Physiology of Hemostasis

10

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The Hemostatic System

(A) *Overview*

Development of much of our understanding of the hemostasis and thrombosis protection systems in vivo derived from translation of clinical observations seen in patients with unique biochemical and genetic processes. More recently mutant mice deleted of specific proteins in this system have additionally contributed to our understanding.

1. *Hemostasis*, the cessation of bleeding, occurs within the intravascular compartment lined with endothelium. Normal hemostasis and thrombosis (the occlusion of a blood vessel) is the sum of activity of two components: (1) a cellular part that consists of circulating cells and the vessel wall and (2) a protein portion from the blood plasma or cells in the intravascular compartment. Some patients have normal blood coagulation proteins but abnormal hemostasis due to a platelet defect (e.g., Bernard-Soulier syndrome; see Chap. 14). Alternatively, other patients have normal platelet and vessel wall function but abnormal hemostasis due to a blood coagulation protein defect (e.g., hemophilia A; see Chap. 12).
2. *Components*. The hemostatic/thrombotic system consists of both cellular and protein components that closely interact. The cellular components consist of leukocytes (neutrophils and monocytes), platelets, and endothelium. It is still not clear what cellular component provides the initial event in hemostasis and if it is the same under different circumstances. Platelets, anucleate cell fragments, historically have been considered the initial nidus upon which hemostatic reactions occur. This notion has led to the idea that platelets initiate primary hemostasis and on or about the locus of the platelet plug, blood coagulation protein reactions occur (secondary hemostasis). However, in certain models of hemostasis, vessel wall clot occurs first and on or about this formed fibrin, platelets are recruited into a dense and later loose platelet plug [1]. Adding complexity to the systems, vessel walls themselves constitutively are anticoagulant surfaces which when injured become procoagulant [2]. Monocytes and neutrophils contribute tissue factor initiating hemostasis both in arteries and veins and have potent clot-lysing system. The protein components that contribute to hemostasis and thrombosis include three protein systems: the blood *coagulation* (clot-forming), the *fibrinolytic* (clot-lysing), and *anticoagulant* (regulating) protein systems. Each of the proteins in these three systems balances the activities of the others.
3. *Regulation*. Physiologic hemostasis is a tightly regulated balance between the formation and dissolution of hemostatic plugs by the *coagulation and fibrinolytic systems*, respectively. Blood coagulation proteins circulate as zymogens or proenzymes and are not activated. When a stimulus/injury occurs, the proenzymes of the system are activated to enzymes initiating a series of proteolytic reactions that lead to thrombin formation, the main clotting enzyme. [Note: the convention in the coagulation protein field is to indicate a proenzyme (zymogen) as a Roman numeral and its active enzyme with the small letter "a" after the Roman numeral]. The blood coagulation proteins become activated in an apparent cascade-like fashion. The *anticoagulation* proteins regulate the coagulation and fibrinolytic systems. The proteins of the anticoagulation system join those of the fibrinolytic system to prevent or counterbalance coagulation reactions. Thus, the hemostatic system is tightly modulated by a

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series of serine proteases (enzymes), their cofactors for activity, and serine protease inhibitors that regulate their function. All these events occur on or about cells in the intravascular compartment that have their own levels of regulation.

(B) *Process*. A number of events are involved in hemostasis.

