Molecular Pathogenesis of the Antiphospholipid Syndrome

Jacob H. Rand

Abstract—The antiphospholipid (aPL) syndrome is an acquired autoimmune disorder of unknown etiology in which patients present with thrombosis together with laboratory evidence for antibodies in blood that recognize anionic phospholipid-protein complexes. The main antigenic target for the aPL antibodies has been identified to be β2 glycoprotein I (β2GPI), a phospholipid-binding protein. The high affinity of aPL antibody-β2GPI complex for phospholipid membranes seems to be a critical step in the mechanism of this disease. This review focuses on some of the major mechanisms that have been proposed to explain this disorder. (Circ Res. 2002;90:29-37.)

Key Words: antiphospholipid antibodies ■ anticardiolipin antibodies ■ lupus anticoagulants ■ thrombosis ■ annexins

The antiphospholipid (aPL) antibody syndrome is an autoimmune disorder in which vascular thrombosis or recurrent pregnancy losses—often attributable to thrombosis within the placental vasculature—occur in patients having laboratory evidence for antibodies against phospholipids or phospholipid-binding protein cofactors in their blood. The clinical manifestations of the syndrome include venous and arterial thrombosis and embolism, disseminated large and small vessel thrombosis with accompanying multiorgan ischemia and infarction, stroke, premature coronary artery disease, and spontaneous pregnancy losses. The reader is referred to Rand1 for a more comprehensive recent review that includes diagnosis and treatment of this syndrome and to Boffa and Piette2 for a recent collection of reviews on this subject.

aPL antibodies are detectable by immunoassays that use solid-phase phospholipids and protein cofactors as antigenic targets and with coagulation assays that indicate the inhibition of phospholipid-dependent coagulation reactions (the lupus anticoagulant phenomenon). The syndrome was first proposed to be a distinct entity, “the anticardiolipin (aCL) syndrome” in 19853 and was later renamed “the antiphospholipid antibody syndrome.”4 The aPL antibody syndrome is classified as primary in the absence of another major autoimmune condition such as systemic lupus erythematosus and secondary in the presence of such disorders.

In retrospect, the first serological evidence for the disorder was the observation of the biological false-positive serological test for syphilis (BFP-syphilis test), described by Moore and Mohr in 19525. This laboratory anomaly was associated with systemic lupus erythematosus6 and with an anticoagulant phenomenon.7 In the early 1950s, the development of the partial thromboplastin time coagulation test, which used a phospholipid extract of animal brain (cephalin) as a platelet equivalent to accelerate coagulation,8 led to the recognition of an anticoagulant activity in patients with systemic lupus erythematosus—frequently accompanied by BFP-syphilis tests.9 This phenomenon, named the “lupus anticoagulant,”10 (LA) was puzzling since the anticoagulant activities were only displayed in vitro and were not associated with bleeding problems unless other hemostatic abnormalities were present.7 Paradoxically, this anticoagulant activity was associated
with thrombosis, embolism,11 and recurrent pregnancy losses.12 A major step toward the description of this syndrome occurred in 1983 when a quantitative test was developed to measure antibodies against the anionic phospholipid cardioli
(diphosphatidyl glycerol), the primary antigen in the syphils test reagent.13 This led to the recognition of the aPL syndrome and to the development of the current assays for these antibodies.

The genesis of the antibodies in this disorder and even their antigenic specificities are not yet established. The disorder is considered to fall into the category of autoimmune conditions. Antibodies against anionic phospholipid moieties that arise in response to infections such as syphils and Lyme disease are distinct from those generated in patients with the syndrome. The antibodies generated in response to infection generally recognize phospholipid epitopes directly (ie, they are not cofactor dependent) and are not associated with the clinical manifestations of the syndrome whereas those generated in patients with the aPL syndrome recognize epitopes on phospholipid-binding proteins—primarily β2 glycoprotein I (β2-GPI)—and thus are referred to as being cofactor dependent. However, the fastness of this distinction has recently been questioned with the finding of anti-β2-GPI antibodies in patients with syphils, lepsoptisis, and leishmaniaisis.14

It has recently been demonstrated that there is a seasonal influence on the prevalence of these antibodies in normal healthy populations, with a higher prevalence in the winter months than in the summer; the significance of these findings with respect to the etiology of this disorder and to thrombembolism is not yet known.15 Familial clustering of raised aPL antibody levels16 and HLA linkages17–20 indicate that the antibodies probably occur in genetically susceptible hosts in response to some antigenic challenge.

