32 Mechanism of Thrombosis in Antiphospholipid Syndrome: Binding to Platelets

Joan-Carles Reverter and Dolors Tàssies

Introduction

Antiphospholipid antibodies (aPL) are related to thrombosis in the antiphospholipid syndrome (APS) [1, 2] and numerous pathophysiological mechanisms have been suggested involving cellular effects, plasma coagulation regulatory proteins, and fibrinolysis [3, 4]: aPL may act as blocking agents directly inhibiting antigen enzymatic or co-factor function of hemostasis; may bind fluid-phase antigens of hemostasis involved proteins and then decrease plasma antigen levels by clearance of immune complexes; may form immune complexes with their antigens that may be deposited in blood vessels causing inflammation and tissue injury; may cause dysregulation of antigen–phospholipid binding due to cross-linking of membrane bound antigens; and may trigger cell mediated events by cross-linking of antigen bound to cell surfaces or cell surface receptors [3, 4]. Moreover, several characteristics of the aPL, such as the concentration, class/subclass, affinity or charge, and several characteristics of the antigens, as the concentration, size, location or charge, may influence which of the theoretical autoantibody actions will occur in vivo [3].

Among the cellular mechanisms supposed to be involved, platelets have been considered as one of the most promising potential target for circulating aPL that may cause antibody mediated thrombosis as a part of the clinical spectrum of the autoimmune disorder of the APS. In the present chapter we will focus on the interactions that involve aPL binding to platelet membrane or platelet membrane bound antigens.

Platelets as Target for aPL

Platelets play a central role in primary hemostasis involving platelet adhesion to the injured blood vessel wall, followed by platelet activation, granule release, shape change, and rearrangement of the outer membrane phospholipids and proteins, transforming them into a highly efficient procoagulant surface [5]. In addition, thrombocytopenia is also a clinical manifestation of APS. For these reasons platelets

itself have been considered as a potential target for aPL and this fact has been extended to thrombotic mechanisms [3].

Several facts support platelets as the target for aPL. Studies performed in the aggregometer or in flowing conditions and the evaluation of platelet activation markers in vitro and in vivo in patients with the APS are used as demonstration.

Activation and spontaneous aggregation of platelets was reported in aggregometric studies to be caused directly by aPL in early reports [6, 7]. Other authors did not find this ability of aPL to initiate platelet activation [8, 9] or report inhibition of aggregation caused by aPL [10]. However, the most realistic interpretation is that in the aggregometric studies aPL may cooperate in platelet activation by making platelets more reactive to the action of weak or low-dose agonists [8, 11–13]. A calcium independent platelet aggregation (thromboagglutination) has also been found in patients with APS [14].

Other studies performed using flowing systems that simulate physiological conditions [15, 16] demonstrated, in both systemic lupus erythematosus (SLE) patients and in primary APS patients, increased formation of platelet thrombi when small amounts of patients' plasmas or purified immunoglobulins with anticardiolipin activity were added to normal blood, but this increase only occurs when plasma or immunoglobulins from patients with thrombotic history was employed. Similar results were obtained in the same system when the experiments were performed using human monoclonal anticardiolipin (anti–β_2-glycoprotein I) antibodies [17], and the β_2-glycoprotein–dependence of this phenomenon has been evidenced [18]. Additionally, dimers of β_2-glycoprotein I, that mimic effects of β_2-glycoprotein I–anti–β_2-glycoprotein I antibody complexes, have been found to increase platelet adhesion and thrombus formation in a flow system but not increased aggregation in an aggregometer [19].

Several studies have been performed to identify platelet activation markers in patients with APS. Some of them investigate the eicosanoid regulation in these patients showing inhibition of prostacyclin synthesis [20–22] and/or increased platelet thromboxane production [13, 22–24]. These results were found in in vitro experiments and in vivo in patients with the APS. However, these results have not been found by others [25]. More recently, anticardiolipin–β_2-glycoprotein I complexes have been found to induce platelet overactivity resulting in excessive production of thromboxane A2, presumably by decreased platelet cyclic AMP activity, causing increased platelet aggregation [26].

Looking for more direct markers of platelet activation, other authors have found an increase of the CD62p (P-selectin), an integral protein found in the α-granules, on platelet surface [27, 28] and/or the soluble CD62 [29, 30], loss from the activated platelet membranes to the plasma, in patients with APS, but not all the authors found the same results [31, 32]. Moreover, platelet CD63 expression, a lysosomal granule protein exposed after platelet activation, has been found increased in primary APS patients [30], but not in all the studies [28]. PAC-1, an antibody that detects the conformational change of the platelet membrane glycoprotein IIb–IIIa complex that occurs when the platelet is activated and probably a more sensitive index of platelet activation than degranulation proteins, binding has been also reported significantly increased in patients with primary APS [30]. In these patients, a significantly increased number of circulating platelet microparticles have been found [33], supporting an increased platelet activation in vivo, but these results have not been confirmed by others [30]. Annexin V binding to platelets, which indi-