1. *Overview of the role of blood coagulation proteins in hemostasis*: When a vessel wall is injured, several events occur simultaneously. Von Willebrand factor helps flowing platelets to adhere to the vessel wall. Collagen in the vessel wall, now exposed, allows platelets to adhere also by their collagen receptors leading to activation. Platelet activation leads to thrombin formation on or about the platelet surface. Alternatively, before, simultaneously with or independent of platelet adherence depending upon the circumstance, vessel injury leads to exposure of subendothelial tissue factor (TF) along with factor VIIa which activates factor IX to factor IXa. Factor IXa activates factor X to factor Xa that leads to thrombin formation. Thrombin proteolysis of fibrinogen forms fibrin, which is the protein basis of a clot. Thrombin also recruits more platelets to the site of injury to initiate or enhance a platelet thrombus. It is recognized that in vivo, several pathways lead to thrombin formation. Similarly, when injured, endothelium too becomes a procoagulant surface. The procoagulant nature of endothelial cells is due to increased expression of TF and factor VIIa to initiate thrombin formation, increased synthesis of factor V to serve as a cofactor for more thrombin formation, inactivation of thrombomodulin for protein C activation, and increased plasminogen activator inhibitor expression with reduced tissue plasminogen activator.
2. *Overview of anticoagulation and fibrinolysis in hemostasis*. Circulation anticoagulants include antithrombin, tissue factor pathway inhibitor, and protein C. Under resting conditions, endothelial cells provide an anticoagulant surface. The anticoagulant nature of the endothelial cell membrane consists of a number of entities: antithrombin that inhibits all coagulation enzymes (see below); thrombomodulin for protein C activation (see below); tissue plasminogen activator release that stimulates fibrin clot lysis; nitric oxide and prostacyclin that stimulate induced vasodilation and inhibit platelets, respectively; and membrane-associated ectoADPases, CD39, that degrade ADP to limit platelet activation [3]. Prostacyclin also has an ability to downregulate vessel tissue factor through a Sirt1- and KLF4-mediated mechanism [4].

Coagulation Protein System

(A) *Coagulation Proteins* (Table 10.1)

Blood coagulation proteins can be grouped into three categories:

1. *Phospholipid-bound proenzymes (zymogens) of the vitamin K proteins* make up the physiologically essential hemostatic system.
   (a) These proteins are vitamin K-dependent and are synthesized in the liver. Vitamin K is required for an essential γ-carboxylation reaction that takes place on each of these proteins' Gla residues located on their amino terminal ends, making them an α-carboxyglutamic acid. This carboxylation reaction allows these proteins to bind to lipid and cell membranes, where they are activated. Without this carboxylation reaction, these proteins do not function normally by not assembling on membrane phospholipids. Inhibition of the carboxylation reaction is the basic mechanism on how the common oral anticoagulant warfarin works.
   (b) These proenzymes (zymogens) include factor VII, factor IX, factor X, and factor II (prothrombin). These proteins are essential for normal blood coagulation hemostasis and life. A complete deletion of factors VII, X, or II leads to lethal hemorrhage in utero or at the time of delivery. Factor IX deficiency is hemophilia B, one of the most severe bleeding states that survives gestation and delivery.
2. *Surface-bound proenzymes (zymogens) of the contact activation system*. This additional system to initiate hemostasis is not considered physiologic but participates in disease states and, independent of hemostasis, has a role in thrombosis.
   (a) Surface-bound proenzymes include factor XII (Hageman factor) (FXII), prekallikrein (Fletcher factor) (PK), and factor XI (FXI). The terms Hageman and Fletcher factor were used to name

Table 10.1 Proteins of the plasma blood coagulation system

Phospholipid-bound zymogens of the vitamin K-dependent protein system	Surface-bound zymogens of the contact activation system	Cofactors and substrates of the enzymes of the blood coagulation system
Factor VII	Factor XII	Tissue factor
Factor IX	Prekallikrein	Factor VIII
Factor X	Factor XI	Factor V
Factor II		Fibrinogen
		High M_r kininogen[a]

[a]M_r, Molecular weight

these proteins based upon the first patients recognized with the protein deficiency. Factor XI deficiency is associated with clinical bleeding; factor XII or prekallikrein deficiency is not. Factor XII levels, however, influence thrombosis (see sections "The Anticoagulation System" and "Cohesive Hypotheses for the Initiation of the Hemostatic System" below). However *all* of these proteins influence the common blood coagulation screening test called the activated partial thromboplastin time (aPTT). This test and its interpretation will be discussed in detail in Chap. 11.

(b) These protein zymogens are also known as the "contact proteins" because factor XII autoactivates when associated with a negatively charged surface (e.g., a glass tube in vitro or collagen, aggregated protein, RNA, DNA, or inorganic polyphosphate (polyP) released upon platelet activation or bacterial or human cell destruction in vivo). Autoactivation is the process whereby a coagulation protein zymogen when bound to a surface has a structural change such that a proenzyme changes an active enzyme. The molecular basis for this event has not yet been fully explained for factor XII.

