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PATHOGENESIS OF THE BLOOD COAGULATION SYSTEM: KEY ASPECTS

Savytskyi I.[1], Savytskyi V.[2], Karabut L.[3]

[1] International European University, Kyiv, Ukraine

[2] National Pharmaceutical University, Kharkiv, Ukraine

[3] Odesa National Medical University, Odesa, Ukraine

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ПАТОГЕНЕЗ СИСТЕМИ ЗГОРТАННЯ КРОВІ: ОСНОВНІ АСПЕКТИ

Савицький І., Савицький В., Карабут Л.

У статті розглянуто основні сучасні теоретичні уявлення про систему гемокоагуляції. Детально описано не тільки механізми судинно-тромбоцитарного та коагуляційного гемостазу, а й основні ланки системи протизгортання крові та фібринолізу. Таким чином, система тромбоутворення являє собою ланцюг складних каскадно-комплексних ферментативних реакцій, які включають багато клітинних і гуморальних агентів з тонкими механізмами нейроендокринної регуляції.

Ключові слова: гемокоагуляція, тромбоцити, фактори згортання крові, фібриноліз.

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PATHOGENESIS OF THE BLOOD COAGULATION SYSTEM: KEY ASPECTS

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The article considers the main modern theoretical concepts of the hemocoagulation system. Described in details not only the mechanisms of vascular-platelet and coagulation hemostasis, but also the main components of the anticoagulation system and fibrinolysis. Thus, the thrombogenesis system is a chain of complex cascade-complex enzymatic reactions that involve a many of cellular and humoral agents with subtle mechanisms of neuroendocrine regulation.

Key words: hemocoagulation, platelets, coagulation factors, fibrinolysis.

One of the manifestations of the blood protective function is its ability to coagulate, which is aimed at stopping bleeding. In violation of this mechanism, even minor damage of the vascular wall can lead to significant blood loss [1, 2, 3].

Hemostasis – biological system of the organism, the main function is to keep the blood in a liquid condition, stop bleeding when the vessel wall is damaged, as well as the dissolution of blood clots that have performed their function [4].

The hemocoagulation system must quickly identify damage and form an adequate clot in vessels of different lumens at different blood flow rates and types of damage. It is necessary to prevent the spread of activated plasma coagulation factors in the bloodstream [5]. This is due to the high complexity of this system, which is a cascade of enzymatic reactions characterized by numerous positive and negative feedbacks and active interaction with blood cells, subendothelium and endothelium [6].

The components of the hemostasis system include: coagulation (plasma factors) and anticoagulant (physiological anticoagulants) links, activators and inhibitors of fibrinolysis, cellular factors of blood cells (platelets, leukocytes, erythrocytes), coagulation factors and and tissue fibrinolysis [7, 8]. Their interaction allows the hemostasis system to be within physiological balance: between hypocoagulation and hypercoagulation [9].

Structural and functional integrity of the vascular endothelium is required to keep the blood in physiological condition. Normally, it prevents the entry of thromboplastin into the bloodstream, activates Hageman factor, secretes natural anticoagulants (antithrombin III, plasminogen activator), activates platelet aggregation – ADP and Willebrand factor [10]. The vascular wall responds to damage by vasoconstriction, the vascular endothelium is transformed into a powerful procoagulant surface, which promotes the adhesion of platelets and leukocytes [10, 11].

Among the blood cells involved in the formation of the primary thrombus, platelets are best studied [12]. These are nonnuclear biconvex cell fragments 2–4 μm in diameter, which are formed in the red bone marrow from megakaryocytes and are responsible for key stages of the hemocoagulation process: hemostatic thrombus formation and accelerated blood clotting response, are actively involved in local vasoconstriction. Upon activation of platelets, dense granules (containing serotonin, ADP) and alpha granules (including proteins – fibrinogen, factor V, von Willebrand factor) begin to be secreted in their cytoplasm [11].

In addition to platelets, leukocytes and erythrocytes are involved in the formation of the primary thrombus. Leukocytes accelerate the process of cell aggregation, activate coagulation hemostasis due to the presence of thromboplastic, antiheparin and fibrin stabilizing factors. In turn, erythrocytes can affect the process of activation of vascular-platelet hemostasis in two ways: the release of ADP, increasing the adhesive and aggregation properties of platelets by changing the size and deformation of erythrocytes [7].

One of the primary roles in blood clotting is played by cellular factors. Most of them are contained in platelets, but they are also present in other cells (erythrocytes, leukocytes). However, in hemocoagulation, the largest number of destroyed cells – platelets, so the most important role in blood clotting belongs to platelet factors, of which there are about 14 [13, 14, 15].

Depending on the size of the damaged vessel, there are two main mechanisms of hemostasis: vascular-platelet and coagulation. [4, 16].