Antigenic Specificities: β2 Glycoprotein I

As mentioned, aPL antibodies from patients with the syndrome are usually dependent on a serum phospholipid-binding protein, most commonly β2-glycoprotein or apolipoprotein H, for recognition of the phospholipid in ELISAs. In contrast, antibodies against phospholipid that arise in the course of the immunological response to syphils infection are not cofactor dependent and recognize the anionic phospholipid epitopes directly.21

β2-GPI is a highly glycosylated single-chain plasma protein composed of 326 amino acids with a molecular mass of 50 kDa22 (Figure 1) that seems to be the major, but not the only, cofactor for the recognition of anionic phospholipid by aPL antibodies.23 The protein is a member of the complement control protein or short consensus repeat (SCR) superfamily, characterized by repeating stretches of ~60 amino acid residues, each with a set of 16 conserved residues and 2 fully conserved disulfide bonds and has 5 of the repeating SCR domains (also known as "sushi domains").23 aPL antibodies can recognize β2-GPI directly (ie, in the absence of phospholipid) if the protein antigen is present on microtiter plates at a sufficient density.24 It seems that most aPL antibodies recognize domain I of β2-GPI.25,26 The crystal structure of the protein has been solved27,28; its structure suggests that the protein binds to phospholipid membranes via the cationic portion of its fifth SCR domain (Figure 1) and that aPL antibody binding to domains I and II promotes the increased binding of the protein to membrane phospholipid,27 perhaps as a consequence of the increased affinity of the divalent IgG-β2-GPI complexes.29

The physiological function of β2-GPI has not been established; it has been suggested that the protein may play a scavenging role for exposed anionic phospholipid after apoptosis.30,31 Although human β2-GPI deficiency was first described more than 30 years ago,32 it is unclear whether this is associated with a thrombotic tendency. Heterozygosity for β2-GPI was found in ~6% of 812 Japanese subjects and was not associated with thrombosis.33 One patient with thrombosis and homozygous β2-GPI deficiency was described; however, his homozygous deficient brother and several heterozygous family members were asymptomatic.34 In patients with systemic lupus erythematosus, there seems to be an association between thrombosis and heterozygosity for mutation in the putative phospholipid-binding domain of β2-GPI.

β2-GPI-null mice have been bred and appear anatomically and histologically normal. However, impairment of thrombin generation has been detected in their plasmas in vitro. Less than the expected percentage of offspring of the β2-GPI-null heterozygotes possessed both disrupted alleles. This finding
suggested that β2GPI may play a role early in the reproductive process.35 It is intriguing that the binding of β2GPI to endothelial cells is mediated by annexin-II, which also serves as a receptor for plasminogen and tissue plasminogen activator.36

Although currently available data from animal models support a causal role for the antibodies in the development of thrombosis, the relationship between antibody recognition of β2GPI and thrombosis is not yet definitive.35 The possibility has not yet been completely excluded that the antibodies are an effect of thrombosis rather than the cause—i.e., the primary pathogenic process might involve the exposure of thrombogenic anionic phospholipids, and the development of aPL antibodies could be the effect of autoimmune reactivity to anionic phospholipid-cofactor complexes in susceptible individuals. It also remains possible that aPL antibodies may be both an effect and a cause of thrombosis. Anionic phospholipids, exposed during blood clotting, could trigger immunological recognition and formation of aPL antibodies that could then promote a vicious cycle through their thrombogenic properties. A description of primary aPL syndrome in a patient who was a compound heterozygote for 2 mutations of the phospholipid-binding binding domain of β2GPI and did not have any evidence for antibody recognition of β2GPI37 raises the interesting possibility that β2GPI plays a protective role against thrombosis and that aPL antibodies are an effect rather than a cause.

