Thrombosis Research 136 (2015) 699–711

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Review Article

Hemostasis and thrombosis beyond biochemistry: roles of geometry, flow and diffusion

Mikhail A. Panteleev [a,b,c,d,e], Natalia M. Dashkevich [a,c], Fazoil I. Ataullakhanov [a,b,c,d,e,*]

[a] Center for Theoretical Problems of Physico-Chemical Pharmacology, Russian Academy of Sciences, Moscow, Russia
[b] Federal Research and Clinical Center of Pediatric Hematology, Oncology and Immunology, Moscow, Russia
[c] HemaCore Labs LLC, Moscow, Russia
[d] Physics Department, Moscow State University, Moscow, Russia
[e] Faculty of Biological and Medical Physics, Moscow Institute of Physics and Technology, Dolgoprudny, Russia

ARTICLE INFO

Article history:
Received 11 June 2015
Received in revised form 22 July 2015
Accepted 26 July 2015
Available online 29 July 2015

Keywords:
Blood coagulation
Hemostatic plug
Enzymatic cascade
Diffusion
Blood flow
Blood coagulation tests

ABSTRACT

An important trend in the modern concept of blood coagulation is the growing agreement that, in order to understand regulation of coagulation *in vivo* and disorders of its function, it is essential to take into account its spatial heterogeneity, diffusion, and flow. In a way, this suggests that the idea of the "coagulation cascade" itself becomes increasingly misleading because there is no such place in an organism where reactions of this cascade really co-exist: activation, propagation and termination of coagulation are regulated by different subsets of chemical reactions that have different spatial localization and depend on cofactors expressed by different cell types in different tissues, so that only diffusion and flow can link these distinct "compartments" together into the one functional system. Here we review the last two decades of evidence obtained from in vitro, in vivo and computational systems biology approaches. When combined, the data comprise into an adequately comprehensive picture of the spatial regulation and organization of blood coagulation. In addition to the basic insights into the regulatory mechanisms, these approaches provided interesting results in the fields of coagulation diagnostics and other applications. Finally, the remaining unresolved and conflicting issues in the spatiotemporal regulation of coagulation are discussed.

Contents

1. Introduction: Is there Anything in Blood Coagulation beyond Biochemistry?

It is traditional to think about blood coagulation as a cascade (Fig. 1A), or more accurately network of proteolytic reactions [1].

* Corresponding author at: FRCCPH 1, Samory Mashela Str, GSP-7, Moscow 117997, Russia.
E-mail address: ataullakhanov.fazly@gmail.com (F.I. Ataullakhanov).

