A Highly Expressed Human Protein, Apolipoprotein B-100, Serves as an Autoantigen in a Subgroup of Patients With Lyme Disease

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To discover novel autoantigens associated with Lyme arthritis (LA), we identified T-cell epitopes presented in vivo by human leukocyte antigen (HLA)–DR molecules in patients’ inflamed synovial tissue or joint fluid and tested each epitope for autoreactivity. Using this approach, we identified the highly expressed human protein, apolipoprotein B-100 (apoB-100), as a target of T- and B-cell responses in a subgroup of LA patients. Additionally, the joint fluid of these patients had markedly elevated levels of apoB-100 protein, which may contribute to its autoantigenicity. In patients with antibiotic-refractory LA, the magnitude of apoB-100 antibody responses correlated with increased numbers of plasma cells in synovial tissue, greater numbers and activation of endothelial cells, and more synovial fibroblast proliferation. Thus, a subset of LA patients have high levels of apoB-100 in their joints and autoreactive T- and B-cell responses to the protein, which likely contributes to pathogenic autoimmunity in patients with antibiotic-refractory LA.

Keywords. apolipoprotein B; autoantibodies; Borrelia burgdorferi; erythema migrans; autoimmunity; Lyme arthritis; Lyme disease.

Lyme arthritis (LA) is a late manifestation of infection with the tick-borne spirochete, Borrelia burgdorferi [1–3]. Although arthritis resolves in most patients with appropriate oral or intravenous antibiotic therapy, some patients have persistent synovitis for months or years after antibiotic treatment, called antibiotic-refractory LA [4]. Highly inflammatory strains of B. burgdorferi more commonly cause antibiotic-refractory LA [5–7], but this outcome is not thought to result from persistent infection [8–10]. Rather, excessive joint inflammation triggered by the infection [7, 11], immune dysregulation [12, 13], and infection-induced autoimmunity [14, 15] are thought to have important roles in this outcome.

To identify autoantigens associated with antibiotic-refractory LA, we developed a novel approach using individual patient’s inflamed synovial tissue or joint fluid (JF) to identify immunogenic T-cell epitopes presented in vivo by human leukocyte antigen (HLA)–DR molecules at these sites [16]. First, the HLA-DR-presented peptides are isolated and identified by liquid chromatography–tandem mass spectrometry (LC-MS/MS), synthesized, and tested for immunogenicity using the matching patient’s peripheral blood mononuclear cells (PBMCs). Next, immunogenic peptides and their source proteins identified in the original patient are tested for T- and B-cell responses in large numbers of case and control subjects.

Using this approach, we recently identified 2 novel autoantigens, endothelial cell growth factor (ECGF) and annexin A2, as targets of T- and B-cell responses in Lyme disease [14, 17]. With both proteins, low-level T- and B-cell responses were occasionally apparent early in the illness in patients with erythema migrans.
(EM). Later in the disease, approximately 30% of patients with either antibiotic-responsive or antibiotic-refractory LA had robust T-cell reactivity and about 15% had autoantibody responses to each protein. Moreover, ECGF autoantibody responses in antibiotic-refractory patients correlated with obliterative microvascular lesions in synovial tissue [15], and annexin A2 autoantibody responses correlated with greater numbers of synovial fibroblasts and tissue fibrosis [17].

Herein, we report the identification of a third novel autoantigen, the highly expressed human protein apolipoprotein B-100 (apoB-100), as a target of T- and B-cell responses in a subgroup of LA patients.

METHODS

Samples From Patients and Control Subjects

All patients met the Centers for Disease Control and Prevention criteria for Lyme disease [18]. LA patients were categorized as having antibiotic-responsive or antibiotic-refractory arthritis, as previously defined [4]. In patients with LA, serum samples, PBMCs, and if available, synovial fluid or synovial tissue, were tested. In patients with EM, all of whom had positive cultures for B. burgdorferi from lesional skin, serum samples and PBMCs were assayed. Serum samples, which were stored at –80°C, were obtained from 1988 to 2014; and PBMCs, stored in liquid nitrogen, were collected from 2002 to 2014.