Additional cofactors and antigenic targets have also been identified.38 These include prothrombin (coagulation factor II), coagulation factor V, protein C, protein S, annexin-V, high molecular weight kininogen, and low molecular weight kininogen. Interestingly, protein C can be a target of aCL in the presence of cardiolipin and β2GPI, leading to protein C dysfunction.39 Also, antibodies of some aPL patients have been found to recognize heparin and inhibit the formation of antithrombin III-thrombin complexes.40 Indeed, the remarkable heterogeneity of these aPL antibodies in even a single patient, as recently demonstrated by clonal analysis,41 adds to the difficulties in defining the pathogenic aPL response(s).

The oxidation of phospholipids may be necessary for aPL antibody recognition.42 The epitopes for some aPL antibodies seem to be adducts of oxidized phospholipid and protein such as β2GPI.43 Thus, some affinity-purified cardiolipin-binding antibodies in sera from patients with systemic lupus erythematosus seem to cross-react with oxidized LDL.44 Elevated levels of these antibodies have been proposed to be markers for arterial thrombosis.45

Proposed Pathogenic Mechanisms

Evidence accumulated from animal models of the aPL syndrome indicate that aPL antibodies can play a causal role in the development of thrombosis and pregnancy loss. Mice immunized against β2GPI46 and with aPL antibodies47 developed fetal wastage. Also, mice infused with the aPL antibodies developed significantly larger thrombi in femoral veins after experimental injury than mice infused with control antibodies.48,49 A monoclonal human anticardiolipin antibody derived from a patient with the aPL syndrome promoted thrombosis in mice.50 Also, atherosclerosis in a susceptible mouse model (the LDL-receptor knockout mouse) was accelerated by immunization with human anticardiolipin antibodies from an aPL syndrome patient,51 providing additional evidence for a causal pathogenic effect. A direct causal relationship between aPL antibodies and thrombotic manifestations or pregnancy losses in humans has not yet been proven. The recent characterization of chimpanzee β2GPI along with the finding of a high prevalence of anti-β2GPI antibodies in these animals52 holds the possibility of primate models for investigating the aPL syndrome.

The present hypotheses for pathogenic mechanisms in the aPL syndrome are summarized in the Table. Under defined laboratory conditions, these antibodies exhibit multiple effects because of the many biological processes that involve phospholipids and phospholipid membranes. It is difficult to determine whether these are clinically relevant. Many of these effects, including the paradoxical LA phenomenon, are a consequence of the many roles for phospholipids in the hemostatic system and in biological processes in general. Therefore, any proposed aPL-mediated effects that are based on in vitro studies must be evaluated for in vivo relevance in animal models and in rigorously designed clinical studies. Also, any plausible explanation for the aPL syndrome needs to account for the paradoxes of the absence of bleeding and

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the presence of thrombosis in patients whose blood demonstrates the LA phenomenon.

**aPL Antibody-Mediated Disruption of the Annexin-V Anticoagulant Shield**

The annexin family of proteins was recognized in 1990. Thus far, the genes for several hundred different annexins, including 10 in mammalian cells, have been described (for a brief review, see Rand). The remainder have been described in other organisms including a wide range of plants. Their canonical structure is composed of repetitive homologous domains consisting of sequences of \( \approx 70 \) amino acids, with almost all of the annexins having 4 of these domains. Annexin-V has potent anticoagulant activity in vitro, which is based on its high affinity for anionic phospholipids and its capacity to displace coagulation factors from phospholipid surfaces. The protein is shaped like a concave disk with the phospholipid- and calcium-binding domains present on the convex surface. Interestingly, annexin-V clusters on exposed membrane phospholipid, on which it forms 2-dimensional crystalline arrays. The surface topography of 2 crystal forms of annexin-V, designated p3 and p6, has been described using atomic force microscopy and correlated with the structure determined by x-ray crystallography (Figure 2). The potent anticoagulant properties of the protein are a consequence of this crystallization, which forms a lattice of annexin-V over the phospholipid surface, blocking its availability for coagulation reactions. Affinity of heparin oligosaccharides for annexin-V suggests that cell surface heparan sulfate may also play a role in assisting or stabilizing the binding of annexin-V to the bilayer.

