

Fibrinolytic (Thrombolytic) System

The **fibrinolytic system** restricts the propagation of clots and removes fibrin as wounds heal. Fibrinolysis is initiated by the activation of the circulating proenzyme plasminogen, which is present in clots and plasma, into plasmin, a nonspecific protease enzyme normally absent in blood, by plasminogen activators, such as tissue plasminogen activator, t-PA, and single chain urokinase type plasminogen activator, scu-PA, released from the endothelium. The endothelium also liberates plasminogen activator inhibitor-1 (PAI-1), which complexes with and inactivates t-PA in plasma.

Both t-PA and scu-PA bind with high affinity to fibrin on the clot surface to form a ternary complex consisting of fibrin, activator, and plasminogen. Therefore, in a physiological setting, the specificity of t-PA and scu-PA binding to fibrin localizes plasmin protease activity to thrombi.

Circulating plasmin is rapidly neutralized by alpha-2-antiplasmin, a physiological serine protease inhibitor. In contrast, fibrin-bound plasmin is resistant to **inactivation** by alpha-2-antiplasmin, which localizes the physiological effect of plasmin to the clot. Plasma t-PA is usually inactive because it is inhibited by PAI-1, while t-PA bound to fibrin is unaffected by PAI-1. The very short (5–8 min) half-life of plasma t-PA aids in localizing the formation of fibrin to the thrombus.

Fibrinolytic drugs are plasminogen activators, and provoke stimulation of the fibrinolytic pathway. Fibrinolytic (thrombolytic) drugs are not substitutes for anticoagulants. Anticoagulant and antiplatelet drugs do not promote lysis of clots that are already present, but rather are used prophylactically to prevent **thrombus formation** and propagation. Fibrinolytic therapy is instituted to help dissolve clots that have already formed.

Fibrinolytic drugs can elevate circulating plasmin activity and cause proteolysis of fibrinogen (fibrinogenolysis), plasminogen, and coagulation factors, leading to a lytic state and bleeding.