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Review Article

Hemostasis: A Cell Based Model

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Abstract

For centuries homeostasis have been explained on the basis of the coagulation cascade where two separate pathways converge on a common pathway leading to the formation of thrombin. Thrombin in turn converts fibrinogen to fibrin. Monitoring of homeostasis is done based on this cascade model but certain discrepancies exist between the laboratory finding and the clinical findings. Hence a new cell based model of coagulation was designed which could provide reliable explanations to the pitfalls noted in the cascade model. Tissue factor bearing cell and platelets are mainly involved in the coagulation process based on cell based model. This new concept of coagulation is already accepted in the clinical settings. Hence it is high time that this model be included in the standard physiology textbooks where still the cascade model is described in detail.

Keywords: Hemostasis, coagulation cascade, cell based model, platelets.

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Introduction

Coagulation is the process to stop bleeding. For centuries coagulation model accepted is the cascade model of coagulation. This model proposed by Macfarlene (1964) is still the accepted model of coagulation in standard physiology textbooks. The process of coagulation or hemostasis involves the role of platelets and coagulation factors. Platelets help in formation of primary hemostasis and the activation of coagulation factors result in the formation of secondary hemostasis. Based on the basic physiology of coagulation the tests used clinically are designed to identify the abnormalities in platelet and coagulation cascade. These tests of coagulation have been accepted for centuries but many questions remain unanswered.

Coagulation Cascade Model

All the clotting factors are in inactive state and through the cascade mechanism clotting factors are activated. It has two separate pathways which converge on a common pathway leading to the formation of thrombin which then converts fibrinogen to fibrin. The two pathways namely the extrinsic and intrinsic pathways are redundant with no overlap.

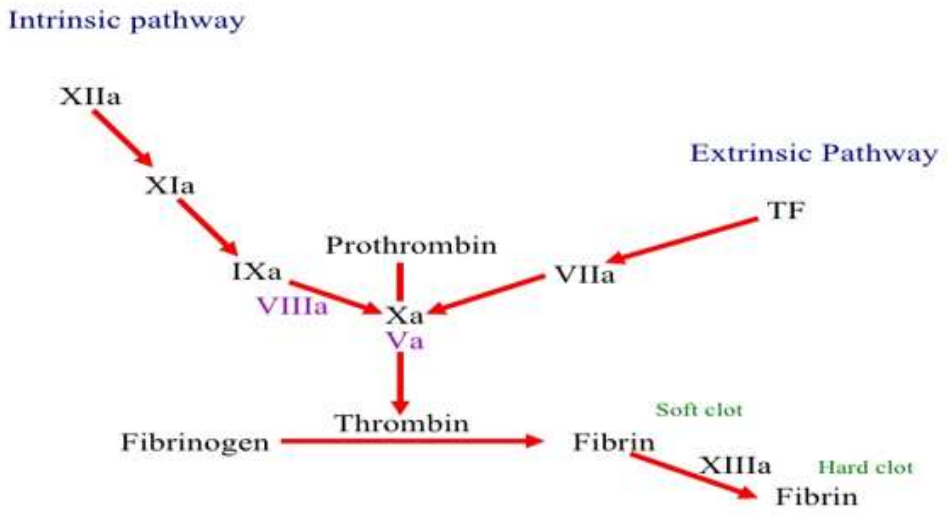

Fig. 1: Coagulation cascade system.

Monitoring Hemostasis

The main coagulation tests used to monitor hemostasis are bleeding time, clotting time, activated partial thromboplastin time and prothrombin time. Defects in bleeding time helps us to analyse the functioning of platelets. While the prolonged clotting time points towards anomaly in the coagulation cascade. aPTT level abnormality indicates abnormal intrinsic and common coagulation pathway and PT prolongation indicates extrinsic and common cascade anomaly. Thrombin time defect indicates anomaly in the common pathways. Pitfalls exists in this model of assessment of coagulation pathways.

