Lyme disease is the most common tick-borne disease in North America and Europe, however, current biomarkers inconsistently detect the disease. In this issue of the *JCI*, Gwynne et al. revealed how the Lyme disease agent *Borrelia burgdorferi* relies on host lipids for growth. The authors used a murine model to show that *B. burgdorferi* infection led to the production of antibodies against phospholipids, possibly as a consequence of incorporation into the spirochete membrane. Antibodies were induced against phosphatidic acid, phosphatidylcholine, and phosphatidylserine. Notably, no antibodies against cardiolipin were found, distinguishing Lyme disease from syphilis and some other diseases. Sera samples from patients with Lyme disease suggested that these antibodies may help diagnose *B. burgdorferi* infection and that antibody titers may effectively indicate the response to treatment. These findings suggest that *B. burgdorferi*–induced anti-lipid antibodies, in conjunction with a careful clinical assessment, may aid in the diagnosis of Lyme disease.
Use of host lipids by the Lyme disease spirochete may lead to biomarkers

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Insights into the challenges of Lyme disease diagnosis

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Conflict of interest: EF has an equity interest in and serves as a consultant for L2 Diagnostics.

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Antiphospholipid antibodies in different diseases

Gwynne and co-authors demonstrate that *Borrelia* infection may induce antibodies recognizing host phospholipids, revealing a potential biomarker of infection (4). Although antiphospholipid antibodies are most commonly associated with autoimmune disorders, such antibodies are sometimes generated following infection. Syphilis, caused by the spirochete *Treponema pallidum*, induces antibodies against the phospholipid cardiolipin (16). Interestingly, cardiolipin antibodies are also induced during autoimmune antiphospholipid syndrome (APS). Beyond syphilis, antiphospholipid antibodies have been reported in various infectious diseases including COVID-19, tuberculosis, malaria, leprosy, leptospirosis, and Lyme disease, as well as during *Helicobacter pylori*, hepatitis C, varicella, and other infections (16, 17). HIV infection is associated with antibodies against cardiolipin as well as PS, PC, and phosphatidylinositol (16, 18). *Plasmodium* infection similarly induces the development of PS-specific antibodies in mice and humans (19, 20). Such antiphospholipid antibodies are often due to erroneous activation of B cells that are induced because of inflammation and marked by expression of the T-bet transcription factor (21, 22). The broad development of these types of antibodies may limit their overall utility, however, anti-PA, anti-PS, and anti-PC antibodies might be used, in conjunction with a careful clinical assessment and current serologic tests, as biomarkers for Lyme disease.

Antiphospholipid-specific diagnosis of Lyme disease

Gwynne et al. showed that *B. burgdorferi* infection in a mouse model induced antibodies against PA and PC and against the phospholipids PS, PE, PG, and galactosycholesterol (gC) (4). The mice did not develop antibodies against cardiolipin, the phospholipid associated with syphilis infection, implying that the detected antibodies were specific to Lyme disease. The authors then compared the diagnostic value of PA-, PS-, and PC-specific antibody responses using standard assays in patients with early symptoms of Lyme disease. In a small number of patients, the diagnosis using antiphospholipid antibodies outperformed standard diagnostic tests and even correctly identified antibody responses in individuals who only presented with erythema migrans. In addition, the antiphospholipid antibodies peaked during *B. burgdorferi* infection in humans and declined following antibiotic treatment, which contrasts with the more prolonged antibody response toward *Borrelia* antigens. These antiphospholipid responses could depend on invariant natural killer T (iNKT) cells, which are capable of recognizing lipid antigens and assisting B cells with antibody production (23, 24). Future studies to validate antiphospholipid responses with *B. burgdorferi* infection should include a larger number of patients with Lyme disease and individuals with other infectious and autoimmune illnesses. The lipid autoantibodies described in the study by Gwynne and colleagues represent potentially promising biomarkers that could aid clinicians in the diagnosis of Lyme disease and meaningfully impact patient outcomes.

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