Induction of Early Atherosclerosis in LDL-Receptor–Deficient Mice Immunized With $\beta_2$-Glycoprotein I

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Background—Immunization with $\beta_2$-glycoprotein I ($\beta_2$GPI), the probable target of autoimmune anticardiolipin antibodies, results in experimental antiphospholipid syndrome in different mouse strains. The present study was undertaken to evaluate the effect of $\beta_2$GPI immunization on the progression of atherosclerosis.

Methods and Results—In the first experiment, 3 groups of LDL receptor–deficient (LDL-RD) mice (n=15 per group) were immunized with either $\beta_2$GPI or ovalbumin or were not immunized and were fed a chow diet for 12 weeks. In a second experiment, 3 groups of LDL-RD mice (n=10 per group) were immunized similarly and fed an atherogenic diet for 6 weeks. All $\beta_2$GPI-immunized mice developed high titer of anti-$\beta_2$GPI antibodies as well as a specific lymph node proliferation to $\beta_2$GPI. The average cholesterol levels did not differ between the mice fed similar diets, regardless of the immunization protocol. Atherosclerosis was enhanced in the $\beta_2$GPI-immunized mice (mean aortic lesion, 26 000±5700 $\mu m^2$) in comparison with their ovalbumin-immunized (mean, 3000±1099 $\mu m^2$; $P<0.01$) and nonimmunized (mean, 2250±770 $\mu m^2$; $P<0.01$) littermates. The average lesion size in the $\beta_2$GPI-immunized mice fed an atherogenic diet (mean, 98 000±8305 $\mu m^2$) was larger than the ovalbumin-immunized mice (mean, 81 250±12 933 $\mu m^2$; $P=NS$) or the nonimmunized controls (mean, 75 625±7281 $\mu m^2$; $P=NS$). The atherosclerotic plaques in the $\beta_2$GPI-immunized mice appeared to be more mature, and denser infiltration of CD4 lymphocytes was present in the subendothelium of the aortic sinuses from this group of mice.

Conclusions—The results of the present study provide the first direct evidence for the proatherogenic effect of $\beta_2$GPI immunization and establish a new model for immune-mediated atherosclerosis. (Circulation. 1998;98:1108-1115.)

Key Words: atherosclerosis ■ glycoproteins ■ antibodies ■ lipoproteins

The antiphospholipid syndrome (APS) is characterized by a prothrombotic predisposition manifested by thromboembolic events, thrombocytopenia, recurrent fetal loss, and additional systemic phenomena. The syndrome is associated with high titer of anticardiolipin antibodies (aCLs), which have traditionally been suggested to target negatively charged phospholipids. Circumstantial data imply that patients with systemic lupus erythematosus (SLE) (a high proportion of whom have high titers of aCLs) are prone to develop premature atherosclerosis. However, the mechanisms underlying the proatherogenic predisposition are still unresolved.

The issue of target recognition by aCLs has been the subject of intensive research in recent years. Some authors suggested that aCLs bind native phospholipids, whereas others proposed that certain plasma cofactors, on binding to phospholipids, could allow for aCL attachment. $\beta_2$-Glycoprotein I ($\beta_2$GPI) is a 50-kD plasma protein that possesses several in vitro anticoagulant effects (eg, inhibition of prothrombinase activity, ADP-induced platelet aggregation, and factor Xa generation).

This glycoprotein has recently been considered to be the target of autoimmune aCLs, which are sometimes referred to as anti-$\beta_2$GPI antibodies. Several authors have shown that immunization of mice and rabbits with $\beta_2$GPI results in the production of antibodies that bear similarities to human autoimmune aCLs. Moreover, it has been shown by us and others that immunization with $\beta_2$GPI leads to manifestations resembling human APS in mice or exacerbates the respective syndrome in susceptible MRL/+ mice.

Macrophages and smooth muscle and endothelial cells play a major role in the development of atherosclerotic plaque. Foam cells (the early, reversible lesions composed of lipid-containing macrophages) gradually develop into complicated plaques during the progression of atherosclerosis. These sequential events are thought to be accelerated by oxidation of plasma lipids. Oxidized LDL (oxLDL) has attracted major interest in view of its various effects on different cellular
components, attesting to its immunogenicity and probable causal effect on atherosclerosis progression.\textsuperscript{20,21} Several mechanisms could associate aCLs with enhanced atherogenesis, taking into consideration the effects on the cellular components within a mature atherosclerotic plaque. aCL and anti-oxLDL antibodies were shown to be cross-reactive,\textsuperscript{23,24} and some suggest that aCLs actually target oxidized rather than native phospholipids.\textsuperscript{25} Very recently, Hasunuma et al\textsuperscript{26} showed that anti-\(\beta\)-2GPI antibodies enhance the in vitro uptake of oxLDL to macrophages (the candidate progenitors of foam cells), postulating that it could contribute to enhanced atherogenesis.