For comparison, serum samples were tested from patients with new-onset rheumatoid arthritis (RA), all of whom met the 2010 American College of Rheumatology/European League against Rheumatism criteria for that disease [19]. For healthy controls (HCs), serum samples and PBMCs were collected from healthy hospital personnel who did not have a history of LA, and serum samples were obtained from healthy blood bank donors.

The studies conducted from 1988 to 2002 were approved by the Human Investigations Committee at Tufts Medical Center, and those conducted after 2002 were approved by the Committee at Massachusetts General Hospital. All patients and control subjects gave written informed consent.

Enzyme-Linked Immunosorbent T-Cell Assay

A detailed description of the methods for isolation and identification of in vivo HLA-DR-presented peptides from patients’ synovial tissue was published previously [16]. For this study, the 216 HLA-DR-presented peptides identified from the synovium or JF of patient LA5 were synthesized by Mimotopes (Victoria, Australia). Individual peptides (1 µM) were first pooled (4 peptides per set) and tested in duplicate wells (2 × 10^5 cells/well) for antigenicity with that patient’s PBMCs; the peptides in immunoreactive pools were then restested individually. For validation, testing was done with samples from multiple case and control patients. Because they would be expected to have different HLA-DR genotypes, a computer algorithm TEPITOPE [20, 21] was used to identify 3 additional predicted promiscuous peptides (those predicted to bind >10 HLA-DR molecules) for the 6 implicated source proteins. The original and predicted peptides for each source protein were pooled together for testing. Finally, full-length recombinant human apoB-100 (1.32 nM) (Millipore), the source protein studied in detail, was used for testing.

All assays were performed using a human interferon (IFN)–γ ELISpot kit (Mabtech); negative controls (no antigen) and positive controls (phytohemagglutinin) were included with each assay. After 5-day incubation, the cells were transferred to IFN-γ enzyme-linked immunospot (ELISpot) plates and analyzed according to the manufacturer’s instructions. Images of wells were captured using an CTL ImmunoSpot S5 Analyzer, and spots were counted using Immunospot software. A positive response was defined as >3 standard deviations (SDs) above the mean value in 13 HCs.

Enzyme-Linked Immunosorbent Assay for Immunoglobulin G Anti-apoB-100 Antibodies

Immulon-1B enzyme-linked immunosorbent assay (ELISA) plates (Thermo Scientific) were coated with 0.5 µg/mL recombinant human apoB-100 (Millipore) in carbonate coating buffer and incubated overnight at 4°C. For each case or control subject, duplicate apoB-100-coated and apoB-100-uncoated wells were used. All subsequent steps were performed on a platform shaker at room temperature. The plates were incubated with a 3% bovine serum albumin (BSA; Equitech-Bio, Inc) in phosphate-buffered saline (PBS) −0.05% Tween 20 (PBST) blocking buffer. After washing with PBST, the plates were incubated with patients’ serum or JF (1:200) or with the positive control, goat antiapolipoprotein B antibody AB742 (1:20 000; Millipore), followed by horseradish peroxidase (HRP)–conjugated goat antihuman immunoglobulin G (IgG; 1:2000; Santa Cruz Biotechnology) or donkey antigoat IgG (1:2000; Life Technologies), and then 3,3′,5,5′-tetramethylbenzidine (TMB) substrate (BD Biosciences). For interplate standardization, the positive control AB742 was included on each plate. A positive response was defined as >3 SD above the mean value in 57 HC (>0.34 optical density [OD]_{450}).

ELISA for apoB-100 Protein Concentrations

ELISA plates were coated with mouse antihuman apolipoprotein B MAB012 (1 µg/mL; Millipore) and incubated overnight at 4°C. The next day, plates were incubated with blocking buffer (3% BSA in PBST), followed by each patient’s JF or serum sample (1:8000). To generate a standard curve, serial dilutions of apoB-100 protein were added to each plate. The plates were then incubated with AB742 (1:5000), followed by HRP-conjugated donkey antigoat IgG (1:2000), and then TMB substrate (BD Biosciences).
Immunohistochemistry
In a previous study [15], fresh frozen synovial tissue samples from 14 patients with antibiotic-refractory LA who underwent synovectomies were examined for histologic features and specific cell types. Each finding was ranked from 1 to 14, with 14 being the highest-ranked patient. In the current study, these histologic data were correlated with anti-apoB-100 antibody values ranked from the highest to the lowest absorbance value. The researchers who ranked the histologic findings and who determined the apoB-100 antibody titers were blinded to each other’s findings. Microscopic images (40×) were obtained with a Nikon Eclipse ME6000 microscope using a Nikon digital camera DXM1200C and processed with NISelements AR2-30 imaging software.