http://dx.doi.org/10.1016/j.thromres.2015.07.025
0049-3848/

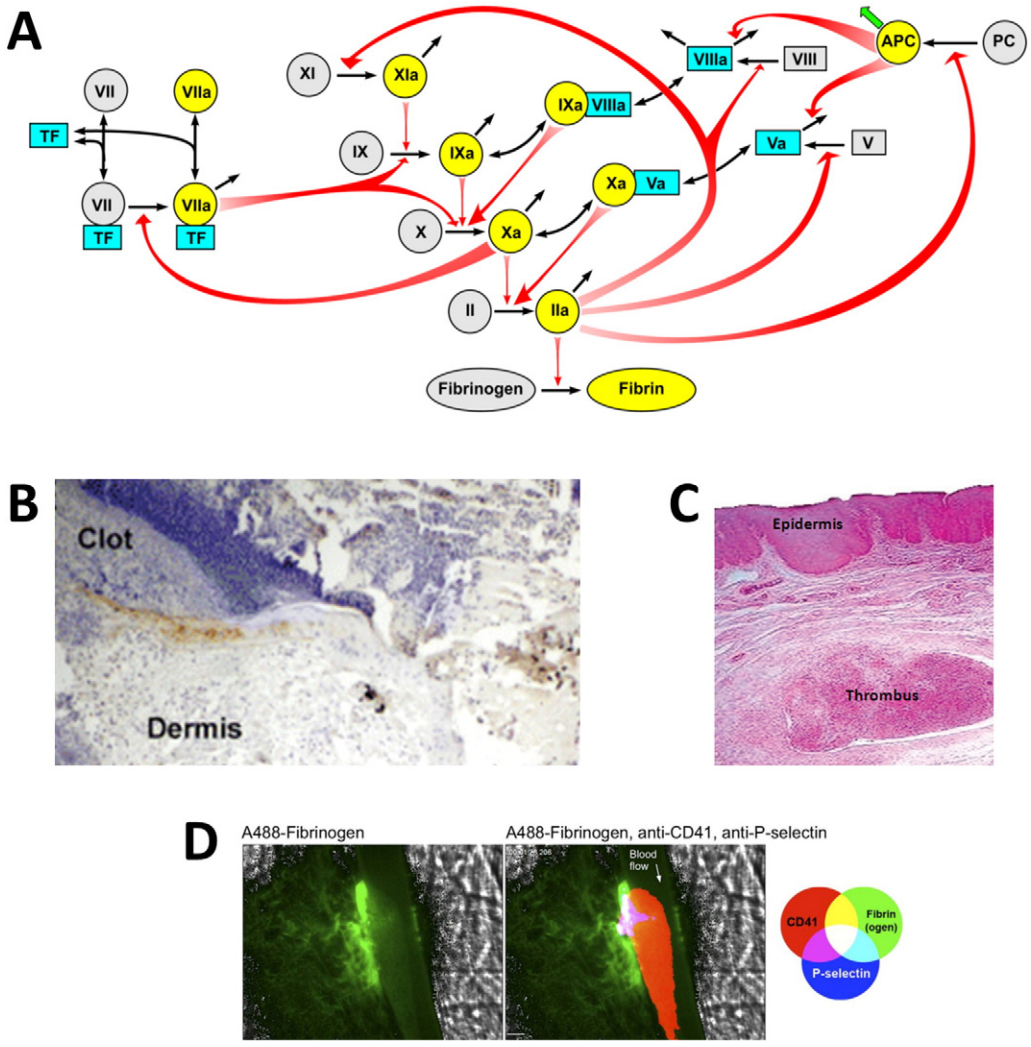

Fig. 1. ***Blood coagulation: biochemistry and the real process in vivo under different conditions.*** **(A)** The traditional cascade representation of blood coagulation biochemistry [22]. **(B)** Hemostatic fibrin plug formed in a skin wound: notice a clear boundary between the clot and the tissue. Reproduced with permission from [66]. Copyright John Wiley & Sons. **(C)** Histological staining of a classical fibrin-rich "red" venous thrombus [87]. **(D)** Confocal microscopy imaging of fibrin formation in the core of a platelet thrombus in a mouse arteriole: noteworthy, fibrin clot grows into the tissue as well thereby providing "roots" for the thrombus . Republished with permission of American Society of Haematology, from Stalker et al. [11]; permission conveyed through Copyright Clearance Center, Inc.

Although new reactions and components are still sometimes added to this scheme [2,3], and some of the mechanisms are subject of discussion [4], its main elements have remained unchanged since early 1990-ies.

According to the cascade concept [5], coagulation is initiated by a contact of plasma with a transmembrane protein tissue factor (TF) that is normally present only in the extravascular cells, so such a contact can occur only as a result of either mechanical vascular damage or other injury, e.g., inflammation. A low active serine protease factor VIIa binds TF to become a fully functional enzyme that activates factors IX and X via limited proteolysis, factor IXa then additionally activates factor X, and factor Xa activates prothrombin into thrombin. Thrombin produces fibrin that spontaneously polymerizes resulting in gelation of plasma at the site of injury. Gelled plasma stops bleeding thus fulfilling the ultimate purpose of the hemostatic system.

In addition, thrombin strongly amplifies its own production through activation of cofactor proteins factors V and VIII. Factors Va and VIIIa greatly accelerate action of factors Xa and IXa, respectively, when assembled in factor Va:factor Xa (prothrombinase) and factor VIIIa:factor IXa (intrinsic tenase) complexes on the negatively charged lipid surfaces, such as those found on activated platelet membranes. Thrombin also activates platelets (not shown in Fig. 1A) and factor XI; the latter then provides an additional pathway of factor IX activation. Factor XI can also be activated by factor XIIa in a so-called contact pathway of coagulation triggered by the contact of foreign surface with blood or plasma. Contact pathway is not shown on Fig. 1A because factor XII deficiency is not associated with bleeding phenotype and therefore it probably plays a minor role in normal hemostasis [6].

A number of anticoagulation pathways are known to regulate the procoagulant cascade: some are based on a straightforward inhibition of serine proteases by plasma inhibitors (antithrombin III), others include multi-domain inhibitors with a complex mechanism of action (TFPI), and cofactors that are inactivated via either spontaneous dissociation (factor VIIIa) and cleavage by activated protein C. The activation of the protein C pathway [7] is also triggered by thrombin and is greatly promoted by two transmembrane endothelial cofactor proteins, thrombomodulin and endothelial protein C receptor that bring the enzyme and the substrate together.

This cascade concept is a beautiful and logical design, beginning with the TF exposure at the site of damage and the assembly of extrinsic tenase (the factor VIIa:TF complex), leading on to the activation of zymogens one after another into active proteases and ending with the fibrin formation, with amplifying positive feedbacks of factors' V and VIII stimulation to form complexes on the membranes of activated platelets, and negative feedbacks of the TFPI and protein C pathways to down-regulate and contain the procoagulant response. Although this cascade concept may invite philosophical questions like *why all*