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LYME ARTHRITIS

Spirochaete remnants could explain antibiotic-refractory Lyme arthritis

Lyme disease caused by infection with the spirochaetal bacteria *Borrelia burgdorferi* is generally responsive to antibiotic therapy, but in some patients musculoskeletal symptoms can continue for months after treatment, and still others develop Lyme arthritis that is refractory to treatment with antibiotics. New research in a mouse model of Lyme borreliosis suggests that immunogenic spirochaete antigens, but not infectious spirochaetes, persist near cartilage after treatment and might contribute to these phenomena.

The research, led by Linda Bockenstedt at Yale University, shows that continous administration of doxycycline eliminates established infection in mice infected by tick-borne *B. burgdorferi*. "With the exception of a single immunodeficient mouse, we could not find live spirochaetes in any mouse treated with antibiotics," says Bockenstedt, "even though we used multiple modalities to detect them." Live imaging with two-photon microscopy revealed that "antibiotics rapidly eliminated the vast majority of spirochaetes in mice within a day or two of treatment." Infectious spirochaetes could not be detected in culture, by xenodiagnosis with ticks or after tissue transplant into a new mammalian host.

> "...the *B. burgdorferi* antigens were shown to be immunogenic and inflammatory..."

Even though live spirochaetes were not found, direct immunfluorescence staining revealed the presence of *B. burgdorferi* antigens adjacent to ear cartilage and at the patellofemoral entheses of antibiotic-treated mice; live imaging showed the antigen deposits to be amorphous and nonmotile. "These deposits," Bockenstedt adds, "were in locations where patients can experience symptoms after Lyme disease; that is, in tendon adjacent to bone."

Notably, the *B. burgdorferi* antigens were shown to be immunogenic and inflammatory: patellar tissue containing the antigens induced antibodies when transplanted into naive recipients, and elicited the production of the proinflammatory cytokine TNF from mouse macrophages *in vitro*.

Bockenstedt contends that the findings could have implications for human disease: "Bacterial antigens that persist in tendons after the live bacteria are gone may provide a stimulus for perpetuating inflammation in antibiotic-refractory Lyme arthritis."

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Original article Bockenstedt, L. K. *et al.* Spirochete antigens persist near cartilage after murine Lyme borreliosis therapy. *J. Clin. Invest.* **122**, 2652–2660 (2012)

Image courtesy of Centers for Disease Control and Prevention.