Data Analysis and Statistics
Quantitative data were analyzed using unpaired t test, categorical data were analyzed using Fisher exact test, and matched patient serum and JF samples were analyzed using paired t test. Correlations were analyzed using Pearson correlation test. All analyses were performed using GraphPad Prism 6.

RESULTS
Preliminary Screen for Identification of Autoantigens
Patient LA5, a 53-year-old woman with HLA-DRB1*0301/0305 alleles, had persistent, proliferative synovitis in a knee after the completion of antibiotic therapy for LA. Afterward, she was treated with methotrexate and then etanercept. Because of incomplete responses, she underwent a therapeutic synovectomy 3 years after the completion of antibiotic therapy.

The approach used for the identification of HLA-DR-presented peptides in synovial tissue and JF is presented in Figure 1. From these sites, 216 nonredundant, self-peptide sequences were identified, which were derived from 156 source proteins. In the first screen, the 216 synthesized peptides were pooled in sets with 4 peptides per well for initial testing using her PBMCs. Six peptide sets, consisting of 24 peptides, induced the highest responses in IFN-γ ELISpot assays. In the second screen, the 24 peptides were restested individually, and 6 of the 24 peptides induced a response that was >3 times background.

In the third screen, the 6 immunoreactive HLA-DR-presented peptides, which were derived from 6 different source proteins, were tested using PBMCs from 13 randomly selected patients with antibiotic-refractory LA and 7 HCs (Figure 1). In addition, because these patients and control subjects would be expected to have different HLA-DR genotypes, 3 peptides, predicted to be promiscuous HLA-DR binders, were synthesized for each source protein, and pooled together with the original peptide for testing. Of the 6 peptide sets, the set derived from the source protein apolipoprotein B-100 (apoB-100) (peptide sequences shown in Figure 1), which was identified from synovial tissue,

Figure 1. Initial screening process for identification of candidate autoantigens. Abbreviations: apoB-100, apolipoprotein B-100; HLA, human leukocyte antigen; LA, Lyme arthritis; LC-MS/MS, liquid chromatography–tandem mass spectrometry; PBMC, peripheral blood mononuclear cell.
showed the greatest difference in reactivity between patients and control subjects. Thus, we chose to test apoB-100 in detail as a potential autoantigen in LA.

**T-Cell Responses to apoB-100**

To characterize more fully the response to the exceptionally large monomeric apoB-100 protein (4536 aa), which has many predicted T-cell epitopes, we examined T-cell reactivity with full-length recombinant apoB-100 in larger numbers of patients with different manifestations of Lyme disease and in HCs using the IFN-γ ELISpot assay. Of 12 patients with EM, the initial skin lesion of the infection, none had T-cell responses to apoB-100 that was ≥3 SD above the mean value of 13 HCs (Figure 2A). In comparison, 8 of 17 patients (47%) with antibiotic-responsive LA and 6 of 20 patients (32%) with antibiotic-refractory LA (including the 13 patients tested in screen 3) had positive T-cell responses to this protein compared with HCs (P = .004 and .06, respectively; Fisher exact test) (Figure 2B). The mean T-cell response in responsive LA patients was significantly higher than that in HC or EM patients (P = .009 and P = .008, respectively; unpaired t test), and a similar trend was observed for the refractory LA patients (in both, P = .08) (Figure 2A). Altogether, 14 of 37 patients (38%) with LA had T-cell reactivity with apoB-100 compared with none of the patients with EM and none of the HCs.