Pitfalls in the Coagulation Cascade Model

Prolongation of aPTT time indicates defect in the intrinsic pathways but it was noted that absence of factor XII or HMWK which is the initiator of intrinsic pathway does not result in bleeding abnormalities. Deficiency of factor XII results in prolonged aPTT but the patients have only variable bleeding. Deficiency of F IX i.e hemophilia B results in bleeding but the question remains why does the extrinsic pathway not contribute to the formation of thrombin. Researchers have addressed these ambiguity between the tests and the clinical presentation of factor deficiencies and have come

upon a new pathway of coagulation which are based on the role of cells in coagulation.

Cell Based Model of Coagulation

According to this model of coagulation we do not have two separate discrete pathways instead coagulation is brought about by three overlapping stages occurring on the surface of two different types of cells.

The cells involved are platelets and cells with tissue factors on their surface. The three important stages are initiation, propagation and amplification phases.

Initiation Phase

The basic initiator of coagulation is the tissue factor which are proteins present on the surface of cells outside the vascular system 4.eg: fibroblast or smooth muscle cells. These TF bearing cells binds with factor VII and activates it. This complex of TF and factor VII a activates factor X and factor IX. Factor Xa along with Va then activates factor II to thrombin. These thrombin sparks formed will then shift their activity to the surface of platelets. During normal circulation also small amounts of thrombin is being generated but this is kept in check by the tissue pathway inhibiting factors. This phase of formation of minute amounts of thrombin is known as an initiation phase of coagulation.

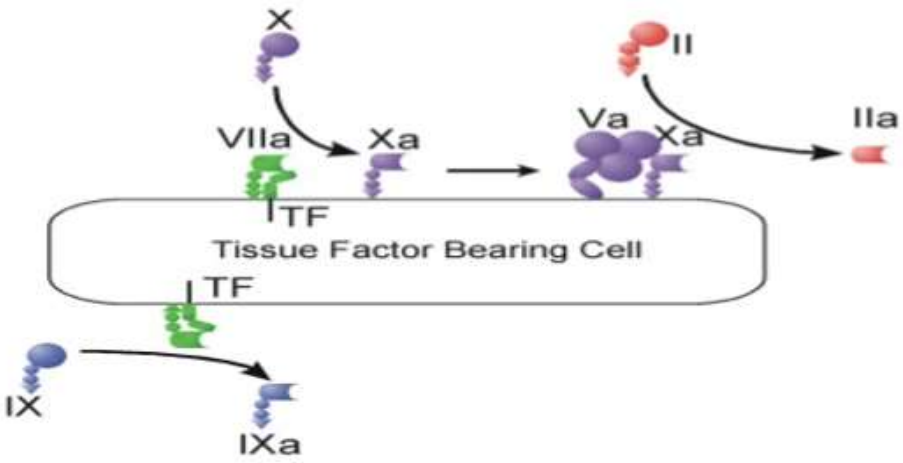

Fig. 2: Initiation phase of cell based model.

Amplification Phase

For further amplification of this phase the activity shifts from TF bearing cells to platelets. This phase is known as amplification phase. The thrombin formed in the initiation phase activates platelets by binding with protease activated receptors (PAR) present on platelet cell surface. On activation of receptors it leads to activation of phospholipase C and results in increase in calcium which activates myosin light chain kinase (MLCK) which helps to alter the platelet morphology. The platelet membrane expresses phosphatide serine on the cell surface this makes the platelet surface a very active procoagulant surface. It also leads to release of the granular contents of platelets. Thrombin cleaves the VIII and VWF complex. This VWF binds with GPIb on the platelet surface hence forming bridges between platelets and help in aggregation effect of platelets. Thrombin also activates XI to XI a and factor V to Va. Hence the platelets now form an active procoagulant surface with factors VIIIa, Va and XIa.