Vascular-platelet hemostasis stops bleeding in microcirculatory vessels with low blood pressure [17]. When the endothelium of small vessels is damaged under the influence of

vasoconstrictive compounds (epinephrine, norepinephrine, serotonin, thromboxane A2) there is a reflex spasm of damaged vessels. Due to the mechanical blockage of the lumen of the damaged vessel, adhesion (adhesion) of platelets to the positively charged connective tissue collagen fibers of the wound edges is observed, as a result of which ATP and ADP are released. Platelet adhesion lasts 3 to 10 seconds [18]. Simultaneously with the adhesion at the site of injury begins reversible aggregation (accumulation) with the formation of a loose thrombus, which passes blood plasma. Then, under the action of thrombin, the platelet membrane is destroyed, which leads to the release of physiologically active substances (serotonin, histamine, nucleotides, enzymes, coagulation factors), in which platelets lose their structure and merge into a homogeneous mass – there is irreversible dense cork. This reaction contributes to secondary vasospasm. The release of factor III initiates the formation of platelet prothrombinase, i.e. the inclusion of the mechanism of coagulation hemostasis. A small amount of fibrin threads is formed on platelet aggregates, in the network of which uniform blood elements are retained. Due to the reduction of thrombostenin protein, the thrombus is compacted and fixed in the damaged vessel, the so-called retraction of the blood thrombus.

In vessels with big lumen the platelet thrombus cannot withstand high blood pressure and blood flow – it is "washed away". Therefore, in vessels of big lumen hemostasis is carried out by forming of stronger fibrin clot, for the formation of which requires an enzymatic cascade of sequential reactions (Fig. 1).

Coagulation hemostasis includes 13 coagulation factors. Most of them are proteins that circulate in small quantities in plasma as inactive proenzymes. When the initiating reaction starts the clotting process, the factors begin to activate each other in a certain order [4]. According to the current International Nomenclature, plasma coagulation factors are denoted by Roman numerals (the letter "a" is added to these numbers to indicate the activated factor). The biochemical components of hemocoagulation also include Fletcher factor, von Willebrand factor, and Fitzgerald-Flozhe-Williams factor [9, 11].

Activation of coagulation hemostasis begins with the formation of prothrombinase (tissue and blood) and proceeds in two ways: "external" and "internal". Their difference is based on the source of phospholipids, which are a matrix for fixing coagulation factors and, at the same time, their catalysts. The "external" pathway (tissue prothrombinase formation) is triggered by tissue thromboplastin, which is released from damaged vessel walls and surrounding tissues. Tissue factor interacts with factor VII, activating it, thus triggering a further cascade that leads to the activation of factor X. This phase lasts 5–10 seconds. The initial reaction to the formation of blood prothrombinase is the activation of Hagemann factor, which is carried out by contact of blood with phospholipids of the outer membrane of activated platelets. Activated factor XII in turn activates factor XI, under the influence of which factor IX is activated. The latter reacts with calcium ions (factor IV) and factor VIII, forming a tenase complex. In turn, it activates factor X and forms a complex: factor X + factor V + factor IV (calcium ions), which completes the formation of blood prothrombinase. The "inner" path lasts 5–10 minutes.

Due to the activation of factor X and the participation of factor V and calcium ions, thrombin is formed from prothrombin. Activation of the factor with participation leads to the formation of thrombin from prothrombin. This phase lasts 2–5 seconds.

The final stage of coagulation hemostasis is the formation of insoluble fibrin from fibrinogen. Under the influence of thrombin, fibrin monomers are formed, which then undergo spontaneous polymerization with the formation of calcium ions with the