3. *Hemostatic cofactors and substrates* of the enzymes of the coagulation system facilitate coagulation enzyme activity (see below in the next section).
   (a) *Tissue factor* (TF) is an essential cofactor for activated factor VIIa. It is found in most tissues and cells. Its synthesis is upregulated in inflammatory and injury states. Upregulation of TF results in the formation of complexes with factor VII that produces the initiation of hemostatic reactions. The absence of tissue factor is incompatible with successful mammalian gestation leading to intrauterine death.
   (b) *Factor VIII* (antihemophilic factor) is a cofactor that greatly facilitates the ability of the enzyme factor IXa to activate factor X in "tenase" (see below). Its absence is associated with the most severe clinically recognized bleeding disorder that survives gestation and delivery, hemophilia A.
   (c) *Factor V* (proaccelerin) is a cofactor that facilitates the ability of the enzyme factor Xa to activate factor II (prothrombin) to factor IIa (thrombin) in "prothrombinase" (see below). Its deficiency is associated with death from intrauterine hemorrhage or at delivery.
   (d) *Fibrinogen* is the main substrate of thrombin (factor IIa). When fibrinogen is proteolyzed by thrombin, fibrin monomer is formed. Fibrin monomer associates end to end and side to side to become insoluble and cross-linked to form a fibrin mesh that is an actual clot (thrombus). Severe deficiencies of fibrinogen survive gestation and delivery.

   Once formed, stability of the fibrin clot is produced by an enzyme called *factor XIII*, a tissue transglutaminase that cross-links the strands of associating fibrin to make a stronger insoluble structure. Factor XIII is like mortar and stabilization rods in a brick wall.
   (e) *High-molecular-weight kininogen* (Fitzgerald or Williams factor) (HK) is a cofactor for the activation of all the contact system proenzymes (zymogens), factor XII, prekallikrein, and factor XI. High-molecular-weight kininogen also is a substrate of the activated forms of the contact system enzymes to liberate a biologically active peptide called bradykinin. Bradykinin stimulates nitric oxide and prostacyclin formation in endothelial cells to produce vasodilation and platelet inhibition and reduce vessel wall tissue factor. Deficiency of high-molecular-weight kininogen is not associated with bleeding, but it delays induced arterial thrombosis.

(B) *Critical Protein Assemblies in Hemostatic Reactions*. The essential proteins of the blood coagulation system were identified by observation of patients, and the first recognized defect was named for the patient (e.g., Stuart factor, factor X deficiency). Deficiencies in coagulation factors VIII and IX are the most severe bleeding disorders that occur in patients who survive gestation and birth. The rare patients who have congenital deficiencies of coagulation factors VII, X, V, and II usually do not have severe bleeding states because these individuals must have some small amounts of functional coagulation factor to have survived gestation and birth. Directly or indirectly, all of these proteins participate in two critically important assemblies, "tenase" and "prothrombinase" that are essential for kinetically fast blood coagulation protein activation for thrombin generation. The tenase and prothrombinase assemblies are important because they are anticoagulant targets.

1. *Tenase assembly* (Fig. 10.1) is the ability of activated factors VIII and IX to assemble on phospholipid surfaces or cell membranes to accelerate the activation of factor X to factor Xa. When all of these components are present, the rate of factor X activation by factor IXa (i.e., catalytic efficiency) is increased a billion-fold, 1×10^9 faster over the rate of factor IXa activation of factor X alone. This fast rate is what makes it physiologic and an important juncture point in the system.