Endothelial cells are also essential to the development of atherosclerosis, possibly by a prior activation resulting in expression of adhesion molecules.\textsuperscript{19} aCLs as well as rabbit atherosclerosis, possibly by a prior activation resulting in postulating that it could contribute to enhanced atherogenesis.

In the present study, we examined the effects \(\beta\)-2GPI immunization on the development of atherosclerosis. We have shown that LDL-receptor–deficient (LDL-RD) mice fed a chow diet and immunized with \(\beta\)-2GPI developed accelerated atherosclerosis.

### Methods

#### Animals

Six-week-old female LDL-RD mice (hybrids of the C57BL/6J and 129Sv strains) were created by homologous recombination as described by Ishibashi et al.\textsuperscript{27} The mice were obtained from the Jackson Laboratory (Bar Harbor, Me). We used LDL-RD mice for the experiments because this mouse maintains high cholesterol levels on a chow diet (levels similar to human values) and develops significant atherosclerosis only when fed a high-fat diet. Thus, the problem of the relative resistance of mice to atherosclerosis is overcome. BALB/c mice (8 weeks old) were purchased from the animal house of the Sackler School of Medicine, Tel Aviv University, Israel. The LDL-RD and the BALB/c mice were either fed normal chow diet containing 4.5% fat by weight (0.02% cholesterol) or an atherogenic diet (Harlan, Teklad Premier Laboratory Diets) containing 1.25% cholesterol, 7.5% casein, and 0.5% (wt/wt) sodium cholate. The mice were maintained on 12-hour dark/12-hour light cycles and were allowed access to food and water ad libitum.

#### Antigens and Antibodies

Human \(\beta\)-2GPI was purified from the serum of a healthy adult as previously described by Gharavi et al.\textsuperscript{15} Mouse \(\beta\)-2GPI was purified from the serum of LDL-RD mice by a similar method. For preparation of LDL and copper-oxidized LDL, blood for lipoprotein isolation was collected in EDTA (1 mg/mL) from mice after 12 hours of fasting. LDL (density, 1.019 to 1.063 g/mL) was isolated from the plasma after density adjustment with KBr by preparative ultracentrifugation at 50,000 rpm for 22 hours with a type 50 rotor as previously described.\textsuperscript{30} LDL preparations were washed by ultracentrifugation, dialyzed against 0.15 mol/L EDTA (pH 7.4), passed through an Acrodisc filter (0.22-\(\mu\)m pore size) to remove aggregates, and stored under nitrogen in the dark. Copper oxidation of LDL was performed by incubation of postdialyzed LDL (1 mg of protein/mL in EDTA-free PBS) with copper sulfate (10 \(\mu\)mol/L) for 24 hours at 37°C. Lipoprotein oxidation was confirmed by analysis of thiobarbituric acid–reactive substances (TBARS).\textsuperscript{30} Recombinant heat shock protein (HSP)-65 was kindly provided by Dr M. Singh, Braunschweig, Germany.

Mouse monoclonal anti-\(\beta\)-2GPI antibodies Cof-21 and Cof-18 (both of which bind human and mouse \(\beta\)-2GPI)\textsuperscript{31} was a generous gift of Professor Takao Koike, Hokkaido University, Japan.

Rat monoclonal antibodies H129.19 (L3T4) anti-mouse CD4+ and S3-6.7 (Ly-2) anti-mouse CD8α were from PharMingen; MCA 497 (F4/80) anti-mouse macrophages were from Serotec.

#### Immunization Protocol

In the first experiment, LDL-RD mice (n=15) were immunized subcutaneously with a single dose of human \(\beta\)-2GPI (10 \(\mu\)g per mouse) emulsified in complete Freund’s adjuvant (CFA). The 2 additional groups (15 mice each) either were immunized with ovalbumin (10 \(\mu\)g in CFA) or were not immunized. Fifteen BALB/c mice were immunized similarly with either \(\beta\)-2GPI or ovalbumin. All mice in the first experiment were given a normal chow diet and were killed 3 months after the immunization.