There are significant data to support a thrombomodulatory function for annexin-V in the placental circulation. Annexin-V is highly expressed by placental trophoblasts, in an apparently constitutive manner, and is abundant on the apical surfaces of syncytiotrophoblasts, which express phosphatidyserine. Removal of annexin-V from the cell surface by treatment with EGTA exposes the apical membrane to circulating blood and accelerates the coagulation of plasma exposed to the cells. Infusion of pregnant mice with polyclonal anti-annexin-V antibodies resulted in placental infarction and pregnancy wastage, indicating that annexin-V is necessary for maintenance of placental integrity. Cultured human umbilical vein endothelial cells also express significant quantities of annexin-V, and treatment of these cells with chelator or with a polyclonal anti-human annexin-V also resulted in acceleration of the coagulation of plasma exposed to these cells.

Annexin-V expression is decreased on trophoblasts of preeclamptic placentas, and the degree of the decrease correlated with elevation of markers for activation of blood coagulation. At the time of this writing, there has been no report of a successful transgenic annexin-V knockout animal. Whether this is because annexin-V is critical for viability, or because of other technical factors, remains to be determined. Taken together, the available data support the hypothesis that annexin-V has a thrombomodulatory function on the surfaces that line the intervillous space through which the maternal blood circulates. In addition, the expression of annexin-V by endothelial cells indicates that annexin-V may play a similar role at the vascular-blood interface of the systemic circulation.

Since both aPL antibodies and annexin-V have affinity for anionic phospholipids, it was hypothesized that the aPL antibodies might interfere with the formation of the antithrombotic annexin-V shield over phospholipids on apical cytoplasmic membranes. There was a marked reduction of annexin-V expression on the apical membranes of the syncytiotrophoblasts that line placental villi in aPL syndrome placentas compared with the control groups, which included uncomplicated term deliveries, non-aPL-related pregnancy losses, and elective abortions. There was a similar reduction of immunohistochemically detectable annexin-V when placental villi from uncomplicated pregnancies were cultured with IgG fractions from aPL syndrome patients. Also, the quantity of annexin-V, as determined by immunoassay, was decreased on apical membranes isolated from placental villi cultured with the aPL IgG fractions. IgG fractions from aPL syndrome patients reduce the quantity of annexin-V on cultured trophoblasts (primary cultures of trophoblasts as well as the BeWo cell line) and endothelial cells, and aPL IgGs also accelerate the coagula-

**Figure 2. Crystal structure of the p6 form of annexin-V.** A, An atomic force image of the p6 crystal form of annexin-V. The alternative p3 crystal is not shown because of space limitations. Image size (Z-scale): 250 × 125 (2.5) nm. B, 2D projected structure of membrane-bound annexin-V at 1.5-nm resolution. Annexin-V molecules are viewed from the aqueous solution. One of the trimers is circled and the 4 domains that compose 1 annexin-V monomer are indicated. Image size, 36 × 36 nm. C, Average topographic map of the p6 crystal form of annexin-V. One of the trimers is circled. The arrowhead indicates the connection between 2 adjacent trimers. The smaller arrowheads indicate a topographically lower region corresponding to domain 1 and its junction with the (3,2) module of the adjacent monomer. (Reprinted with permission from Reviaikine I, Bergsma-Schutter W, Mazeres-Dubut C, Govorukhina N, Brisson A. Surface topology of the p3 and p6 annexin V crystal forms determined by atomic force microscopy. J Struct Biol. 2000;131:234–239).
postulation of plasma that is incubated with these cells after their exposure to the antibodies. The reasons for this are not fully understood, but it is likely that annexin-V is removed recently, we have extended the findings with IgG fractions to monoclonal aPL antibodies and found that monoclonal murine aPL antibodies also displace annexin-V and accelerate coagulation reactions. IgG fractions isolated from patients with the aPL antibodies reduce annexin-V binding or reduce annexin-V activity in normal sera is an apparent anticoagulant effect. The LA effect occurs when the aPL antibodies reduce the binding of annexin-V to phospholipid-coated microtiter plates; this reduction of annexin-V binding is dependent on anti-β2GP1 antibodies and correlates with clinical thrombosis. One group reported that it has been unable to find that aPL IgG antibodies reduce annexin-V binding or reduce annexin-V-mediated anticoagulant activity. The reasons for this are not yet clear and probably relate to undetermined differences in methodology.

