Thrombosis, in both the arterial and the venous circulation, is one of the major manifestations of antiphospholipid syndrome (APS), a prothrombotic disorder associated with recurrent thrombotic events and pregnancy morbidity in the presence of antiphospholipid antibodies (aPL) [1].

In the past decade, many studies have investigated the pathophysiology of thrombosis in APS and considerable interest has focused on the role of aPL as a clue to the mechanism of thrombosis. Results of intensive research have significantly advanced our understanding of the mechanisms by which these antibodies may play a direct role in clot formation. It is now recognized that many of the autoantibodies associated with APS are directed against phospholipid-binding plasma proteins, such as β2-glycoprotein I (β2GPI) and prothrombin, or phospholipid–protein complexes, expressed on or bound to the surface of vascular endothelial cells (EC), platelets or other cells.

Classically, the clinical features of APS have been considered as a form of coagulopathy. In vitro evidence suggests that aPL are involved in the haemostatic abnormality. β2GPI, 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. β2GPI suppresses the thrombomodulin–protein C system [2], factor XII activation, factor X activation and prothrombinase activity. Antibodies against β2GPI (anti-β2GPI) may modify the properties of β2GPI and favour a prothrombotic state. Prothrombin, another plasma protein, is the second major target of aPL and the zymogen of the serine protease thrombin. Thrombin is one of the most potent enzymes, and it catalyses several reactions which may be important in blood coagulation, including the conversion of fibrinogen to fibrin as procoagulant and protein C activation as anticoagulant. Therefore, aPL may also modify prothrombin properties, ultimately leading to a thrombotic state.

In the last two decades researchers have focused on the coagulopathy story, investigating the mechanism involved in the coagulation cascade abnormality mediated by aPL. However, individuals with β2GPI deficiency do not have a thrombotic tendency [3]; thus, aPL-associated thrombosis cannot be explained merely by β2GPI insufficiency.

Investigators then turned their focus upon the function of EC or other cells which might be modified by aPL. In particular, EC form one of the major organs that cover all of the inner surface of blood vessels. They have various properties, including antithrombotic functions. Alterations in endothelial functions play a crucial role in the development of pathological conditions, and ‘endotheliology’ is a new term for research on EC. The cellular interactions of aPL have gained increased attention and in recent years APS has been defined as an ‘endotheliopathy’. In this new scenario, phospholipid-binding proteins are seen as cofactors that prepare receptors for the binding of autoantibodies to cells. Autoantibodies against phospholipid-binding proteins, irrespective of the functions of these proteins, may alter the properties of bound EC from antithrombotic to prothrombotic, leading to the production of procoagulant substances such as tissue factor (TF), plasminogen activator inhibitor 1 (PAI-1) and endothelin 1 (ET-1).

From this point of view, the TF pathway has been an important focus of research. TF is the major initiator of the extrinsic coagulation system, functioning in coagulation by serving as the protein cofactor for the plasma serine protease activated factor VII (FVIIa) [4]. Induced TF forms a complex with FVIIa that triggers the blood-clotting cascade by activation of factors IX and X, leading to thrombin generation. In normal conditions, TF is not expressed on intravascular cells, but it can be induced by some stimuli, such as lipopolysaccharides, tumour necrosis factor α, interleukin 1 and shear stress.

In recent years, evidence has supported the role of the TF pathway in the pathogenesis of aPL-related thrombosis. Experimental data have shown that procoagulant activity in cultured EC is induced by plasma from patients with APS and by purified aPL [5]. Furthermore, there is up-regulation of TF in patients with APS [6, 7], and we have demonstrated that antibodies against β2GPI induce the expression and activity of TF in vitro [8]. Patients with APS have a prothrombotic state, as evidenced by elevated basal thrombin generation. Increased TF expression on EC or monocytes induced by aPL could be responsible, in part, for the hypercoagulability, and might explain the existence of the thrombosis in both the arterial and the venous circulation that characterizes these patients.

After these findings, the interest of many researchers has moved to the clarification of the signal transduction...
mechanisms associated with the increased expression of TF in response to aPL. The binding of aPL to EC and platelets is clearly dependent upon the presence of β2GPI or other phospholipid-binding proteins [9]. However, the nature of these protein receptors on the cells and the signal transduction pathways leading to TF expression are not known. A potential role of Fcγ receptors (FcγR) in the pathogenesis of APS, based on a comparison with heparin-induced thrombocytopenia, was suggested [10] but Pierangelli et al. [11] showed in a murine model that these effects are not dependent on the binding of antibody to FcγR. Annexin II, a phospholipid-binding protein, has been identified as an EC or monocyte surface molecule and might be involved in aPL-mediated cellular signalling, playing a critical role in the up-regulation of monocyte TF [12].

Recently, it has been demonstrated that EC activation by anti-β2GPI is mediated by nuclear factor κB (NFκB). Anti-β2GPI induces translocation of NFκB from the cytoplasm to the nucleus, leading to the transcription of a large number of genes that have a NFκB-responsive element in their promoter. This nuclear translocation of NFκB mediates, at least in part, the increased expression of TF by EC, and of the adhesion molecules [13]. However, the signal transduction pathways for the nuclear translocation of NFκB remain to be elucidated. Apart from TF, other substances, such as ET-1, adhesion molecules [E-selectin, VCAM-1 (vascular cell adhesion molecule 1) and ICAM-1 (intercellular adhesion molecule 1)] and PAI-1, have been reported to be induced by aPL on EC. The prothrombotic state characteristic of patients with aPL is the result of the expression of these procoagulant substances by the activated/damaged EC, but among them TF is the most potent procoagulant substance associated with aPL-mediated thrombosis.

The discovery of the contribution of TF to the hypercoagulable state in patients with APS provides new insight into possible antithrombotic therapies in these patients. The necessity of innovative approaches and new antithrombotic strategies to the treatment and prevention of recurrent thrombosis in APS has now become evident. TF pathway inhibitor (TFPI) is the major physiological inhibitor of the TF pathway, and plays a major role in regulating TF-induced coagulation [14]. Recombinant TFPI has been shown to be effective in animal models of diseases in which TF-mediated coagulation is important [15]. Other agents that behave like TFPI could be therapeutically useful in the treatment of patients with APS, neutralizing the overproduction of TF. These include antibodies against TF and recombinant nematode anticoagulant peptide c2 (NAPc2), which binds to a non-catalytic site on factor X and Xa to inhibit FVIIa interaction.

Other strategies are focused on preventing the induction of TF by aPL. New lipophilic statins, such as fluvastatin and simvastatin, can inhibit the EC activation induced by anti-β2GPI [16], and the up-regulation of TF on EC can also be inhibited by these drugs, providing an additional therapeutic tool in the treatment of thrombosis in APS [17].

In conclusion, increased expression and activity of TF mediated by antibodies against phospholipid-binding proteins contribute to the coagulation mechanisms leading to the prothrombotic state in patients with APS. The exact mechanisms by which these antibodies induce the transduction signal to produce TF are not yet clarified. Such clarification might help us understand the pathogenesis of the disease and in developing new therapeutic approaches in the management of these patients.

O. AMENGUAL, T. ATSUMI and M. A. KHAMASHTA

Department of Medicine II, Hokkaido University School of Medicine, Sapporo, Japan and 1Lupus Research Unit, The Rayne Institute, St Thomas’ Hospital, London SE1 7EH, UK

Correspondence to: M. A. Kamashita. E-mail: munther.khamashta@kcl.ac.uk

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