In the second experiment, 3 groups of LDL-RD mice (n=10 per group, 6 weeks old) were immunized with a regimen resembling the first experiment and fed an atherogenic diet for 6 weeks before they were killed.

#### Cholesterol Level Determinations

At the end of the experiment, 1 to 1.5 mL of blood was obtained by cardiac puncture; 1000 U/mL heparin was added to each sample. Total plasma cholesterol levels were determined by an automated enzymatic technique (Boehringer Mannheim).

#### Detection of Anti-\(\beta\)-2GPI Antibodies and Inhibition Studies

Anti-\(\beta\)-2GPI antibodies were detected by ELISA using either human or mouse \(\beta\)-2GPI (10 \(\mu\)g/mL) for coating and performed as previously described.\textsuperscript{32} Inhibition assays were performed to confirm the specificity of the mouse anti-\(\beta\)-2GPI antibodies and to check for their possible cross-reactivity with oxLDL. The concentration of serum from LDL-RD mice giving half of the maximal binding to \(\beta\)-2GPI was determined, and different inhibitors (at concentrations of 0 to 200 \(\mu\)g/mL) were used for inhibition (ic, oxLDL, LDL, human \(\beta\)-2GPI, BSA) with the anti-\(\beta\)-2GPI ELISA.

#### Detection of Mouse \(\beta\)-2GPI in Immune Complexes

For detection of mouse \(\beta\)-2GPI in immune complexes in sera from mice immunized with human \(\beta\)-2GPI, a dot blot assay was performed as previously described.\textsuperscript{33} Briefly, 10 \(\mu\)L of protein G–Sepharose beads were added to 20 \(\mu\)L of serum. After 30 minutes of incubation at room temperature, the beads were washed with PBS and resuspended in 10 \(\mu\)L of PBS. Five microliters of the suspension was applied to a BAS 85 nitrocellulose membrane (Schleicher and Schuell), and 5 minutes later, 2 \(\mu\)L of 0.1 mol/L glycine buffer (pH 2.5) was added to the beads. After blocking with 3% BSA and washings, the membranes were incubated for 1 hour with anti-\(\beta\)-2GPI biotinylated mouse monoclonal antibody (MAb). After additional washings (3 times, 15 minutes each), the membranes were transferred into a solution of streptavidin–horseradish peroxidase conjugate in PBS (1 : 25 000), and after extensive washing with PBS, a mixture of enhanced chemiluminescence detection reagents 1 and 2 (Amersham) were applied directly to the membranes. The membranes were exposed to x-ray film and after development were analyzed on a computing densitometer (model 300A, Molecular Dynamics). All sera were run in duplicate, and results of experiments were expressed as densitometry units.

#### Evaluation of Mouse \(\beta\)-2GPI Levels

For detection of mouse \(\beta\)-2GPI levels, we used capture ELISA. Ninety-six ELISA wells were coated with 10 \(\mu\)g of cof-18 (mouse MAb that binds human and mouse \(\beta\)-2GPI) in bicarbonate buffer overnight at 4°C and blocked with BSA. After washings, mouse sera from all experimental groups were added for 2 hours. After additional washings, 2 \(\mu\)g/mL of biotinylated cof-21 (mouse MAb that binds human and mouse \(\beta\)-2GPI) was added for 1 hour. Subsequently, the wells were incubated with alkaline phosphatase conjugated to avidin, and the reaction was developed with p-nitrophenylphosphate. For quantification of mouse \(\beta\)-2GPI levels, the OD values were evaluated by construction of a standard curve with...
purified mouse β2GPI. To confirm specificity, mouse β2GPI was added to some wells containing mouse sera.

Detection of Anti-HSP-65 Antibodies
Antibodies to HSP-65 were detected with ELISA as previously described. This assay was used to rule out the possibility that the immune response to HSP-65, which has been shown to be proatherogenic, influenced atherosclerosis progression.

Detection of Anti-oxLDL Antibodies
ELISA plates (Nunc) were coated with either copper-oxLDL, native LDL (at a concentration of 5 μg/mL in PBS), or PBS overnight at 4°C. Serum fractions were diluted to 1:50, and ELISA was performed as previously described. The assay was performed to rule out the possibility of cross-reactivity between anti-β2GPI and anti-oxLDL antibodies, which may have affected lesion formation in the mice.

