The formation of fibrin via a series of reactions within the coagulation system is central in the hemostatic process (Figure 1.1). Coagulation is initiated \textit{in vivo} mainly through exposure of tissue factor, TF, on damaged tissue or endothelium. Activated monocytes can also expose TF. TF binds FVII/VIIa (\(\alpha = \text{activated}\)). The TF-FVIIa complex initiates coagulation by activating FIX and FX. The activated FX transforms prothrombin into thrombin. The process continues, mainly as surface-bound enzymatic reactions, where activated platelets probably offer the phospholipid surface to which coagulation factors (enzymes as well as co-factors) can bind, for example by means of Ca\(^2+\) bridges. Moreover, the coagulation inhibitors (antithrombin, activated protein C (APC)) quickly react with non-surface connected enzymes and co-factors, which help to limit the spread of fibrin formation. Thrombin cleaves off fibrinopeptides A and B to form fibrin monomers, which then polymerize and cross-link, by the action of FXIII, to form an insoluble fibrin network.

The formation of thrombin is accelerated initially by a positive feedback, whereby the thrombin activates FVIII and FV in order to produce more thrombin. Thrombin also promotes coagulation by activating platelets and endothelium.

The physiological importance of the contact activation system for blood coagulation is partly unclear. It has been suggested that when the FXII initiated coagulation is activated \textit{in vivo} it could lead to excessive fibrin formation resulting in thromboembolic manifestations.

The thrombin specificity is modified by its binding to the endothelial receptor thrombomodulin (TM). The TM–thrombin complexes then
Figure 1.1 Cell and tissue injury.
activate protein C into APC, which then decomposes FVIIIa and FVa. Consequently, thrombin is involved both in the *stimulation and inhibition* of the hemostatic process.

A model for cell-associated blood coagulation has also been proposed where the reaction sequence has been divided into three stages:

1. **The initiation phase** where a small amount of thrombin is generated via the TF-induced pathway to activate platelets and coagulation cofactors FV and FVIII to their activated forms.

2. **The priming phase (amplification phase)** where coagulation factors bind to receptors and phosphatidylserine-enriched surfaces such as activated platelets.

3. **The propagation phase** where thrombin is formed via both the contact and TF pathways in order to generate large amounts of thrombin that will transform fibrinogen to fibrin.

Antithrombin and APC are the most important coagulation inhibitors. Another is tissue factor pathway inhibitor (TFPI) but its physiological role is not yet entirely clear. Antithrombin inhibits thrombin by irreversible complex binding, thrombin-antithrombin (TAT) complexes. In a similar way, antithrombin also inhibits most of the activated coagulation factors, except for FVIIa, with different affinities. Heparin accelerates the reaction about 500 times.

It has recently been discovered that thrombin also has antifibrinolytic effects. It activates thrombin activatable fibrinolysis inhibitor (TAFI) to its active form, thereby inhibiting fibrinolysis.

The activation of fibrinolysis is probably secondary to the activation of coagulation. Tissue plasminogen activator (t-PA) is released from the endothelium and transforms plasminogen into plasmin. The reaction is substantially accelerated by the presence of fibrin, and plasmin formation normally occurs only locally on and in a fibrin clot. Plasmin breaks down fibrin and fibrinogen into a number of fragments, fibrin(ogen) degradation products, for example X, Y, D and E fragments, and cross-linked fibrin fragments, fibrin D-dimers. t-PA is inhibited by the release of plasminogen activator inhibitor (PAI-1) from the endothelium. Free plasmin, not bound to fibrin, is rapidly inhibited by the plasmin inhibitor. Plasmin inhibitor and plasmin form an enzymatically inactive complex.