The available data support the hypothesis that the reduction of annexin-V on the surfaces of placental trophoblasts and vascular endothelial cells, which come into contact with flowing blood, may provide a thrombogenic mechanism for this disorder (Figure 3). This potent anticoagulant protein may play a thromboregulatory role at the vascular-blood interface by shielding anionic phospholipids, which would otherwise serve as efficient cofactors for the assembly of coagulation factor complexes, from participating in coagulation reactions. We further propose that the high-affinity binding of aPL antibodies to phospholipids—or protein-phospholipid complexes, which may contain β2GP1, prothrombin, or other proteins—sterically interfere with the ability of an ordered crystal structure of annexin-V to form on the surface. This would increase the availability of phospholipids for coagulation reactions. The aPL-mediated increase of prothrombin binding to trophoblasts in the presence of annexin-V and acceleration of the prothrombinase reaction are consistent with this model.

This mechanism provides an attractive explanation for the paradox of the LA effect. The LA effect occurs when the aPL antibodies with specificities for cofactors, such as β2GP1 and prothrombin, inhibit the Xa and prothrombinase complex assembly on the phospholipid surface in the absence of significant quantities of annexin-V (the concentration of annexin-V in normal sera is <10 ng/mL). In that situation, high-affinity antibody-cofactor complexes reduce the availability of phospholipid for coagulation reactions and will indicate an apparent anticoagulant effect (Figure 3C). In contrast, when annexin-V is present in the system, aPL antibodies will accelerate coagulation by disrupting the ordered structure of the annexin-V shield and thereby increase the availability of phospholipid for coagulation reactions (Figure 3D). The reason LA tests correlate with the clinical risk for thrombotic events may be because they are surrogate tests for detecting antibodies that have sufficient affinity for phospholipids or cofactors to disrupt the annexin-V shield.

**Effects of aPL Antibodies on Platelets and on Eicosanoid Metabolism**

Some investigators have demonstrated that activated platelets are present in patients with the aPL syndrome and that aPL antibodies can stimulate platelet aggregation to otherwise subthreshold concentrations of agonists or aggregate platelets directly. aPL antibodies may alter the balance of eicosanoid synthesis toward prothrombotic moieties as indi-
olated by the presence of an increased quantity of thromboxane metabolites in the urine of aPL patients compared with control subjects. However, other studies have not found aPL antibodies to affect eicosanoid metabolism.

Effects of aPL Antibodies on Vascular Endothelial Cells

aPL antibodies have been found to recognize, injure, and/or activate cultured vascular endothelial cells. Cultured endothelial cells incubated with aPL antibodies express increased levels of cell adhesion molecules, an effect that is mediated by β2GPI, and may increase the adhesion of leukocytes to the vascular wall and promote inflammation and thrombosis. Thrombogenic effects of aPL antibodies are mediated by intercellular cell adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and P-selectin. It has recently been demonstrated that both the aPL antibody–mediated enhancement of leukocyte adhesion and increased thrombosis in the pinch-injury model are reduced in transgenic ICAM-1–deficient mice, ICAM-1/P-selectin–deficient mice, and in mice infused with anti–VCAM-1 antibodies. It has also been demonstrated that incubation of cultured endothelial cells with aPL antibodies results in the increased expression of tissue factor. Significantly increased plasma levels of endothelin-1, which is thought to play a role in arterial tone, vasospasm, and thrombotic arterial occlusion, were found in aPL syndrome patients with arterial thrombosis. Human monoclonal aCL-induced prepro-endothelin-1 mRNA levels significantly more than control monoclonal antibody. A subset of aPL antibodies that recognizes annexin-V induces apoptosis in endothelial cells. LAs have also been shown to stimulate the release of microparticles and possible prothrombotic activity from endothelial cells.

