CHAPTER

196

Coagulation Cascade - What's New

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Deficiencies of coagulation factors have been recognized for centuries. Patients with genetic deficiencies of plasma coagulation factors exhibit life-long recurrent bleeding episodes into joints, muscles, and closed spaces, either spontaneously or following an injury. The most common inherited factor deficiencies are haemophilia, X-linked diseases caused by deficiency of factor (F) VIII (haemophilia A) or factor IX (F IX, haemophilia B). Acquired deficiencies of plasma coagulation factors are more frequent than congenital disorders; the most common disorders include haemorrhagic diathesis of liver disease, disseminated intravascular coagulation (DIC), vitamin K deficiency and lupus anticoagulant associated thromboembolism.

Haemostasis is a tightly regulated homeostatic mechanism that maintains blood flow under physiologic conditions and permits rapid, localized coagulation in the event of tissue damage. A delicate balance exists between four components the vascular endothelium, platelets, the coagulation pathway and fibrinolysis & the major events are:

1. Primary haemostasis(vasoconstriction and platelet plug formation)
2. Secondary haemostasis (activation of coagulation factors and generation of thrombin)
3. Fibrin clot formation and stabilization
4. Inhibition of coagulation (inhibition of thrombin generation and fibrin clot breakdown)

There are 2 pathways: Intrinsic pathway and extrinsic pathway. The extrinsic pathway, involving tissue factor and factor VII, and the intrinsic pathway, in which factors XII, XI, IX, VIII, and V participate. Both pathways converge to activate factor X and lead to transformation of prothrombin into thrombin and, through the action of thrombin, of fibrinogen into fibrin. The role of platelets in coagulation was considered independent.

There is new perspective built on the classic coagulation cascade (Figure 1) in the following ways: The complex formed by tissue factor and factor VII participates in the activation of factor IX, indicating that the intrinsic and extrinsic coagulation pathways are linked almost from the beginning of the process; The complete process does not occur continuously but rather requires 3 consecutive phases: an initial phase, an amplification phase, and a propagation phase. Platelets and thrombin are actively involved in the last 2 phases. Initial Phase: The tissue factor–factor VII complex activates factor X, either directly or indirectly via factor IX, and transforms prothrombin into thrombin in small amounts that are insufficient to complete the process of fibrin formation. Amplification Phase: The thrombin that has been formed, along with calcium from the blood and acidic phospholipids derived from platelets, actively participates in a positive feedback process for the activation of factors XI, IX, VIII, and V, and, especially, to accelerate platelet activation. Simultaneously, the factors mentioned are attracted through chemotactic mechanisms to the surface of the platelets, where very rapid and extensive activation and amplification occurs. Propagation Phase: The amplification of the process through feedback mechanisms involving thrombin and platelets and the activation of all these factors allow large quantities of factor X to be activated and form the prothrombinase complex to convert prothrombin into thrombin and, through the action of thrombin, fibrinogen into fibrin. The final process, always occurring on the surface of the platelets, accelerates and leads to the explosive generation of large quantities of thrombin and fibrin.

Activation of platelets alters the permeability of the membrane and allows entry of calcium and release of chemotactic substances that attract coagulation factors to the surface. At the same time, factor V and acidic phospholipids are released, providing the necessary complement for the coagulation process. The new coagulation cascade presents fibrin formation as the result of 2 complementary processes: coagulation (represented by thrombin) and platelet activation.

The prothrombin time (PT) measures the integrity of extrinsic and common pathways of coagulation (factors VII, X and V; prothrombin and fibrinogen). The activated partial thromboplastin time (aPTT) measures the integrity of the intrinsic and common pathways of coagulation (high molecular weight kininogen; prekallikrein; factors XII, XI, IX, VIII, X and V; prothrombin and fibrinogen). The sensitivity of the PT and aPTT in detecting coagulation factors deficiencies may vary with the reagent used to perform these tests, and each laboratory must determine its own reference standards. The thrombin time (TT) is a screen for quantitative deficiencies and qualitative defects of plasma fibrinogen.

Heparin increases PTT, it also activates Antithrombin III and affects the intrinsic pathway. Fibrinogen levels are decreased by heparin. Antidote to heparin is protamine sulfate. Warfarin increases PT, inhibits vitamin K. Thus warfarin affects the extrinsic pathway and factors II, VII, IX & X. It also affects the protein C & S. Warfarin is

