The coagulation pathway and approaches to anticoagulation

A brief overview of the coagulation pathway

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Intact endothelium is smooth, lacks thrombogenic proteins on its surface and protects circulating blood from exposure to subendothelial proteins such as collagen. As a result, blood constituents flow freely without adhering to endothelial structures. However, when endothelium is damaged and its integrity is disrupted, subendothelial structures come into contact with the constituents of blood (including coagulation factors and platelets), and this triggers an intricate process responsible for platelet attraction and deposition and, simultaneously, the coagulation cascade.

The coagulation cascade comprises two principal elements:
- the tissue factor (extrinsic) pathway
- the contact activation (intrinsic) pathway.

Both pathways ultimately lead to the formation of an insoluble fibrin clot. Each involves a series of reactions in which inactive enzyme precursors are transformed into their active forms, which catalyse the subsequent reactions of the cascade.

The fundamental role of the coagulation system is to facilitate haemostasis when there is haemorrhage due to blood vessel injury. Physiologically, a self-maintained balance of procoagulant and anticoagulant factors/regulators provides a negative feedback system for the prevention of excessive coagulation or haemorrhagic diathesis.

The coagulation cascade

The tissue factor (extrinsic) pathway [1]

When the coagulation cascade is activated, tissue factor (TF), which is normally located in subendothelial tissue, comes into contact with circulating factor VII and forms an activated complex (TF–VIIa) in the presence of Ca^{2+}.
(Figure 1.1). TF–VIIa catalyses the conversion of factor X into factor Xa and, following binding of activated factor Va, initiates formation of the serum protease thrombin. Thrombin is formed from prothrombin via a complex reaction in which factors Xa and Va cleave prothrombin fragments 1 and 2 in the presence of Ca\(^{2+}\). Subsequently, thrombin cleaves fibrinopeptides A and B from fibrinogen, resulting in the formation of insoluble fibrin.

**The contact activation (intrinsic) pathway**

The contact activation (intrinsic) pathway begins with the formation of a complex made up of Hageman factor (factor XII), prekallikrein, high-molecular-weight kininogen (HMWK) and collagen. Given that the absence of factor XII, prekallikrein or HMWK does not induce a clinically apparent pathology [2], the physiological role of this complex is unclear and it is assumed to have only a minor function in clot formation.