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Review Article

Spatial aspects of blood coagulation: Two decades of research on the self-sustained traveling wave of thrombin

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ABSTRACT

In a number of experimental studies, it has been demonstrated that the forefront of blood coagulation can propagate in the manner of a signal relay. These data strongly support the concept that the formation of a blood clot is governed by a self-sustained traveling wave of thrombin. The present review critically appraises the experimental data obtained in recent decades concerning the self-sustained spatial propagation of thrombin. Open questions regarding the experimental detection of the self-sustained propagation of thrombin are discussed.

Contents

Introduction

It is well-known that blood under certain conditions can change its aggregative state. This particular property of blood normally prevents excessive bleeding in case of injury [1,2]. An unfading interest in the issues of blood coagulation is largely accounted for by the fact that disorders in the regulation of the blood aggregative state cause a range of severe pathologies that pose a threat to human health and life [3,4]. These include not only bleeding disorders but also a number

Abbreviations: PFP, platelet-free plasma; PPP, platelet-poor plasma; PRP, platelet-rich plasma; UFP, ultra-free plasma; TAFI, thrombin-activatable fibrinolysis inhibitor; TF, tissue factor

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of thrombotic diseases such as myocardial infarction, stroke, pulmonary embolism, disseminated intravascular coagulation, etc. [5–7].

Coagulation mechanisms responsible for the velocity of thrombus formation sufficient for the termination of bleeding are a matter of great interest. These mechanisms appear all the more vital because the rapidity of the blood coagulation processes determines not only the efficiency of bleeding termination but also the precipitated threat with which some of thrombotic complications may emerge [8,9].

The most significant step in the understanding of the kinetic aspects of blood coagulation was the suggestion that the network of enzymatic reactions participating in the generation of thrombin acts as a type of biochemical amplifier [10,11]. This network of reactions is now known as the coagulation cascade, and its major components and reactions have been thoroughly studied [1,12]. The network of reactions leading to the generation of thrombin is traditionally divided into the so-called intrinsic and extrinsic pathways [12,13]. The former is presumed to be initiated by a negatively charged surface, whereas the latter is activated by the exposure of tissue factor on phospholipid membranes. The diagram illustrating the current view of the network of biochemical reactions that participate in thrombin generation is shown in Fig. 1.

It is remarkable that this reaction network contains a few positive feedback loops that provide up to 10^5 – 10^7-fold catalytic amplification of the generation of thrombin as soon as even a small amount of thrombin appears in the blood [10,14]. Such autocatalytic amplification provides explosive (exponential) thrombin generation in response to a single stimulus [15].

It is noteworthy that this explosive generation of thrombin only takes place in response to a stimulation exceeding a certain threshold value [16,17]. Therefore, the blood coagulation system can be considered to be a trigger-type kinetic system acting in accordance with the "all-or-nothing" principle. The rapidity of its trigger is determined by a powerful autocatalytic biochemical cascade mechanism that provides explosive self-accelerating generation of thrombin.

Spatial Aspects of Blood Coagulation

During the 1960–80s, numerous details about the *temporal* aspects of the physiological and biochemical mechanisms regulating the development of the coagulation processes were discovered [12,18–20]. Nonetheless, in the early 1990s, it was still unclear how sufficient rapidity of the *spatial* formation of the thrombus could be achieved. This issue was particularly unclear in the case of non-homogeneous initial distribution of the coagulation activator throughout the blood. For instance, consider the case of an injury to the internal surface of a vessel wall where the stimulation of the coagulation occurs only at the periphery of the blood volume.

At first, it may seem that the mere diffusion of coagulation factors from the site of injury to the inner areas of the blood volume can account for the spatial formation of the clot. However, basic estimates show that even in the case of explosive generation of coagulation factors at the border of the blood volume, the diffusional mass-transfer of the factors deep into the vessel can hardly ever provide a rate of clot growth sufficient for the formation of a macroscopic thrombus comparable with the size of the vessel lumen [21,22]. However, it is known that the formation of macroscopic occlusive thrombi blocking the vessel lumen entirely is not uncommon in clinical practice [23,24].

Thus, although the kinetic mechanisms providing the *temporal* rapidity of blood coagulation have already been researched extensively, in the early 1990s, the mechanisms that provide sufficient *spatial* rapidity of formation of blood clots remained poorly understood. Two conceptual frameworks soon appeared that suggested possible

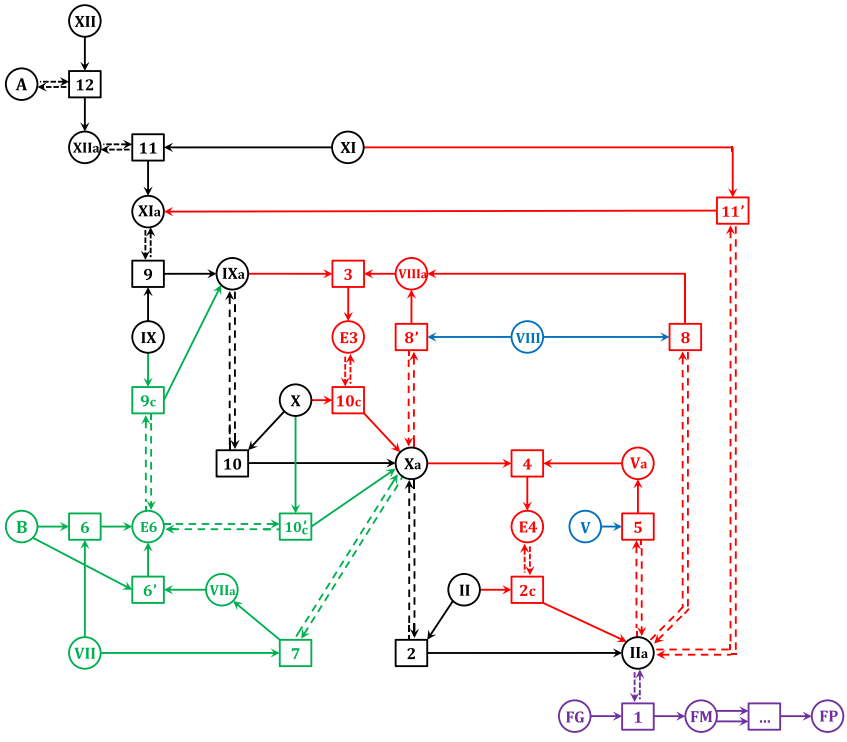

Fig. 1. Simplified diagram of the blood coagulation cascade. The circles represent the coagulation factors and the rectangles the biochemical reactions. Solid arrows from a factor to a reaction indicate participation in the reaction, and arrows from a reaction to a factor signify that the factor is a product of the reaction. Dotted arrows represent the catalytic activity of the substance. The number given in each rectangle corresponds to the number of the product formed in the course of the reaction. If some substance can be formed as a result of several different reactions apostrophes and subscripts are used to distinguish these reactions. Subscript 'c' is used to denote the reactions catalyzed by enzymatic complexes. 'E3' represents the enzymatic complex of the active forms of factors IXa and VIIIa, 'E4' the complex of factors Xa and Va, and 'E6' the complex of tissue factors and factor VIIa. 'A' and 'B' represent the initiating events of the intrinsic and extrinsic pathways, respectively. Other terms used are: II, prothrombin; IIa, thrombin; FG, fibrinogen; FM, fibrin monomer; FP, fibrin polymer.