**B-Cell Responses to apoB-100**

If an autoimmune response to apoB-100 were pathogenic, apoB-100-reactive CD4+ T cells would likely help B cells to produce anti-apoB-100 autoantibodies. Of 105 patients with EM, 5 (5%) had antibody responses to apoB-100 that were ≥3 SD above the mean value in 57 HCs (Figure 3A). In comparison, 12 of 92 patients (13%) with antibiotic-responsive LA and 12 of 94 patients (13%) with antibiotic-refractory LA had positive IgG autoantibody responses to apoB-100 (Figure 3A). Altogether, 24 of 186 LA patients (13%) had autoantibody responses to the protein. The mean levels in patients with responsive or refractory LA were significantly higher than those in patients with EM (in both instances, P < .0001) or in HCs (P = .003 or P = .04, respectively; unpaired t test) (Figure 3A). Similarly, when the percentages of patients with positive or negative apoB-100 antibody responses were compared with those in HCs, the frequencies of apoB-100 autoantibodies were significantly higher in patients with antibiotic-responsive or antibiotic-refractory LA (P = .004 or .004, respectively; Fisher exact test) (Figure 3A). In addition, low-level IgM reactivity with apoB-100 was found in 3 patients with antibiotic-responsive LA, 1 with antibiotic-refractory LA, and none with EM (data not shown).

Paired serum and JF samples were available from 33 patients with antibiotic-refractory LA and 18 patients with antibiotic-responsive LA. Among the 18 patients with antibiotic-responsive arthritis, the mean apoB-100 antibody values were similar in JF (0.19) and serum (0.15) (Figure 3C). In contrast, among the 33 patients with antibiotic-refractory LA, the mean OD value (0.21) in JF samples was significantly higher than that (0.15) in serum (P = .04; paired t test) (Figure 3D). Thus, primarily in the refractory group, some patients had responses that were greater in JF than serum, consistent with local apoB-100 antibody production.

Altogether, 32%–47% of LA patients with refractory or responsive LA had autoreactive T-cell responses to apoB-100 and 13% of these patients had positive IgG antibody responses to the protein. Of the 30 LA patients in whom both T- and B-cell reactivity were assessed, 9 (30%) had both T and B responses to apoB-100.

**ApoB-100 Protein Levels in Serum and Joint Fluid**

For apoB-100 to become immunogenic, one would predict that it would be present in high concentrations in patients’ inflamed

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**Figure 2.** Testing of PMBCs for T-cell autoreactivity against full-length apoB-100. PMBCs were stimulated with the full-length apoB-100 and T-cell reactivity was measured using the human IFN-γ ELISpot assay. A, A positive response was defined as a mean SFU/10⁶ cells that was 3 standard deviations above the mean of healthy controls (area above the gray shaded region). P values were calculated using an unpaired t test. B, The number of patients with positive responses and percentage of positive responses for each patient group. Groups are compared using Fisher exact test. Abbreviations: apoB-100, apolipoprotein B-100; ELISpot, enzyme-linked immunospot; EM, erythema migrans; HC, healthy control; IFN-γ, interferon-γ; PBMCs, peripheral blood mononuclear cells; SFU, spot forming units.
JF and perhaps in peripheral blood. The mean concentration of apoB-100 in the serum of 16 HCs was 67 mg/dL (Figure 4A), a value within normal physiologic levels [22–24]. In comparison, 10 of 20 patients (50%) with antibiotic-responsive LA and 13 of 20 patients (65%) with antibiotic-refractory LA had serum levels of apoB-100 that were >3 SD the mean of HCs (Figure 4B). The mean value was approximately 150 mg/dL in both patient groups, which was significantly higher than HCs. Although patients with EM or RA usually lacked antibody responses to apoB-100, a subset of patients (6 of 10 and 2 of 9, respectively) had serum levels >3 SD the mean of HCs (Figure 4B). The mean value was approximately 150 mg/dL in both patient groups, which was significantly higher than HCs. Although patients with EM or RA usually lacked antibody responses to apoB-100, a subset of patients (6 of 10 and 2 of 9, respectively) had serum levels >3 SD the mean of HCs, and overall, the mean concentration of apoB-100 was significantly higher than that in HCs (P < .0001 and .01, respectively; unpaired t test).

In the subset of 57 LA patients in whom JF samples were available, refractory and responsive patients had significantly greater levels of apoB-100 protein in JF than in serum (P = .005 and .0005, respectively; unpaired t test), but the levels in JF were similar in both patient groups (mean values, approximately 225 mg/dL) (Figure 4A). Thus, the highest apoB-100 protein levels were found in JF, which may set the stage for autoimmune responses to the protein.