Proliferation Assays of Draining Lymph Node Lymphocytes From Mice Immunized With β2GPI or Ovalbumin
Draining inguinal lymph nodes were collected from 4 β2GPI- or ovalbumin-immunized mice killed 8 days after the primary immunization. The assays were performed as previously described, with minor modifications. Briefly, 1×10^6 cells/mL were incubated in triplicate for 72 hours in 0.2 mL of culture medium in microtiter wells in the presence or absence of various antigens: concanavalin A, human β2GPI, mouse β2GPI, HSP-65, oxLDL, and BSA in 4 different concentrations (20, 10, 5, and 2.5 μg/mL). Proliferation was measured by the incorporation of [3H]thymidine into DNA during the final 12 hours of incubation. The results were computed as stimulation index: the ratio of the mean cpm of the antigen to the mean background cpm obtained in the absence of the antigen. SDs were always <10% of the mean cpm.

Assessment of Atherosclerosis
Atherosclerotic fatty-streak lesions were quantified by calculating the lesion size in the aortic sinus as previously described, with a few modifications. Briefly, the heart and upper section of the aorta were removed from the animals, and the peripheral fat was carefully cleaned. The upper section was embedded in OCT medium and frozen. Every other section (10 μm thick) throughout the aortic sinus (400 μm) was taken for analysis. The distal portion of the aortic sinus is recognized by the 3 valve cusps, which are the junctions of the aorta to the heart.

The extent of atherosclerosis was evaluated at the level of the aortic sinus. Processing and staining of the tissue with oil red O was carried out according to Paigen et al. Lesion area was quantified by the method of Rubin et al.

Immunohistochemistry of Atherosclerotic Lesions
Immunohistochemical staining for CD4, CD8, and macrophages was done on 5-μm-thick frozen sections of the aortic sinus. The sections were fixed for 4 minutes in methanol at −20°C followed by 10 minutes of incubation with ethanol at −20°C. The sections were then blocked with nonimmune goat serum for 15 minutes at room temperature followed by incubation with CAS blocking reagent for 30 minutes at room temperature. Subsequently, the rat anti-mouse CD4/CD8 MAbs were added for 1 hour at room temperature. After washings, affinity-purified biotinylated rabbit anti-rat IgG antibodies (Jackson) were added for 30 minutes at room temperature. After washings, the slides were incubated with 0.3% H2O2, followed by additional rinses and incubation with streptavidin-peroxidase conjugate for 30 minutes at room temperature. After washings, the slides were developed with 3-amino-9-ethylcarbazole (AEC) substrate (Dako) for 15 minutes. Sections were counterstained with hematoxylin. Spleen sections were used as a positive control. Staining in the absence of first or second antibody was used as a negative control.
Specificity of Anti-β2GPI Antibodies

The sera of the LDL-RD mice were inhibited in a dose-dependent manner by fluid-phase β2GPI (inhibition of 91% of the binding to β2GPI by a serum dilution of 1:200) but not with native LDL, oxLDL, or ovalbumin (Figure 3).

Circulating Immune Complexes and β2GPI Levels

Circulating immune complexes (CICs) containing mouse β2GPI were determined from the sera of mice taken at the end point of the experiment. The levels of β2GPI CICs were significantly higher in the chow diet–fed LDL-RD mice immunized with β2GPI (mean, 2264 ± 123 densitometry units [DU]) compared with ovalbumin-immunized (1401 ± 156 DU, P < 0.05) and with nonimmunized (1168 ± 105 DU, P < 0.05) mice (Figure 4).

Levels of β2GPI were similar in the 3 experimental groups fed chow diet and were in the range of 150 to 220 μg/mL (similar to the levels in humans).

Cholesterol Levels in the Studied Mice

No statistically significant differences were found with respect to the levels of cholesterol in the LDL-RD mice (β2GPI-immunized, 219 ± 25 mg/dL; ovalbumin-immunized, 228 ± 25 mg/dL; and nonimmunized, 211 ± 19 mg/dL). Similarly, no significant differences were noted between the atherogenic diet–fed mice: the mean cholesterol levels in the LDL-RD mice were 2348 ± 56.6 mg/dL in the β2GPI-immunized mice, 2434 ± 44.4 mg/dL in the ovalbumin-immunized mice, and 2549 ± 90 mg/dL in the nonimmunized mice. The cholesterol levels in the β2GPI-immunized BALB/c mice were 78 ± 12 mg/dL and in the ovalbumin-immunized mice, 81 ± 11 mg/dL.