Induction of Tissue Factor Activity by Leukocytes

In addition to the expression of tissue factor by cultured endothelial cells mentioned above, aPL antibodies have also been found to promote tissue factor synthesis by leukocytes. Stimulation of monocytes from aPL syndrome patients with β2GPI induced substantial monocyte tissue factor, whereas no induction was observed with cells from patients having aPL antibodies without clinical problems; this effect required CD4+ T lymphocytes and class II MHC molecules. In one study, the ability of IgG to stimulate monocyte tissue factor expression was associated with the presence of decreased free protein S and increased prothrombotic markers. Another means by which aPL antibodies may increase tissue factor activity and resultant Xa generation is via antibody-mediated inhibition of tissue factor pathway inhibitor activity.

Interference With the Components of the Protein C Pathway

The protein C pathway, one of the important endogenous antithrombotic mechanisms, is initiated when thrombin binds to thrombomodulin on endothelial cells. This binding modifies the substrate specificity of thrombin; the enzyme loses its procoagulant specificities and cleaves protein C, concentrated near the cell surface through the presence of an endothelial protein C receptor, to activated protein C (APC). APC complexes with unbound protein S and proteolyzes coagulation factors Va and VIIIa. aPL antibodies can interfere with the protein C system by (1) inhibiting the formation of thrombin; (2) decreasing the activation of protein C by the thrombomodulin-thrombin complex; (3) inhibiting the assembly of the protein C complex; (4) inhibiting the activity of protein C, directly or via its cofactor protein S; and (5) binding to factors Va and VIIIa in a manner that protects them from proteolysis by APC. Interestingly, oxidation of phosphatidyl ethanolamine may enhance the anticoagulant activity of activated protein C; inhibition of this process by aPL antibodies may thereby promote thrombin generation. In addition, patients with aPL syndrome frequently have protein S deficiency.

Inhibition of the Antithrombin-III Pathway

Antithrombin III is a member of the serine protease inhibitor family. Individuals with inherited deficiencies of antithrombin III are at increased risk for deep vein thrombosis. The antithrombotic activity of this protein is markedly accelerated by the presence of heparin. In vivo, heparan sulfate proteoglycans may exert a thrombomodulatory effect. It has been demonstrated that at least some aPL antibodies cross-react with heparin and heparinoid molecules (which are highly polyanionic) and inhibit the acceleration of antithrombin-III activity.

Additional Effects

aPL antibodies may show cross-reactivity against oxidized LDL and may thereby be associated with an increased risk of atherosclerosis. Also, it has been suggested that fibrinolysis may be impaired in the aPL syndrome, since women with the disorder have been described to have elevated plasminogen activator inhibitor-I levels. Fibrinolysis may also be impaired via anti–β2GPI-mediated inhibition of the autoactivation of factor XII and the ensuing reductions of kallikrein and urokinase.

Conclusions

While the pathophysiological mechanisms of the aPL syndrome have not been established, a number of intriguing leads have been developed. These include progress in understanding the role of β2GPI and the elucidation of several potential mechanisms for this disorder. The effects of the antibodies on the annexin-V anticoagulant mechanism—specifically, the effects on the crystallization of this protein over anionic phospholipids within the vasculature—are of particular interest. Additional research is necessary to elucidate how these autoantibodies develop in susceptible individuals, the relationship(s) of the antibodies to the disease process, and to relate this information to improve diagnosis and treatment of affected patients.

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