Histologic Findings in Synovial Tissue According to ApoB-100 Antibody Responses

Of the 14 patients with antibiotic-refractory LA in whom synovial tissue was available, 1 (7%) had a positive result for apoB-100 IgG antibodies that was >3 SD above the mean value in HCs, a similar percentage with positive results as in the larger patient group. Synovial tissue was not available in the responsive group because they never undergo synovectomies. Although 13 of the
Examples of these histologic findings are shown in Figure 7. In contrast, no relationship was observed with fibrosis, cellular infiltration of the sublining layer, lymphoid aggregates, or obliterative vascular lesions, or with the numbers of T or B cells, macrophages, myeloid dendritic cells, or follicular dendritic cells.

**DISCUSSION**

Using our previously described approach of discovery-based proteomics and translational research [14, 16], we determined that HLA-DR-presented peptides of apoB-100 were immunoreactive in an initial patient with antibiotic-refractory LA. This provided a bridge to determine that peptides of this protein and the full-length protein were targets of T- and B-cell responses in a subgroup of patients with Lyme disease. Consistent with the percentages of patients who had reactivity with 2 previously identified autoantigens in Lyme disease, ECGF [14] and annexin A2 [17], we found here that 38% of patients with antibiotic-responsive or antibiotic-refractory LA had T-cell responses to apoB-100, and 13% had autoantibody responses to the protein. Moreover, low-level autoantibody responses to each of these proteins were apparent in a small percentage of the patients with EM. Of the 3 autoantigens identified to date, only 3% of the patients had positive responses to more than 1 of these autoantigens.

In the case of apoB-100, the development of autoimmune responses may be initiated by the intimate relationship between the spirochete and host. Unlike most prokaryotes, the eukaryotic cell membranes, cholesterol and phosphatidylcholine, are essential components of the membrane of B. burgdorferi [25, 26]. However, spirochetes lack the ability to synthesize cholesterol or any long-chain fatty acids [25]. B. burgdorferi can acquire cholesterol from the plasma membrane of eukaryotic cells, and therefore, spirochetes’ lipid composition reflects that of host fluids and tissues [27]. The presence of cholesterol in the membrane of B. burgdorferi allows for lipid raft formation and similar ultrastructural organization between the spirochete and the host [28, 29]. In addition, in mice, higher levels of host cholesterol increased the severity of disease in joints through higher spirochetal burdens and inflammation [30].

The immune response against the spirochetes’ surface lipoproteins and glycolipids could contribute to the development of autoimmunity to apoB-100. First, because the structure and ultrastructural organization of spirochetal glycolipids have similarities with lipids in human apoB-100 complexes [28, 29, 31–36], antibodies against spirochetal glycolipids could cross-react with similar epitopes in human apoB-100 complexes, leading to enhanced uptake and HLA-DR-presentation of apoB-100 peptides [28]. Alternately, the apoB-100 complex may bind spirochetal lipids or lipoproteins directly, as demonstrated in other experimental models [37–39], leading to increased uptake and presentation of apoB-100. Either of these events could constitute a “first hit” in immunogenicity, though this first step does not appear to cause tissue pathology. In LA
patients, apoB-100 was highly expressed in serum and even more in joints, with apoB-100 peptides presented by local HLA-DR molecules, leading to a “second immunologic hit.” RA patients also had high levels of apoB-100, but usually lacked autoantibodies to the protein, presumably because they did not experience the “first hit” of spirochetal infection.

Figure 5. Correlation between histologic rankings (CXCL13 staining, plasma cells, vascularity in the tissue, and ECGF) and anti-apoB-100 antibody rankings in patients with antibiotic-refractory Lyme arthritis who underwent synovectomies. The correlations were determined by Pearson’s correlation test. Abbreviations: apoB-100, apolipoprotein B-100; ECGF, endothelial cell growth factor; IgG, immunoglobulin G.