Proliferation of Lymph Node Lymphocytes on Exposure to β2GPI, oxLDL, and HSP-65

Statistically significant stimulation indexes were observed only in the lymphocytes from the LDL-RD mice immunized with β2GPI incubated with human β2GPI (stimulation indexes in β2GPI concentrations of 20, 10, 5, and 2.25 μg/mL were 2.49 ± 0.156, 3.73 ± 0.55, 3.51 ± 0.55, and 3.83 ± 0.625, respectively) (Figure 5). No reactivity of the lymphocytes was observed after in vitro exposure to mouse β2GPI, oxLDL, HSP-65, or BSA in the LDL-RD mice immunized with β2GPI.

Extent of Aortic Sinus Atherosclerosis

Lesion size in the aortic sinus was most prominent in the LDL-RD mice immunized with β2GPI (mean, 26 000 ± 5700 μm²) compared with the LDL-RD mice immunized with ovalbumin (mean, 3000 ± 1099 μm²; P < 0.01) and with the nonimmunized mice (mean, 2250 ± 700 μm²; P < 0.01) (Figures 6 and 7). No significant differences were noted between the groups of atherogenic diet–fed mice: β2GPI-immunized, 98 000 ± 8305 μm²; ovalbumin-immunized, 81 250 ± 12 933 μm²; and nonimmunized, 75 625 ± 7281 μm². No atherosclerotic lesions were observed in the aortic sinuses of the BALB/c mice immunized with β2GPI or ovalbumin.

Immunohistochemical Analysis of Atherosclerotic Lesions

The lesions of the chow-fed LDL-RD mice immunized with β2GPI appeared to be more mature and contained significantly larger numbers of macrophages. Pronounced infiltration of the aortic sinus valvular and subendothelial intimal...
regions spanning the aortic sinus with CD4+ and CD8+ lymphocytes was noted in the LDL-RD mice immunized with β2GPI (Figure 5). The lymphocytes found in the β2GPI-immunized LDL-RD mice did not appear to reside only in the sites adjacent to the fatty streaks. Only a small number of CD4+ lymphocytes were evident in the aortic sinus of the LDL-RD mice immunized with ovalbumin or the control nonimmunized LDL-RD mice.

Discussion

Atherosclerosis entails the accumulation of lipids in the vessel walls, leading to their subsequent narrowing. In recent years, it has become apparent that the immune system plays a dominant role in mediating atherogenesis, although the exact mechanisms have not been characterized in detail. Several authors postulated that the atherosclerotic process could be triggered or enhanced by immunogens such as the HSP-60/65 or oxLDL. These candidate antigens were shown to promote humoral and cellular immune responses, which were suggested to account for their proatherogenic effects.

The rationale of the present study stems from several in vitro studies suggesting that aCLs could accelerate atherogenesis. Furthermore, clinical studies have shown that patients with SLE are at increased risk of developing premature atherosclerosis, although the exact relationship to anticardiolipin antibody positivity has not been determined. The endothelial cell−activating properties of aCLs and the enhanced in vitro uptake of oxLDL to macrophages induced by aCLs could provide experimental support for this tentative hypothesis. Furthermore, several authors have shown that aCLs and anti-oxLDL antibodies are cross-reactive.

In the present study, we sought to demonstrate the effect of immunization with β2GPI on the progression of atherosclerosis. Immunization of mice with human β2GPI was previously shown to result in production of antibodies resembling autoimmune aCLs and with a clinical picture mimicking human APS. This model seemed appropriate for evaluating the effect of the anti-β2GPI “response” on atherosclerosis.

The LDL-RD mice develop significant atherosclerosis only when fed a high-cholesterol diet, and they were chosen because their basal lipid levels are higher than those of control mice and thus the proatherogenic effect of β2GPI immunization is more likely to be unmasked. As can be observed from the results, the LDL-RD mice immunized with human β2GPI developed brisk and sustained immune response to the human β2GPI. These antibodies also bound immobilized mouse β2GPI, probably as a result of cross-reactivity. The LDL-RD mice developed significantly enhanced early atherosclerosis compared with their littermates immunized with ovalbumin. CD4+ lymphocytes were abundant in the valvular and subendothelial regions of the aortic sinus of the β2GPI-immunized mice. However, their presence was not confined to areas of fatty streak lesions, and it cannot be determined whether these cells contributed to enhancement of atherosclerosis in these mice.

