Molecular Deficiencies of Human Blood Coagulation

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Introduction

Visible clotting takes place as soon as blood is removed from its physiological environment, i.e. the intact endothelium of blood vessels. Two steps are essential for clot formation: 1. the activation of the clot-promoting enzyme, thrombin and 2. conversion of the soluble plasma protein, fibrinogen, into its insoluble and polymerizing derivative, fibrin. The so-called classical coagulation theory was summarized by Morawitz in 1905 (Figure 1) and stated that thrombin was not present in the circulating blood since its in vivo activation or infusion would cause generalized thrombosis. The inactive precursor of thrombin was called thrombogen or prothrombin. The formation of thrombin in vitro and in vivo was found to be initiated or accelerated by lipoproteins originating from blood cells, mainly platelets, and tissues surrounding blood vessels. Formation of thrombin from prothrombin necessitated the presence of calcium ions, whereas preformed fibrin polymerized without additional calcium.

During the past 25 years the concept of hemostasis was expanded by the accumulating evidence of the central role of blood platelets and the discovery of numerous additional 'coagulation factors' participating in the conversion of prothrombin into thrombin. Furthermore, the classical scheme was unable to explain the cause of bleeding in hemophilia since the addition of tissue thromboplastin masked the deficiency. We now know that two pathways lead to the formation of thrombin (Figure 2): firstly, certain tissue lipoproteins (thromboplastin) activate a specific protein, factor VII. Only two additional coagulation factors, bearing the numbers V and X, form in the presence of calcium the prothrombin converting principle. This accelerated pathway probably furnishes trace amounts of thrombin participating in primary hemostasis through platelet aggregation and produces increasing amounts of thrombin by feed-back activation of other coagulation factors. Thus, the clotting systems correspond to a 'biologic amplifier'. The second, slower and probably more persistent pathway is initiated by contact activation, whereby 'contact' signifies a surface which, in contrast to the intact internal vessel wall, activates Hageman factor (factor XII).

Molecular aspects of blood coagulation

The two terms 'coagulation' and 'hemostasis' are not synonymous, since individuals with Hageman factor deficiency or certain abnormal fibrinogens do not bleed excessively, but coagulation of their blood or plasma in vitro is markedly disturbed. The discovery of the so-called coagulation factors was mainly based on cross-match experiments on blood samples obtained from patients with various coagulation disorders. The International Committee on Nomenclature of Blood Clotting Factors undertook the tedious task of retrieving the data obtained from these simple, clinical experiments and finally established a list of coagulation factors which are characterized by Roman numerals (Table). Coagulation factors, with the exception of fibrinogen, are trace proteins, and their biochemical

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Footnotes:
characterization is far from complete. However, recent attempts to purify the single constituents established their respective position in the coagulation system and also confirmed their antigenic individuality. It remains puzzling that three coagulation factors, VII, IX and X, share several physico-chemical properties with prothrombin (factor II), e.g. absorption by barium sulfate. Their complete synthesis depends on the availability of vitamin K.

Fibrinogen was already purified and partially characterized by Hammersten in the 19th century. It is therefore not surprising that his large protein (MW 340,000) became an early target of biochemists studying its interaction with thrombin, transformation into fibrin and the subsequent polymerization of this latter protein. We now know that fibrinogen consists of two identical subunits, which are composed of three peptide chains (Figure 3). Thrombin removes a total of 4 small peptides (MW appr. 2,000), the peptides A and B, from the N-terminal parts of the α- and β-chains, respectively.

The second relatively well-established mechanism concerns the action of factor XIII, the fibrin stabilizing enzyme, on fibrin. Factor XIII is activated by thrombin and induces the formation of glutamyl-lysyl bonds between α- and γ-chains of fibrinogen or of preformed fibrin.

Although other coagulation factors or their activated derivatives, especially thrombin, may be demonstrated and measured by their more or less specific esterolytic activity on artificial substrates, the most widely used assay systems measure the rate of thrombin formation and subsequent fibrin polymerization depending on the critical reduction of a single coagulation factor.

Congenital abnormalities of blood coagulation

One of the criteria for attribution of a Roman numeral to a given coagulation factor was its congenital deficiency. Until recently, it was not clear whether the defect was caused by the absence or reduction of a clot-promoting protein or whether a molecular defect of

\[ \text{Fibrinogen (I)} \rightarrow \text{Fibrin (soluble, Ia)} \]

\[ \rightarrow \text{"stabilized" Fibrin (insoluble, Ia')} \]

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\[ \text{Ca}^{++} \]

\[ \text{Tissue thromboplastin} \]

\[ \text{PL, platelet lipids.} \]