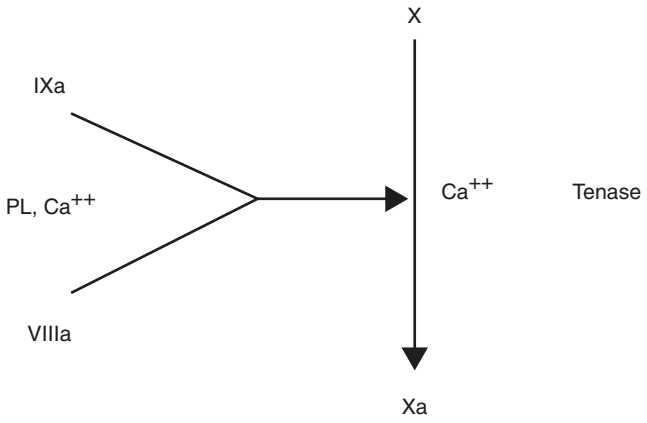

Fig. 10.1 The tenase assembly for factor Xa formation

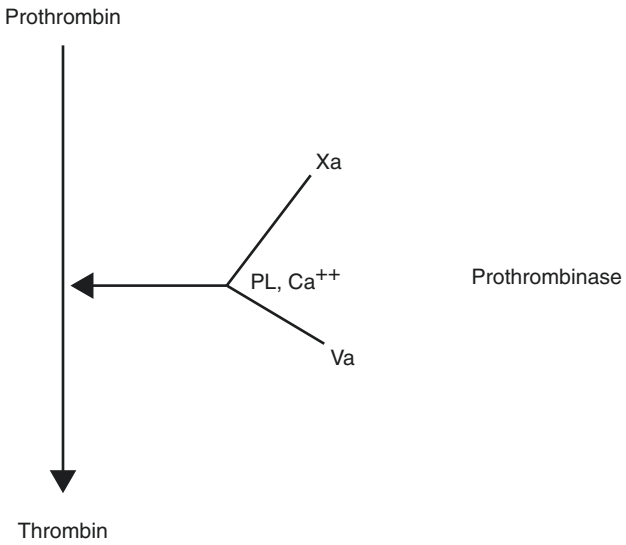

Fig. 10.2 The prothrombinase assembly for thrombin generation

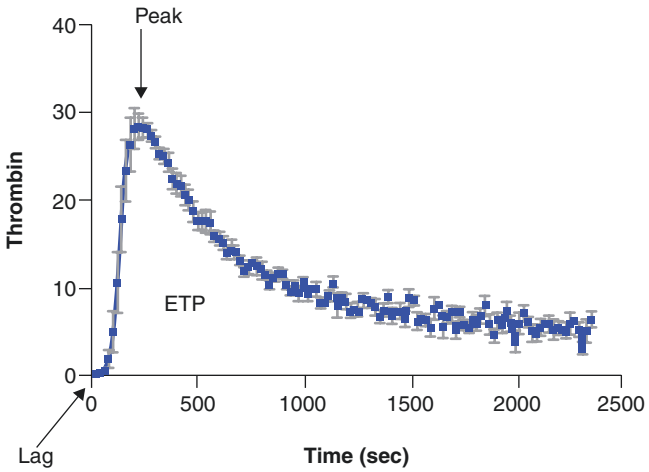

Fig. 10.3 Thrombin generation curve. "Lag" is the time from zero until there is an upward slope. "Peak" is the peak height of the generated thrombin curve. "ETP" stands for endogenous thrombin potential which is the total thrombin generated

2. *Prothrombinase assembly* (Fig. 10.2) is the ability of factor Xa and thrombin-activated factor Va to assemble on phospholipid membranes or cell membranes to accelerate the activation of factor II (prothrombin) to factor IIa (thrombin). When all of these components are present, the rate of factor II activation by factor Xa is increased 400,000-fold over the rate of factor Xa activation of factor II alone.
3. *Thrombin generation* in a kinetically fast manner is the goal of these protein assemblies. In static in vitro systems, as little as 5–10 pM (10^{-12} M) tissue factor is sufficient to induce clot formation leading to a 1000- to 4000-fold amplification of the process that increases the concentration of thrombin to 10–20 nM (10^{-9} M), a concentration sufficient to initiate clot formation. The addition of 5 pM tissue factor results in an average clot time of ~5 min, a time sufficiently fast for physiologic hemostasis.