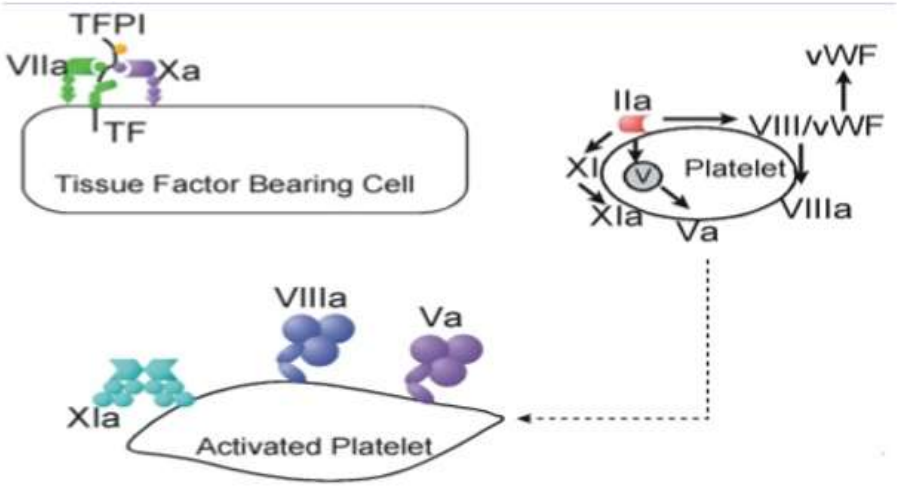

Fig. 3: amplification phase of cell based model of coagulation.

Propagation Phase

During this phase the IXa formed in the initial phase binds with VIIIa forming the tenase complex which inturn leads to formation of factor Xa. This Xa along with factor Va activates prothrombin to thrombin which in turn converts fibrinogen to fibrin. If this phase of propagation is not controlled it may lead on to total thrombosis hence to keep a check on this process we have the termination phase ie the role of natural anticoagulants.

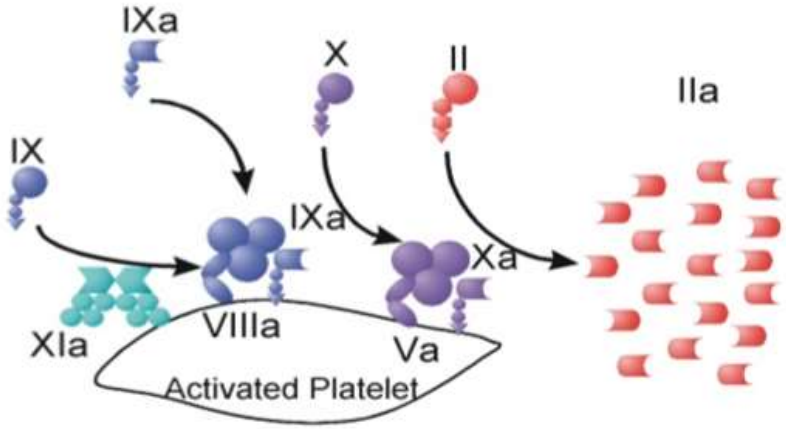

Fig. 4: propagation phase of cell based model of coagulation.

Natural Anticoagulants

Four main mechanisms involved to limit this stage. Tissue factor pathway inhibitor, protein c, protein s and antithrombin are the key regulators of the different phases of coagulation. TFPI inhibits the factor x when it separates off from the TF bearing cell hence keeps a control of unwanted formation of thrombin. TFPI is released from the endothelial cells and it forms a quaternary structure with TF VIIa Xa complex. Protein C and protein S inhibits factor Va and VIIa both these components are vit k dependent. Antithrombin inhibits thrombin, IXa, Xa, XIa, and XIIa.

Conclusion

This new model of coagulation was first proposed by Maureane Hoffman (2001). According to the cell based model coagulation cascade is not two separate pathways converging on the common

pathway instead it is a series of overlapping phases involving initiation, amplification, propagation & termination phase. Coagulation in vivo starts off with the extrinsic system i.e the activation of factor VII, which is brought about by tissue factor bearing cells. This is followed by the intrinsic system ie, the activity shifts onto the surface of platelets. The tests for coagulation remains the same but the interpretation of tests differ. Prothrombin time indicates the functioning of the initiation phase ie TF cell surface. While aPTT indicates the activities on platelet surface. Hence the questions raised by the intrinsic and extrinsic coagulation cascade are better laid at rest by the cell based model. Factor XII deficiency does not result in bleeding disorders as it is not a component of cell based model. Factor IX and VIII deficiency results in bleeding abnormalities as it is an important component of the cell based models.

The current standard textbooks in physiology still follow the cascade model of coagulation when the ambiguity raised by this models have already been clarified by the cell based models. Hence it becomes important that the very basis of the coagulation system need review and the cell based model be incorporated into the basic physiology texts.

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