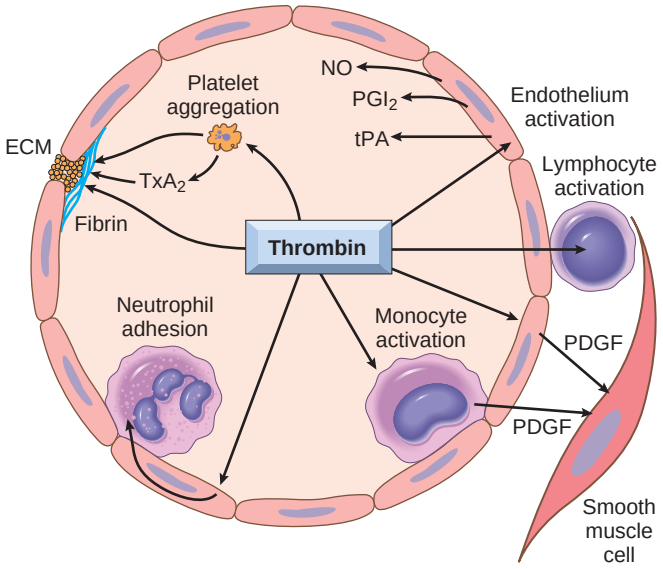

Figure 4-8 Role of thrombin in hemostasis and cellular activation. Thrombin plays a critical role in generating cross-linked fibrin (by cleaving fibrinogen to fibrin and by activating factor XIII), as well as activating several other coagulation factors (see Fig. 4-6*B*). Through protease-activated receptors (PARs, see text), thrombin also modulates several cellular activities. It directly induces platelet aggregation and TxA_2 production, and activates endothelial cells, which respond by expressing adhesion molecules and a variety of fibrinolytic (t-PA), vasoactive (NO, PGI_2), and cytokine mediators (e.g., PDGF). Thrombin also directly activates leukocytes. ECM, extracellular matrix; NO, nitric oxide; PDGF, platelet-derived growth factor; PGI_2, prostacyclin; TxA_2, thromboxane A_2; t-PA, tissue plasminogen activator. See Figure 4-10 for additional anticoagulant activities mediated by thrombin. (Courtesy Shaun Coughlin, MD, PhD, Cardiovascular Research Institute, University of California at San Francisco; modified with permission.)

- *Platelet activation*. Thrombin is a potent inducer of platelet activation and aggregation through its ability to activate PARs, thereby linking platelet function to coagulation.
- *Pro-inflammatory effects*. PARs are also expressed on inflammatory cells, endothelium, and other cell types (Fig. 4-8), and activation of these receptors by thrombin is believed to mediate proinflammatory effects that contribute to tissue repair and angiogenesis.
- *Anticoagulant effects.* Remarkably, through mechanisms described later, upon encountering normal endothelium thrombin changes from a procoagulant to an anticoagulant. This reversal in function prevents clotting from extending beyond the site of the vascular injury.

Factors That Limit Coagulation. Once initiated, coagulation must be restricted to the site of vascular injury to prevent deleterious consequences. One limiting factor is simple dilution; blood flowing past the site of injury washes out activated coagulation factors, which are rapidly removed by the liver. A second is the requirement for negatively charged phospholipids, which, as mentioned, are mainly provided by platelets that have been activated by contact with subendothelial matrix at sites of vascular injury. However, the most important counterregulatory mechanisms involve factors that are expressed by intact endothelium adjacent to the site of injury (described later).

Activation of the coagulation cascade also sets into motion a *fibrinolytic cascade* that limits the size of the clot and contributes to its later dissolution (Fig. 4-9). Fibrinolysis is largely accomplished through the enzymatic activity of *plasmin*, which breaks down fibrin and interferes with its polymerization. An elevated level of breakdown products of fibrinogen (often called fibrin split products), most notably fibrin-derived *D-dimers*, are a useful clinical markers of several thrombotic states (described later). Plasmin is generated by enzymatic catabolism of the inactive circulating precursor *plasminogen,* either by a factor XII–dependent pathway (possibly explaining the association of factor XII deficiency and thrombosis) or by plasminogen activators. The most important plasminogen activator is t-PA; it is synthesized principally by endothelium and is most active when bound to fibrin. This characteristic makes t-PA a useful therapeutic agent, since its fibrinolytic activity is largely confined to sites of recent thrombosis. Once activated, plasmin is in turn tightly controlled by counterregulatory factors such as α_2-plasmin inhibitor, a plasma protein that binds and rapidly inhibits free plasmin.

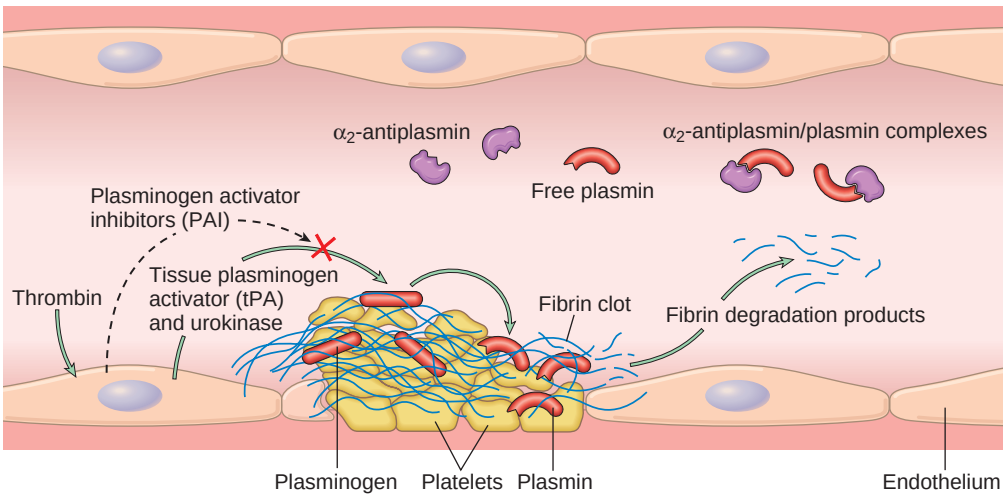

Figure 4-9 The fibrinolytic system, illustrating various plasminogen activators and inhibitors (see text).