Thrombin generation is shown graphically as a thrombin generation time (Fig. 10.3) [5]. Whether thrombin formation is initiated by tissue factor-factor VIIa or contact activation with factor XII, prekallikrein, and high-molecular-weight kininogen, the character of the thrombin generation time (TGT) curve is the same. In essence, the thrombin generation curve is a graphic prothrombin time or activated partial thromboplastin time (see Chap. 11) when it is induced by tissue factor-factor VIIa or a contact-activating surface, respectively. After an initial lag time (Lag) that varies due the potency of the stimulus, there is an acute increase in the formation of thrombin. The rate of rise (ΔTGT) and the peak height (Peak) of thrombin generation are measurable events. Further, the area under the curve (ETP – endogenous thrombin potential) directly correlates with the nM thrombin generated (Fig. 10.3). Thrombin generation curves represent the total amount of thrombin generated but do not indicate why thrombin generation is low (e.g., low factor VIII or high antithrombin levels). In general, it takes about 1 nM formed thrombin to activate platelets; 10 nM formed thrombin to generate a fibrin clot.

(C) *Summary of Physiologic Blood Coagulation System*

The assembly of blood coagulation proteins whose deficiency is associated with bleeding is shown in Fig. 10.4. Blood coagulation leading to hemostasis is initiated by the complex formation between tissue factor and factor VIIa. Tissue factor (TF) is expressed after injury upon exposure of subendothelium or is synthesized in monocytes, neutrophils, endothelium, or platelets in inflammatory states. It has been proposed that there may be TF-VIIa complexes in cryptic microparticles

