Biology of Coagulation and Coagulopathy in Neurologic Surgery

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KEYWORDS

• Coagulation • Hemostasis • Thrombin • Fibrinolysis • Brain • Neurosurgery • Prothrombin time • Partial thromboplastin time

KEY POINTS

- Hemostasis is cell-based and tightly regulated in a tissue-specific manner by differential expression of procoagulant and anticoagulant factors on endothelial cells from different sites throughout the vasculature.
- The brain exhibits unique mechanisms of hemostatic regulation that favor increased tissue factor pathway activity to protect against hemorrhage at the expense of increased thrombotic risk.
- Although the "cascade" model of coagulation is useful for interpreting the PT and aPTT assays, neither of these tests accurately reflects the complexity of hemostasis in vivo.

INTRODUCTION

Hemostasis is a tightly regulated process designed to prevent hemorrhage while maintaining the fluidity of blood in circulation. This process is dependent on interactions among platelets, endothelial cells, and plasma proteins that facilitate coagulation at sites of injury. Meanwhile, hemostasis is limited by the antithrombotic and fibrinolytic systems to prevent thrombosis and facilitate wound healing.

Although blood circulation allows effective communication and trafficking between organ systems, systemic alterations in hemostatic components invariably lead to localized rather than diffuse patterns of hemorrhage or thrombosis. This suggests that the process of hemostasis is regulated in a tissue-specific manner determined by the differential expression of procoagulant and anticoagulant properties within various tissue types.[1–3]

The purpose of this article is to (1) provide a general framework for understanding the process of hemostasis; (2) highlight unique regulatory mechanisms in the brain; and (3) review the limitations of laboratory testing in assessing hemostasis.

MECHANISMS OF HEMOSTASIS

The hemostatic response is divided into 2 concomitant and interdependent stages termed

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primary and secondary hemostasis. Primary hemostasis is initiated by vascular injury leading to vasoconstriction and exposure of the subendothelial matrix. Platelets rapidly adhere to the site of injury where they undergo activation and aggregation to form a temporary platelet plug. Secondary hemostasis involves activation of the coagulation cascade to facilitate the production of thrombin in sufficient amounts to cleave fibrinogen and stabilize the platelet plug. In addition, thrombin triggers the anticoagulant and fibrinolytic systems that limit the hemostatic response while maintaining clot integrity long enough to ensure wound repair.

Early Models of Hemostasis

In 1905, Paul Morawitz[4] proposed the first biochemical model of coagulation in which thrombokinase, also known as thromboplastin or tissue factor (TF), converts prothrombin to thrombin in a calcium-dependent manner. In 1935, A.J. Quick[5] used this model to develop the initial prothrombin time (PT) to assay plasma levels of prothrombin. In 1953, the partial thromboplastin time (PTT) was developed to aid in the diagnosis of hemophilia.[6] It was later modified using kaolin as an activator to make it more rapid and reproducible. Thus, the activated PTT (aPTT) was born.[7]

As additional coagulation factors were discovered over the first half of the twentieth century, updated models of coagulation were needed to explain this increasingly complex system.

Results from the PT and aPTT assays contributed to the development of the waterfall or "cascade" model of coagulation in 1964.[8,9] In this model, each coagulation factor exists as a zymogen that is converted into an active enzyme by proteolytic cleavage. Coagulation occurs via a series of steps in which each factor activates the next. In this manner, a series of proteases acts as a biological amplifier that ultimately generates enough thrombin to produce a stable fibrin clot.

Subsequent modifications of the cascade model resulted in the now familiar Y-shaped scheme consisting of 2 distinct pathways that converge at the level of the prothrombinase (factor Xa [FXa]/FVa) complex (Fig. 1). In this scheme, the "intrinsic" pathway, so called because all components are present in plasma, is initiated by FXII. In contrast, the "extrinsic" pathway is initiated by FVIIa/TF and therefore requires a component that is normally external to the blood.

The cascade model was originally proposed to illustrate biochemical interactions between coagulation factors, and not as a literal model of hemostasis in vivo. Therefore, this model does not include the anticoagulant pathways that provide both spatial and temporal regulation of thrombin formation. In addition, it cannot explain why a functional extrinsic pathway is unable to prevent bleeding in patients with hemophilia or other isolated defects of the intrinsic pathway. Despite these limitations, the cascade model provides an excellent tool for interpreting the PT and aPTT assays on which it was based.

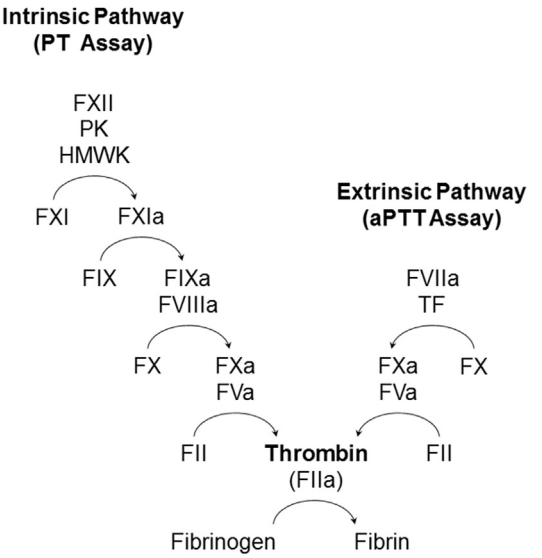

Fig. 1. The cascade model of coagulation. The intrinsic and extrinsic pathways converge at the FXa/FVa complex, which generates enough thrombin to cleave fibrinogen and form a mature clot. This model is an excellent tool for interpreting the aPTT and PT assays, which monitor factor levels in the intrinsic or extrinsic pathway, respectively. HMWK, high molecular weight kininogen; PK, prekallikrein.

A Cell-Based Model of Hemostasis

Since the discoveries of platelets[10] and the Virchow triad[11] in the mid-nineteenth century, cells have been widely recognized as important participants in coagulation. Thus, a current model of hemostasis incorporates the important role of cells that is lacking in the cascade model.[12]

According to the cell-based model, hemostasis occurs in a stepwise process on specific cell surfaces that differentially express procoagulant and anticoagulant proteins and receptors (Fig. 2). This process is divided into 3 overlapping stages: (1) initiation on the surface of a TF-bearing cell, (2) amplification, which sets the stage for large-scale thrombin generation, and (3) propagation on the platelet surface, which facilitates large-scale thrombin generation.