37 Plasminogen Activation, Fibrinolysis, and Cell Proteolytic Activity in Antiphospholipid Syndrome

Eduardo Anglés-Cano

Fibrinolysis and Extracellular Proteolysis in the Vascular Wall

The basic mechanism underlying fibrinolysis and pericellular proteolysis is the transformation of plasminogen into plasmin by tissue type or urokinase type plasminogen activators (u-PA, t-PA) on, respectively, fibrin or cell surfaces (Fig. 37.1). These plasminogen activators and a specific inhibitor (PAI-1) are synthesized and released by endothelial and smooth muscle cells, and by leukocytes infiltrating the vascular wall [1]. These cells also express receptors for plasminogen and u-PA (u-PAR/CD87) that allow their molecular assembly and efficient plasmin formation for pericellular proteolysis [2–4]. The latter includes extracellular matrix remodelling, cell migration, and proteolytic activation of metalloproteinases (collagenases) and growth factors. It has been well demonstrated that single chain u-PA (pro-urokinase) is the most important activator for pericellular proteolysis in the extravascular space. In contrast, fibrinolysis, the basic mechanism for clot dissolution in the intravascular space, is triggered by the assembly of circulating plasminogen and t-PA released from endothelial cells [5] (Fig. 37.1). However, recent studies suggest that pro-urokinase, which has no affinity for fibrin, may induce fibrin specific lysis by activating plasminogen bound to new binding sites unveiled by plasmin on degrading fibrin [6]. Furthermore, although endothelial t-PA is the main plasminogen activator in the intravascular space, it can also be synthesized by vascular smooth muscle cells and by neurons [7] and can locally favor the development of cell proteolytic activity that may participate in cell migration or in cell detachment induced apoptosis [8].

These mechanisms are regulated at the plasminogen activator level by PAI–1 present in plasma or released from cells in the vascular wall (Fig. 37.2). PAI–1 reacts with single chain and two chain t-PA and with two chain u-PA, but not with single chain u-PA. The second order rate constant for inhibition of these enzymes is in the order of 10^7 M^{-1} s^{-1}. A second type of inhibitor of plasminogen activators and plasmin, protease nexin-1, which also inhibits thrombin, has been identified in the

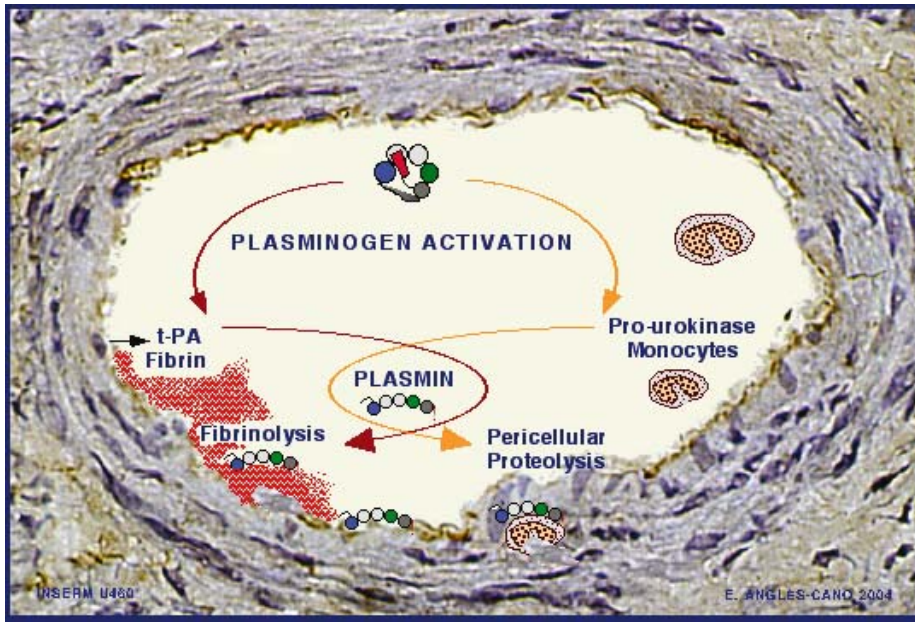

Figure 37.1. Fibrinolysis and extracellular proteolysis in the vascular wall. Cross-section of an arteriole. The endothelial cell lining is marked with a peroxidase labeled antibody directed against the tissue-type plasminogen activator (t-PA) [78]. Circulating plasminogen bound to fibrin and membrane proteins is transformed into plasmin either at the surface of fibrin by fibrin bound t-PA released from endothelial cells or by pro-urokinase bound to its cellular receptor. Plasmin formed in situ specifically degrades fibrin or participate in pericellular proteolytic activities.

central nervous system and in the vascular wall, where it may play a role in the regulation of pericellular proteolysis [9–11].

Plasmin, once formed, remains bound to the cell membrane or to the surface of fibrin, a condition that prevents inhibition by α_2-antiplasmin. However, plasmin released into the circulation during fibrinolysis is rapidly inhibited by α_2-antiplasmin with a second order rate constant of 2 to 4×10^7 $M^{-1}s^{-1}$.

In conclusion, surface activation on fibrin and cells, and fluid phase inhibition in plasma and extracellular fluids, ensure the specificity of fibrinolysis, control the extent of fibrin degradation, and regulate important cellular proteolytic functions.

The activation of plasminogen may be abnormally inhibited, however. For instance, the atherogenic lipoprotein Lp(a) may interfere with fibrinolysis and pericellular proteolysis by its ability to compete with plasminogen for binding to fibrin and cell membranes [12]. The different population of autoantibodies observed in APS may disturb fibrinolysis and contribute thereby to vascular complications [13]. Thrombosis may therefore result from an impaired or insufficient fibrinolytic cellular response to vascular injury provoked by factors such as Lp(a) and autoantibodies. The relationship between auto-antibodies and the plasminogen activation system in APS is analyzed in this chapter.