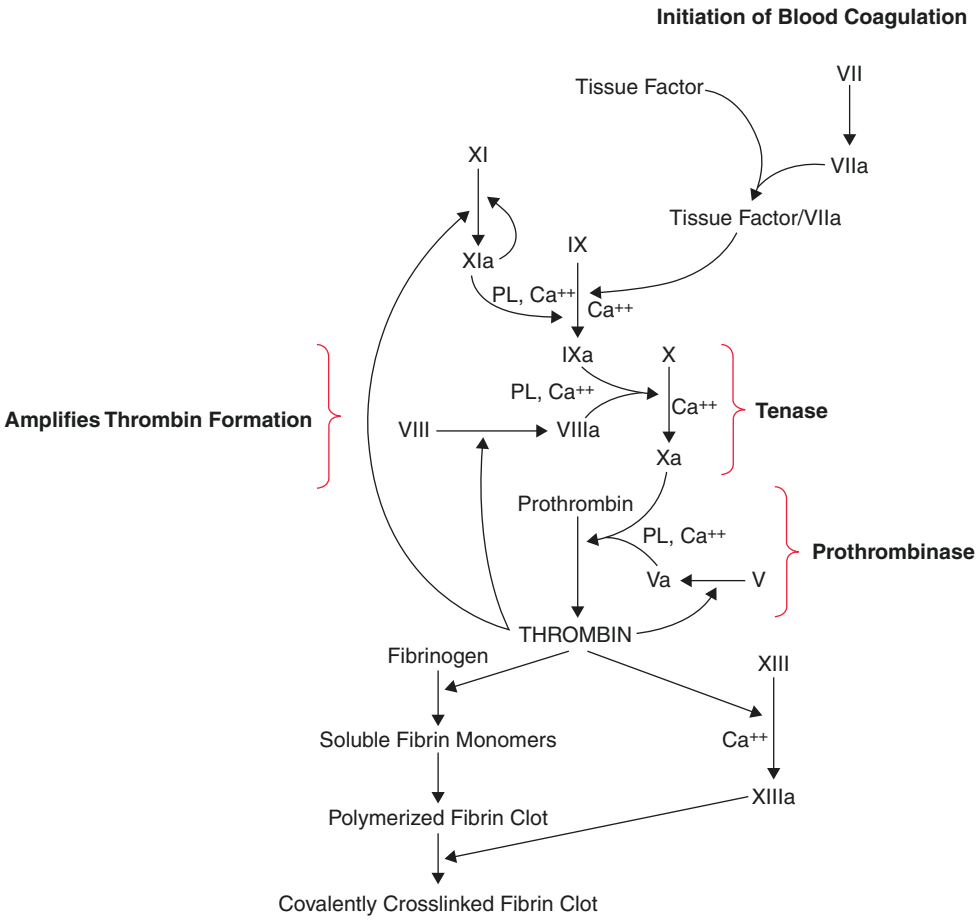

Fig. 10.4 Blood coagulation system leading to hemostasis

circulating in plasma that are available to spring into action if a hemostatic insult occurs. Although factor VIIa directly activates X to Xa in vitro in the prothrombin time assay (see Chap. 11), under physiologic conditions this pathway is blocked by a serine protease inhibitor called tissue factor pathway inhibitor (TFPI) (see below under anticoagulation systems). Physiologic blood coagulation mostly occurs when sufficient tissue factor/VIIa is available to activate factor IX to IXa. Subsequently, IXa in the presence of VIIIa assembles to activate X to Xa in tenase (Fig. 10.4). Formed Xa in the presence of Va leads to prothrombin activation to form thrombin in prothrombinase (Fig. 10.4). Formed thrombin proceeds to proteolyze (chew up) fibrinogen to form soluble fibrin monomers that polymerize to form a fibrin clot. Thrombin also activates factor XIII to XIIIa that cross-links polymerized fibrin monomers to form insoluble cross-linked fibrin, a clot. A clot, for example, is the soft bloody gel that hardens on a severely abraded knee. At times, the stimulus for thrombin formation can be great. Thrombin amplifies its own formation by feeding back to activate factor XI to factor XIa that activates more factor IX to reinitiate the cascade of proteolytic events just described. Please note there is no mention of the contact activation proteins, factor XII, prekallikrein, and high-molecular-weight kininogen in physiologic hemostasis. These proteins do not contribute to the cessation of bleeding. However, as already mentioned, these proteins can be activated to form clots when artificial surfaces are inserted into patients (e.g., cardiopulmonary bypass, extracorporeal membrane oxygenation, indwelling IV catheters) or in disease states like sepsis from any cause and adult respiratory distress syndrome.

The Fibrinolytic System

One process limiting the extent of clot formation is the *fibrinolytic protein system* (Fig. 10.5). It consists of the zymogen plasminogen and its naturally occurring activators. Plasminogen is activated to the main clot-lysing enzyme, plasmin, by the endogenous plasminogen activator tissue plasminogen activator (tPA), single-chain urokinase plasminogen activator (ScuPA), and two-chain urokinase plasminogen activator (tcuPA). These activators are found in the endothelium as well as in neutrophils and monocytes. Plasminogen activation is regulated by the inhibitor plasminogen activated inhibitor-1 (PAI-1). PAI-1 is mostly found in endothelium and cells; it is not a plasma protein. In inflammatory states, its production increases, and it is released into the circulation.

