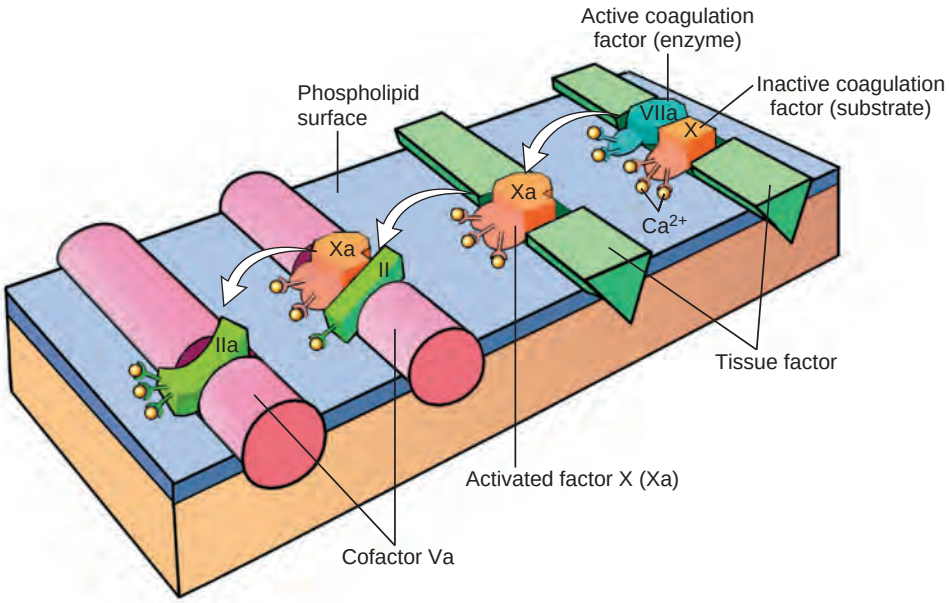

Figure 4-7 Schematic illustration of the conversion of factor X to factor Xa via the extrinsic pathway, which in turn converts factor II (prothrombin) to factor IIa (thrombin). The initial reaction complex consists of a proteolytic enzyme (factor VIIa), a substrate (factor X), and a reaction accelerator (tissue factor), all assembled on a platelet phospholipid surface. Calcium ions hold the assembled components together and are essential for the reaction. Activated factor Xa becomes the protease for the second adjacent complex in the coagulation cascade, converting prothrombin substrate (II) to thrombin (IIa) using factor Va as the reaction accelerator.

However, clotting in vitro and in vivo both follow the same general principles, as follows.

The cascade of reactions in the pathway can be likened to a "dance," in which coagulation factors are passed from one partner to the next (Fig. 4-7). Each reaction step involves an enzyme (an activated coagulation factor), a substrate (an inactive proenzyme form of a coagulation factor), and a cofactor (a reaction accelerator). These components are assembled on a negatively charged phospholipid surface, which is provided by activated platelets. Assembly of reaction complexes also depends on calcium, which binds to γ-carboxylated glutamic acid residues that are present in factors II, VII, IX, and X. The enzymatic reactions that produce γ-carboxylated glutamic acid use vitamin K as a cofactor and are antagonized by drugs such as coumadin, a widely used anticoagulant.

Based on assays carried out in clinical laboratories, the coagulation cascade has traditionally been divided into the *extrinsic* and *intrinsic* pathways (Fig. 4-6*A*).

- The *prothrombin time* (PT) assay assesses the function of the proteins in the extrinsic pathway (factors VII, X, V, II, and fibrinogen). In brief, tissue factor, phospholipids, and calcium are added to plasma and the time for a fibrin clot to form is recorded.
- The *partial thromboplastin time* (PTT) assay screens the function of the proteins in the intrinsic pathway (factors XII, XI, IX, VIII, X, V, II, and fibrinogen). In this assay, clotting of plasma is initiated by addition of negative-charged particles (e.g., ground glass) that activate factor XII (Hageman factor) together with phospholipids and calcium, and the time to fibrin clot formation is recorded.

While the PT and PTT assays are of great utility in evaluating coagulation factor function in patients, they fail to recapitulate the events that lead to coagulation in vivo. This point is most clearly made by considering the clinical effects of deficiencies of various coagulation factors. Deficiencies of factors V, VII, VIII, IX, and X are associated with moderate to severe bleeding disorders, and prothrombin deficiency is likely incompatible with life. In contrast, factor XI deficiency is only associated with mild bleeding, and individuals with factor XII deficiency do not bleed and in fact may be susceptible to thrombosis. The paradoxical effect of factor XII deficiency may be explained by involvement of factor XII in the fibrinolysis pathway (discussed later); while there is also some evidence from experimental models suggesting that factor XII may promote thrombosis under certain circumstances, the relevance of these observations to human thrombotic disease remains to be determined.

Based on the effects of various factor deficiencies in humans, it is believed that, in vivo, factor VIIa/tissue factor complex is the most important activator of factor IX and that factor IXa/factor VIIIa complex is the most important activator of factor X (Fig. 4-6*B*). The mild bleeding tendency seen in patients with factor XI deficiency is likely explained by the ability of thrombin to activate factor XI (as well as factors V and VIII), a feedback mechanism that amplifies the coagulation cascade.

Among the coagulation factors, thrombin is the most important, in that its various enzymatic activities control diverse aspects of hemostasis and link clotting to inflammation and repair. Among thrombin's most important activities are the following:

- *Conversion of fibrinogen into crosslinked fibrin.* Thrombin directly converts soluble fibrinogen into fibrin monomers that polymerize into an insoluble clot, and also amplifies the coagulation process, not only by activating factor XI, but also be activating two critical co-factors, factors V and VIII. It also stabilizes the secondary hemostatic plug by activating factor XIII, which covalently cross-links fibrin.