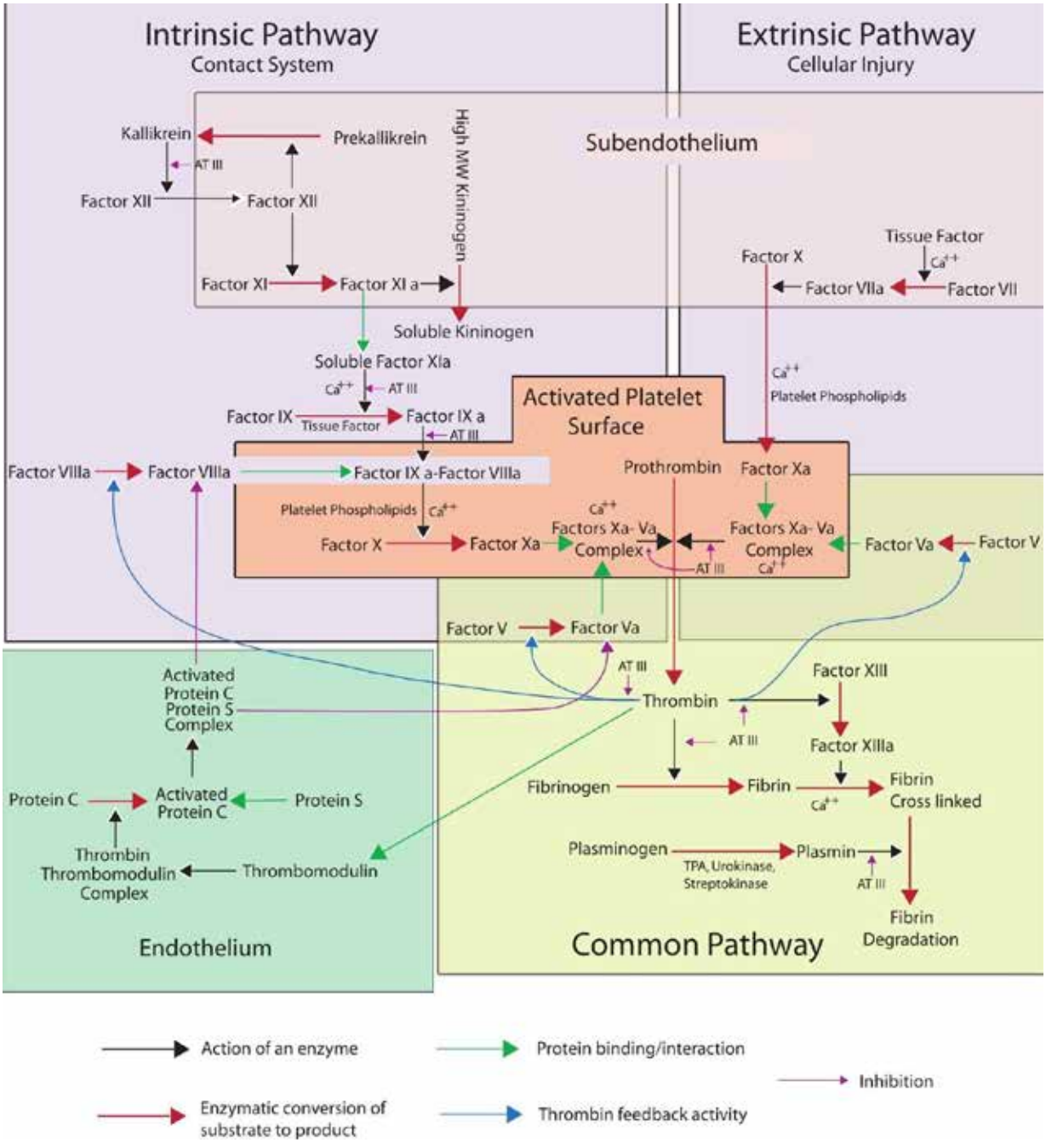

Fig. 1: Coagulation Cascade

teratogenic as its small size allows it to cross the placenta. Its antidote is vitamin K. The goal INR should be kept between 2.0 & 3.0 and in cases of mechanical valves it should be kept between 2.5 to 3.5. Low Molecular Weight Heparin (LMWH) (enoxaparin) inhibits factor Xa. Mostly it needs no monitoring. It should be given once or twice daily. Heparin to warfarin conversion is necessary as warfarin inhibits proteins C & S before other vitamin K dependent factors (like factor II, VII, IX & X) leading to a brief period of paradoxical hypercoagulability before anticoagulation. The unexplained prolongation of PT and aPTT is investigated by simple correction tests by making 50:50 mixtures of patient's plasma and normal plasma. Correction indicates a possible coagulation factor deficiency whereas; failure indicates presence of circulatory anticoagulant. The commonest anticoagulant is lupus anticoagulant (LAC). LAC prolongs phospholipid dependent test such as PT & aPTT. Though these show recurrent venous thromboembolism, cerebrovascular accidents and in women in recurrent abortions and fetal loss. It needs demonstration of LAC in patients with these features.

The paradigm shift in our understanding about classical coagulation cascade occurred due to introduction of a cell based model which emphasizes the importance of tissue factor as the initiator of the coagulation cascade and the pivotal role of platelets for intact haemostasis. This new understanding explains the poor correlation between traditional tests of coagulation and clinical bleeding and has generated renewed interest in viscoelastic tests for

diagnosing derangement in haemostasis and to guide transfusion therapy.

Thromboelastography (TEG) assesses the viscoelastic properties of blood samples under low shear conditions. It measures the clot's physical property by using a stationary cylindrical cup that hold the blood sample and oscillates through an angle of 4°45 with each rotation cycle lasting 10 sec. Besides standard TEG, Platelet Mapping which is an extension of TEG technology, in addition to providing information on clot formation and lyses of whole blood sample, it quantifies the contribution of fibrin, adenosine diphosphate (ADP) receptor and thromboxane A2 (Tx A2) receptor in clot strength. The TEG Platelet Mapping assay enables relating the percent platelet inhibition to the individual's maximum uninhibited platelet function. This information allows monitoring of effectiveness of antiplatelet agents, aspirin and clopidogrel, via inhibition of TxA2 and ADP receptors. Various studies suggest that TEG could be a complimentary test to current standard coagulation assays and in some cases, a superior method altogether. Thromboelastographic results need to be carefully interpreted in presence of severe anaemia, thrombocytopenia and hemodilution as these conditions can variably affect the test results.

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