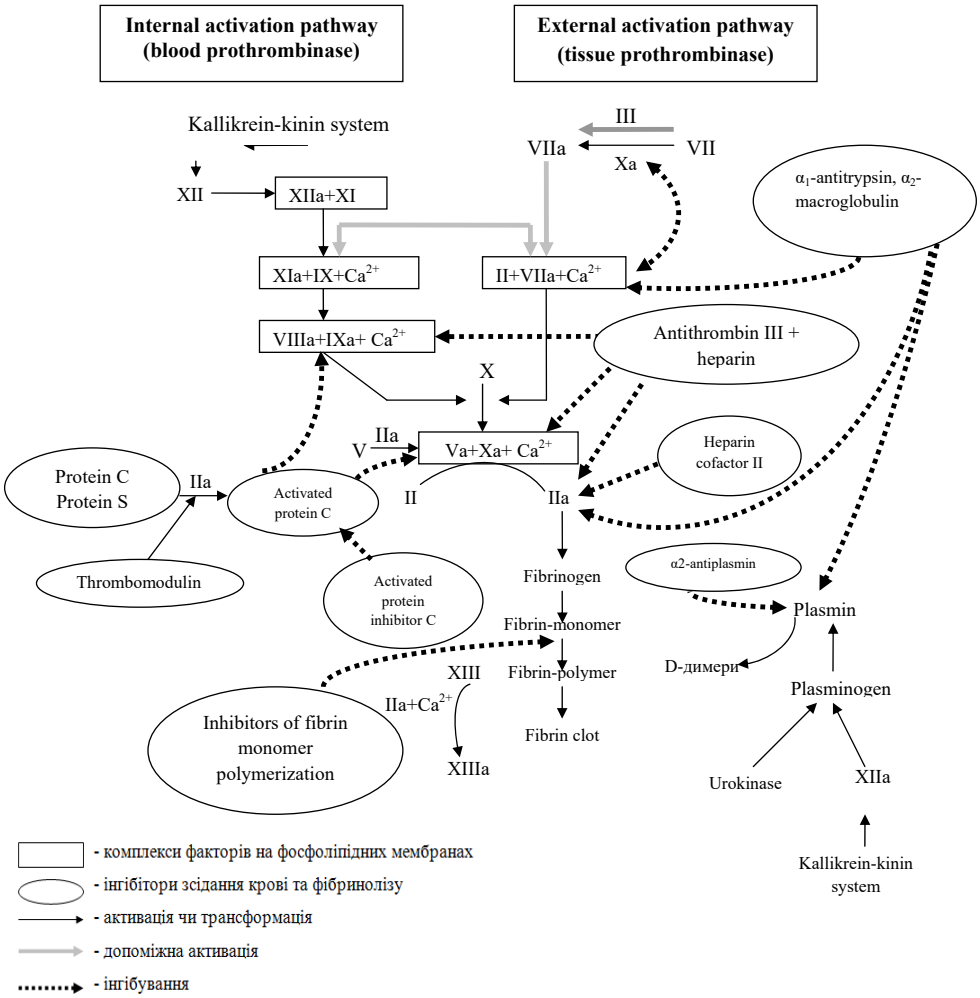

Fig. 1. Scheme of hemocoagulation and fibrinolysis system

formation of soluble and subsequently insoluble fibrin polymer. Fibrinase seals the fibrin network, which traps blood cells, forming a blood clot (thrombus). Sometime after the formation of a clot, the thrombus begins to thicken (under retraction), as a result of which it closes the damaged vessel more tightly and brings the edges of the wound closer [1, 9].

After the coagulation system is activated, fibrin production continues to be supported by positive feedback mechanisms – the formed thrombin reactivates factor VIII and factor V until it is excluded by the anticoagulation system. The anticoagulant system limits coagulation processes by the area of vascular damage and prevents the spread of thrombosis. It consists of blood clotting inhibitors, the most important of which is antithrombin III (AT III), which forms stable complexes with factors XII, XI, X, IX, II. The activity of blood pressure III is enhanced in the presence of negatively

charged heparinoids and heparin. Heparin forms a complex with blood pressure III and increases its anticoagulant properties by 1000–10000 times [4]. Thus, heparin realizes its anticoagulant action through blood pressure III. If BP III inhibits only enzymatic coagulation factors, then two non-enzymatic factors – factor V and factor VIII undergo proteolytic cleavage by protein C, which includes protein C, its cofactor protein S, membrane protein – thrombomodulin. Under the action of the thrombin-thrombomodulin complex on the surface of endothelial cells, protein C is activated (because it circulates in the plasma in an inactive state), which blocks the action of factors V and VIII [19]. An important anticoagulant of the external coagulation pathway is a tissue factor pathway inhibitor. It limits the synthesis of thrombin, blocking it immediately after formation, as well as promoting its absorption and degradation [4, 20, 21].

Restriction of fibrin clot growth occurs by means of fibrinolysis system. The fibrinolytic system is multicomponent and consists of activators, inhibitors and the final enzyme – plasmin, which is formed from plasminogen. Plasminogen activation takes place externally and internally. External is provided by tissue plasminogen activator, internal – urokinase, streptokinase. The process of physiological activation of plasminogen occurs only in the presence of a fibrin clot, which joins plasminogen and its activators. Plasmin is capable of proteolytic degradation of both fibrin and fibrinogen. As a result of fibrin degradation D-dimers are formed, fibrinogen – fragments X, Y, D, E. Limitation of fibrinolysis process is carried out at the expense of its inhibitors) [8, 21, 15, 22].

Thus, the process of blood clotting is a chain of complex cascade-complex enzymatic reactions, which take place with the participation of a large number of cellular and humoral agents with subtle mechanisms of neuroendocrine regulation [13].

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