31 Antiphospholipid Antibody–Induced Pregnancy Loss and Thrombosis

Guillermina Girardi and Jane E. Salmon

Antiphospholipid (aPL) antibodies are a family of autoantibodies that exhibit a broad range of target specificities and affinities, all recognizing various combinations of phospholipids, phospholipid binding proteins, or both. The first aPL antibody, a complement fixing antibody that reacted with extracts from bovine hearts, was detected in patients with syphilis in 1906 [1]. The relevant antigen was later identified as cardiolipin, a mitochondrial phospholipid [2]. The presence of aPL antibodies in serum has been associated with arterial and venous thrombosis and recurrent pregnancy loss [3–7], but the pathogenic mechanisms mediating these events are unknown. Several hypotheses have been proposed to explain the cellular and molecular mechanisms by which aPL antibodies induce thrombosis and fetal loss. There are reports that aPL antibodies activate endothelial cells, monocytes, and platelets [8–10]. In vivo and in vitro studies have shown that exposure to aPL antibodies induces activation of endothelial cells and a prothrombotic phenotype, as assessed by upregulation of the expression of adhesion molecules, secretion of cytokines, and the metabolism of prostacyclins [8, 10, 11]. aPL antibodies recognize β_2-glycoprotein I bound to resting endothelial cells, although the basis for the interaction of β_2-glycoprotein I with viable endothelial cells remains unclear [12, 13]. As β_2-glycoprotein I is considered a natural anticoagulant [14], some authors propose that aPL antibodies interfere with or modulate the function of phospholipid binding proteins involved in the regulation of coagulation, activate platelets, or induce monocytes to express tissue factor [9]. That endothelial cell, monocyte, and platelet activation are associated with aPL antibodies and thrombophilia, and that these cell phenotypes may also occur as a consequence of complement activation products, suggested a role for complement activation in aPL antibody–induced tissue damage.

The Complement System

Complement is part of the innate immune system and provides one of the main effector arms of host defense. Complement was first identified as a heat labile principle in serum that "complemented" antibodies in the killing of bacteria. We now know that complement is a system of more than 30 proteins in plasma and on cell surfaces that act in concert to protect the host against invading organisms, initiates inflammation, and tissue injury [15].

There are 3 pathways of complement activation: the classical, mannose binding lectin, and alternative pathways (Fig. 31.1). These 3 initiation pathways converge at the point of cleavage of the third component of complement (C3) and the steps leading to the cleavage of C3 are amplifying cascades of enzymes, analogous to those in coagulation. The classical pathway is activated when natural or elicited antibodies bind to antigen and unleash potent effectors associated with humoral responses in immune mediated tissue damage. Activation of the classical pathway is initiated by the binding of the C1 complex to antibodies complexed to antigens on cell or bacterial surfaces. C1s first cleaves C4, which binds covalently to the cell (or bacterial) surface, and then cleaves C2, leading to the formation of a C4b2a enzyme complex, the C3 convertase of the classical pathway. Activation of the classical pathway by natural antibody plays a major role in the response to neoepitopes unmasked on ischemic endothelium, and thus may be involved in reperfusion injury [16]. In addition, the classical pathway is activated through the action of

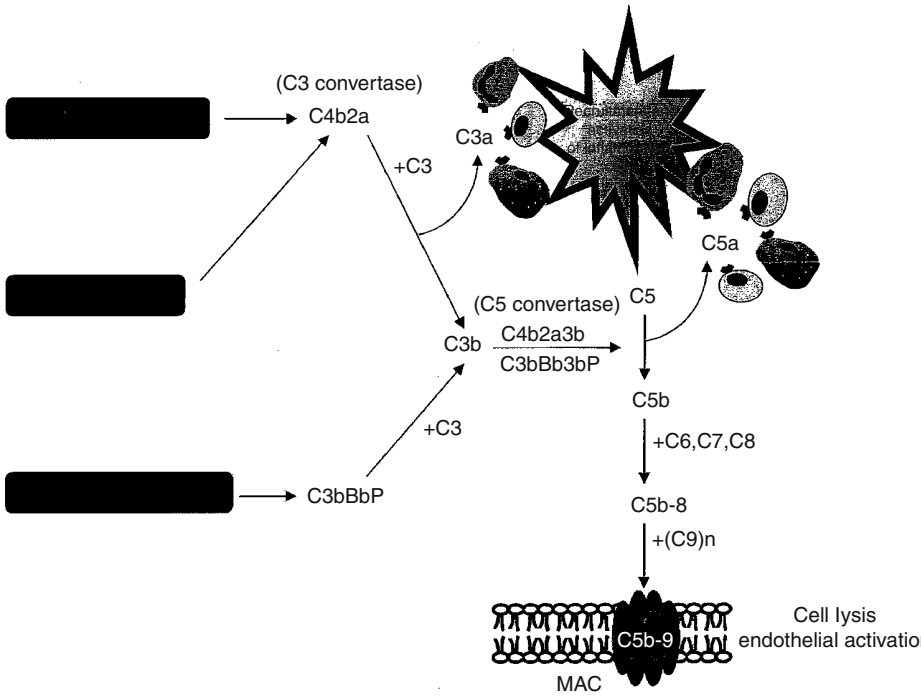

Figure 31.1. Proposed mechanism for the pathogenic effects of aPL antibodies on tissue injury. First, aPL antibodies are preferentially targeted to the placenta where they activate complement via the classical pathway. The complement cascade is initiated; C3 and subsequently C5 are activated. C5a is generated and attracts and activates neutrophils, monocytes, and platelets, and stimulates the release of inflammatory mediators, including reactive oxidants, proteolytic enzymes, chemokines, cytokines, and complement factors. Complement activation is amplified by the alternative pathway. This results in further influx of inflammatory cells and ultimately fetal injury. Depending on the extent of Damage, either death in utero or fetal growth restriction ensues. PMN-neutrophil; MF-monocyte–macrophage. (Adapted from Girardi G, et al Complement C5a receptors and neutrophils mediate fetal injury in the antiphospholipid syndrome. J Clin Invest 2003;112:1652, with copyright permission from the Journal of Clinical Investigation.