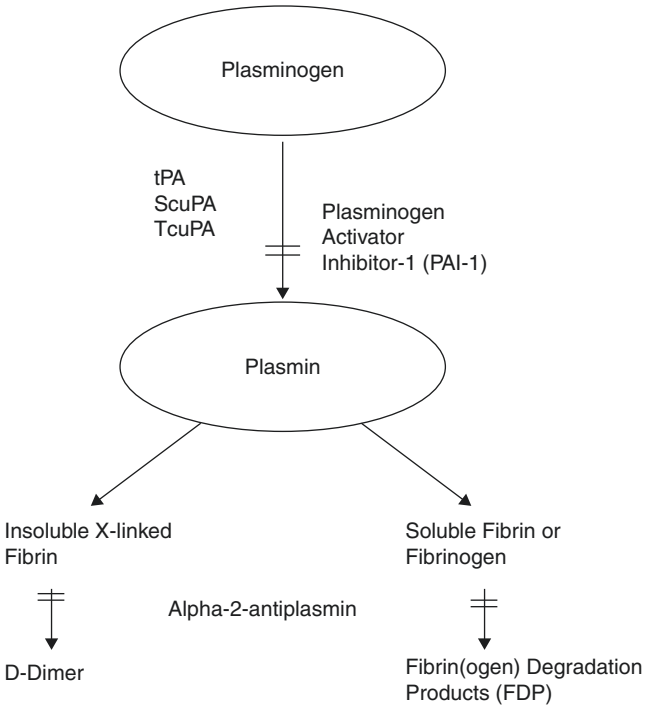

Fig. 10.5 The fibrinolytic protein system

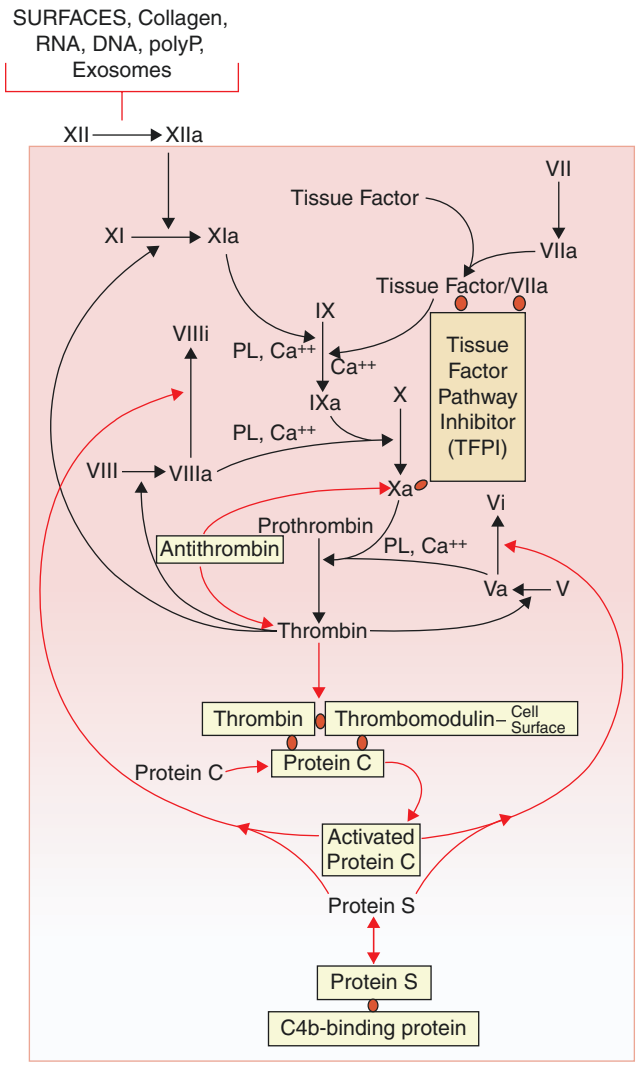

Fig. 10.6 The anticoagulation protein system. The anticoagulants are in the boxes in *yellow*

It is also found in platelets in large concentrations. Formed plasmin degrades fibrinogen, soluble non-cross-linked fibrin, and cross-linked fibrin to liberate fibrin or fibrinogen degradation products (Fig. 10.5). Plasmin degrades insoluble cross-linked fibrin clots to liberate D-dimer, i.e., a two D-domain protein fragments held together by a unique bond between them (Fig. 10.5). Measurement of D-dimer indicates that thrombin-activated factor XIII has cross-linked fibrin to make insoluble cross-linked fibrin and plasmin has cleaved the insoluble cross-linked fibrin. The plasma serine protease inhibitor, alpha-2-antiplasmin, regulates plasmin activity. A defect of plasminogen is associated with thrombosis. An absence or defect in PAI-1 or alpha-2-antiplasmin is associated with a hyperfibrinolytic (high rate of formed clot lysis) bleeding state. Elevations of PAI-1 or alpha-2-antiplasmin are associated with increased risk for myocardial infraction and stroke.

The Anticoagulation System

(A) A second process limiting the activation of the blood coagulation system is the anticoagulation systems. Three *anticoagulant systems* regulate activation of the *blood coagulation proteins* to inhibit clot formation. These systems are the protein C (PC)/protein S (PS) system, the plasma SERPIN serine protease inhibitor antithrombin (AT), and the Kunitz serine protease inhibitor tissue factor pathway inhibitor (TFPI). In Fig. 10.6, these anticoagulation systems with red lines are drawn over the blood coagulation system in black lines.