The second experiment was performed in LDL-RD mice fed an atherogenic diet. However, the differences in the extent of atherosclerosis when the mice were fed the high-fat diet did not reach statistical significance when the β2GPI-immunized mice were compared with their ovalbumin-immunized littermates. The reason for the lack of difference when the atherogenic diet was fed could be that the effect of the high cholesterol levels on atherosclerosis development was so dominant that it made the effect of β2GPI immunization negligible. Moreover, as shown recently, the lymphocyte density within the plaques of these mice seemed to diminish when they were fed a high-fat diet, making them more resistant to immunological modulation.

We immunized the mice with a single injection of 10 µg rather than the traditional multiple-injection protocol for 2 reasons. First, in preliminary studies, a single immunization was sufficient to induce high titers of anti-β2GPI antibodies. Second, we wished to minimize the effects of different components found in adjuvants, some of which (ie, HSP-65) were shown to be associated with enhanced atherosclerosis.

By determining the levels of antibodies to HSP-65 and including a group of mice immunized with ovalbumin emulsified in CFA (which did not differ significantly from the nonimmunized group in the extent of atherosclerosis), we ruled...
out the possibility that the HSP-65 present in CFA was responsible for the accelerated atherosclerosis. The inhibition studies and lymphocyte proliferation assays excluded the possibility that immune response to β2GPI was cross-reactive with oxLDL; cross-reactivity of aCLs with oxLDL could have affected the progression of atherosclerosis, because the latter antibodies are considered by some authors to be protective.42,43

Several mechanisms could explain the enhanced atherosclerosis observed in the study: anti-β2GPI antibodies have recently been shown to activate endothelial cells,27,28 and it is possible that recruitment of immunopotent cell results in accelerated atherosclerosis. Such immune-mediated recruitment could account for the abundance of the CD4+ and CD8+ lymphocytes as well as the accumulation of macrophages within the atherosclerotic plaques.

An additional mechanism that could account for the enhanced atherogenesis in the β2GPI-immunized mice is an effect on macrophages. These latter cells were shown to accelerate the in vitro uptake of radiolabeled oxLDL in the presence of anti-β2GPI antibodies.26 This finding was explained by the association of anti-β2GPI with β2GPI, thus preventing the competition of the latter with oxLDL for the scavenger receptor-mediated binding to the macrophage. In this study, we have shown (Figure 1B) that the anti-human β2GPI antibodies also bound mouse β2GPI and could thus have influenced the uptake of lipids to resident macrophages, as was shown in the in vitro assays.26 Moreover, β2GPI possesses anticoagulant properties, and its “neutralization” by antibodies could contribute to a prothrombotic state, which could accelerate the atherosclerotic process. The issue of binding of anti-human β2GPI antibodies to native mouse β2GPI in vivo was addressed by evaluation of the presence of immune complexes. Indeed, we have found higher levels of CICs containing mouse β2GPI in the sera of the mice immunized with human β2GPI, providing a possible explanation for the proatherogenic effect of the immunization. It should be mentioned in this respect that despite higher levels of CICs containing mouse β2GPI, the serum levels of this anticoagulant molecule did not differ between the experimental groups, thus excluding the possibility that it may have affected atherosclerosis progression.
The control group in this experiment was immunized with ovalbumin. Use of an irrelevant protein for immunization might have been more appropriate in resolving β2GPI specificity by these antibodies. However, this issue was addressed by evaluation of binding of the antibodies to immobilized or to circulating mouse β2GPI (Figure 4).

NZWxBXSB F1 (W/B F1) male mice develop a spontaneous, SLE-like syndrome with production of several autoantibodies and CICs. One of the features of the disease in these mice is a degenerative coronary vascular disease with myocardial infarction and thrombocytopenia. The production of antibodies to platelets and to β2GPI/CL may play a pathogenic role in mediating the coronary vasculopathy, although lesions are not atherosclerotic but rather result from a prothrombotic state.

In conclusion, this study provides the first demonstration of a direct causal association between a cellular and a humoral immune response to β2GPI and atherosclerosis progression. This observation is of particular interest because β2GPI-binding antibodies formerly thought to invariably exist in APS patients are being increasingly reported in various infections. Because the association of infections with atherosclerosis has been raised by several authors (reviewed in References 47 and 48), the occurrence of anti-β2GPI antibodies could provide a possible explanation for this link.

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References


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