Borrelia-vaccinated and -challenged mice. FEMS Immunol Med Microbiol 2008;53:265–74.
10. Nardelli DT, Cloute JP, Luk KH, Torrealba J, Warner TF, Callister SM, et al. CD4+CD25+ T cells prevent arthritis associated with Borrelia vaccination and infection. Clin Diagn Lab Immunol 2005;12:786–92.
11. Dong C. TH17 cells in development: an updated view of their molecular identity and genetic programming. Nat Rev Immunol 2008;8:337–48.