Figure 6. Correlation between histologic rankings (endothelial cells, expression of markers for endothelial cell activation, ICAM and VCAM, and fibroblasts) and anti-apoB-100 antibody rankings in patients with antibiotic-refractory Lyme arthritis who underwent synovectomies. The correlations were determined by Pearson’s correlation test. Abbreviations: apoB-100, apolipoprotein B-100; ICAM, intercellular adhesion molecule; IgG, immunoglobulin G; VCAM, vascular cell adhesion molecule.
Patients with either antibiotic-responsive or antibiotic-refractory arthritis had similar levels of apoB-100 in joints and similar percentages of antibody responses to the protein. However, this immune response appeared to become pathogenic only in refractory patients presumably because of excessive inflammation in their synovial microenvironment. First, patients

Figure 7. Immunohistochemical staining of synovial tissue from representative patients with antibiotic-refractory LA who had the highest or lowest rankings for serum apoB-100 IgG antibodies. The patient with the highest ranking for apoB-100 antibodies had marked staining for CXCL13, plasma cells, endothelial cells, and synovial fibroblasts, whereas the patient with the lowest ranking had minimal staining for these histologic findings. Brown indicates specific staining of the immune cells, and purple is the counter-stain (hematoxylin). A, Staining for CXCL13 and plasma cells. B, Staining for endothelial cells and synovial fibroblasts. Bars = 100 µm. Abbreviations: apoB-100, apolipoprotein B-100; IgG, immunoglobulin G; LA, Lyme arthritis.
with antibiotic-refractory LA have significantly higher levels of inflammatory cytokines in joints, including IFN-γ and tumor necrosis factor (TNF)-α [7, 11], which alter the immunoregulatory set point of T cells, leading to immune dysregulation [12, 13]. Second, we showed here that in refractory patients, the magnitude of the anti-apoB-100 antibody response correlated with larger numbers of plasma cells in the synovial tissue. Third, the refractory group had significantly higher levels of antibody to apoB-100 in JF compared with serum, whereas the responsive group did not. Together, these findings suggest that the refractory group had local production of apoB-100 antibodies in synovial tissue. Presumably, in refractory LA patients, increased levels of cytokines and large amounts of apoB-100 protein in joints combined with locally produced apoB-100 antibodies lead to immune complex formation, which further contributes to joint inflammation.

In addition, higher apoB-100 antibody levels in the refractory group were associated with greater vascularity in the tissue, more endothelial cell proliferation, more intense expression of endothelial cell activation markers, and greater numbers of synovial fibroblasts. Although only 1 of the 14 patients had an apoB-100 antibody response that was >3 SD above the mean value in HCs, the magnitude of anti-apoB-100 antibody levels correlated with numerous histologic rankings, suggesting that apoB-100 values <3 SD may still have biologic relevance. Thus, the percentage of patients with apoB-100 autoantibody levels that apoB-100 values <3 SD may still have biologic relevance.

Although associations do not prove causation, there are parallels between these findings in synovial tissue and those in plaques in atherosclerotic cardiovascular disease, a more thoroughly studied condition. ApoB-100, which is part of the large, low-density protein (LDL) complex [35], is an important component of atheromatous plaques [40]. As a part of the innate immune response, macrophages [41] and to a lesser extent neutrophils [42] infiltrate the plaques, and myeloperoxidases from these cells may oxidize LDL [43]. This process may generate many immunoreactive protein and lipid epitopes [40, 43]. Although the adaptive immune response to LDL is tightly regulated [44, 45], T- and B-cell responses to LDL components have been described in atherosclerosis [45]. Furthermore, oxidized LDL activates endothelial cells, which contribute to the production of proinflammatory cytokines and chemokines [46], including IFN-γ [47, 48] and TNF-α [41, 48], leading to more severe disease [46]. By analogy, we hypothesize that the inflammatory milieu within synovial tissue and JF, which contains macrophages, neutrophils, and synoviocytes, may oxidize LDL in these sites, thereby contributing to endothelial cell activation, apoB-100 antigenicity, and more severe disease [6, 7, 49].

In summary, we have shown that T- and B-cell responses to apoB-100 occur in a subset of patients with Lyme disease. First, the host response to B. burgdorferi may be an initial factor in apoB-100 immunogenicity. Later in the disease, marked abundance of apoB-100 in joints may lead to antigen presentation of apoB-100 peptides, and to T- and B-cell responses to the protein. In patients with antibiotic-refractory arthritis, the intense inflammatory microenvironment may allow this immune response to become pathogenic.

Notes

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