35 Contribution of Tissue Factor to the Pathogenesis of Thrombosis in Patients with Antiphospholipid Syndrome

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Introduction

Antiphospholipid syndrome (APS) is an acquired autoimmune disorder of unknown etiology. The syndrome is defined by the association of arterial or venous thrombosis and/or pregnancy morbidity, in the presence of antiphospholipid antibodies (aPL), anticardiolipin antibodies (aCL), and lupus anticoagulant (LA) [1].

aPLs are a heterogeneous family of autoantibodies with diverse cross-reactivities whose origin and role have not been fully elucidated. It is now recognized that many of the autoantibodies associated with APS are directed against phospholipid binding plasma proteins, such as β_2-glycoprotein I (β_2-GPI) and prothrombin, or phospholipid–protein complexes [2], expressed on or bound to the surface of vascular endothelial cells, platelets, or monocytes [3].

β_2-GPI, a plasma protein bearing the major antigenic epitope for aPL, interacts with negatively charged phospholipids involved in the coagulation process, and has both procoagulant and anticoagulant properties. β_2-GPI suppresses the thrombomodulin–protein C system [4], factor XII activation, factor X activation, and prothrombinase activity. Antibodies against β_2-GPI may modify the properties of β_2-GPI and favor a prothrombotic state. However, individuals with β_2-GPI deficiency do not have a thrombotic tendency [5]; thus, aPL-associated thrombosis cannot be explained merely by β_2-GPI insufficiency.

Prothrombin, another plasma protein, is the second major target of aPL and the zymogen of the serine protease thrombin [6]. Thrombin is one of the most potent enzymes, and it catalyzes several reactions which may be important in blood coagulation. In this way, recent studies have demonstrated that anti-prothrombin antibodies with LA activity can inhibit coagulation reactions in a phospholipid and prothrombin dependent manner, by enhancing the intrinsic inhibitory effect of prothrombin itself [7]. Therefore, aPL may also modify prothrombin properties, ultimately leading to a thrombotic state.

Thrombosis is the key lesion of the APS [8]. Several non-exclusive mechanisms have been proposed to explain the involvement of aPL in the pathogenesis of thrombosis in APS, including the induction of tissue factor (TF) expression by endothelial cells and monocytes [9, 10]. This chapter focuses on the contribution of

TF to the pathogenesis of thrombosis in patients with APS and the intracellular mechanisms involved in TF expression.

TF Pathway and Thrombosis in APS

TF is a specific transmembrane single chain glycoprotein composed of 263 amino acids (47 kDa), that requires interaction with specific membrane phospholipids (PL) to become functionally active [11–13]. TF serves as both high-affinity receptor and enzyme activator for plasma FVII or FVIIa in initiating a localized procoagulant activity (PCA) on the anionic PL cell surface. TF is widely accepted to be the major initiator of in vivo coagulation [14]. It is also believed that TF has a key role in fibrin deposition in immunologic disorders, as well as in disseminated intra-vascular coagulation and clot formation in gram-negative bacterial sepsis, cancer, and inflammatory bowel disease [12, 13, 15]. TF is expressed on the surface of many cell types but, in the resting state, is normally absent from cells in contact with blood. However, TF can be induced, in vitro, to appear on endothelial cells and monocytes in a transcriptionally regulated manner by several physiologic or non-physiologic stimuli [16–18].

In APS patients, our recent in vivo studies have shown that patients with primary APS have increased expression of TF on the monocyte surface, along with increased mRNA-TF, TF antigen, and activity levels in peripheral blood mononuclear cells, where the source of TF is the monocyte [19–21]. Moreover, TF expression was found increased in APS patients with thrombosis when compared with those without and with healthy controls. TF expression in these patients was found to be further increased in those positive for IgG aCL, but not in those positive for IgM aCL of LA. In addition, TF expression in APS did not appear to be related to plasma levels of tumor necrosis factor α (TNF-α) and interleukin 1β (IL-1β), two inflammatory mediators that influence TF production, suggesting that inflammatory changes do not determine TF production in the steady state.

Recent evidence has suggested a role for the TF pathway in the pathogenesis of aPL-related thrombosis. Experimental data have shown that procoagulant activity in cultured EC and monocytes is induced by plasma from patients with APS and by purified aPL [22]. Furthermore, it has been demonstrated that antibodies against β_2-GPI induce the expression and activity of TF in vitro [10]. In addition, β_2-GPI expression on monocytes is significantly increased in patients with APS and correlate with TF expression, thus contributing to the maintenance of a persistent prothrombotic state [23].

Signal Transduction Mechanisms Associated with the Increased Expression of TF in Response to aPL

The mechanism(s) by which aPL induce TF expression is unknown. A potential role or Fcγ receptors (FcγR) in the pathogenesis of APS was suggested [24], but Pierangeli et al [25] showed in a murine model that these effects are not dependent on binding of antibody to FcγR. Rand and coworkers have proposed a thrombogenic mechanisms [26, 27] in which the high affinity of the aPL for anionic PL