1. *Protein C/protein S system***.** When activated, *protein C* (PC), a vitamin K-dependent protein, is an enzyme that functions as an inhibitor. Protein C is activated to its enzymatic form by thrombin when bound in a trimolecular complex with an endothelial cell receptor called thrombomodulin. Activated protein C makes a complex with protein S to function as an inhibitor by degrading factor Va, a cofactor for prothrombinase, and factor VIIIa, a cofactor for tenase (Fig. 10.6). *Protein S* (PS), a vitamin K-dependent protein, is not an enzyme. It serves as a receptor for activated protein C to perform its activities on cell membranes. Protein S levels are modulated by the complement inflammatory protein C4b-binding

protein. Clinical deficiencies of protein C or S are associated with serious risk for thrombosis (see Chap. 16).

2. *Antithrombin anticoagulation system. Antithrombin* (AT), a serine protease inhibitor (SERPIN), exerts its anticoagulant effect primarily by inhibiting factors IIa and Xa (Fig. 10.6). It also inhibits each of the other hemostatic enzymes: factors VIIa, IXa, XIa, kallikrein, and XIIa (not shown in the figure). The presence of antithrombin is what gives heparin its anticoagulant properties. Heparin binds antithrombin and makes the latter a better inhibitor by changing the conformation of its reactive region. The importance of antithrombin is indicated by the fact that in the mouse, a complete deficiency results in fetal death. In the presence of heparin, antithrombin is a 1000-fold more effective inhibitor of factor IIa (thrombin). The clinical state of heterozygous deficiency of antithrombin is associated with venous thrombosis (see Chap. 16).
3. *Tissue factor pathway inhibitor (TFPI)*, a Kunitz-type serine protease inhibitor, is the third anticoagulation system. It is the most potent inhibitor of the factor VIIa/tissue complex. Under physiologic conditions, TFPI makes a quaternary complex with tissue factor, factor VIIa, and factor Xa to prevent the FVIIa-TF complex from activating factor X directly (Fig. 10.6). This fact directs FVIIa-TF to factor IX for activation. The importance of TFPI is indicated by the observation that in the mouse, a complete deficiency results in fetal death.

(B) *Additional Regulators (Anticoagulants) of Coagulation Proteins*

Additional serine protease inhibitors regulate some of the blood coagulation enzymes. However, the significance of their clinical deficiencies is still being defined. Heparin cofactor II is a thrombin inhibitor. Protein Z inhibitor in the presence of its cofactor protein Z is a factor Xa inhibitor. C1 esterase inhibitor (C1 inhibitor), alpha-1-antitrypsin, or the amyloid β-protein precursor are potent inhibitors of factor XIa. C1 inhibitor also is the major plasma protease inhibitor of factor XIIa and plasma kallikrein. Alpha-1-antitrypsin is the major inhibitor of elastase. The amyloid β-protein precursor also inhibits factors IXa, VIIa-tissue factor, and factor Xa, but not thrombin. It appears to be a cerebral anticoagulant, i.e., the major anticoagulant protein in the brain and also has an influence of venous thrombosis. C1 inhibitor deficiency is pathogenetic for the inflammatory disorder, Type I or Type hereditary angioedema. Alpha-1-antitrypsin deficiency is associated early emphysema and chronic obstructive pulmonary disease.

Cohesive Hypotheses for the Initiation of the Hemostatic System

It is challenging to have a cohesive understanding of the many parts contributing to normal hemostasis. Although there is an enormous understanding about the contributors to hemostasis, there is no global model, and several cogent mechanisms have been proposed, each of which may be relevant under different circumstances. In the present chapter, no detailed discussion is presented on the contribution of platelets to hemostasis (see Chaps. 14 and 15), an important additional contributor. Furthermore, physiologic hemostasis or thrombosis is not a linear sequence or cascade of enzymatic reactions. It is an event occurring in the intravascular compartment in the presence of flowing blood that produces shear forces, that is, an additional factor contributing to these events. Additionally, the initiation of hemostasis varies between arteries, a high-flow and -shear vessels, and veins, a low-flow and -shear tissue. With these caveats, a couple of models for in vivo hemostasis and thrombosis can be proposed. In the intravascular compartment, intact endothelium has a constitutive anticoagulant and antithrombotic nature by its secretion of nitric oxide, prostacyclin, and tissue plasminogen activator (tPA) and the presence on its membrane of antithrombin, thrombomodulin, and an ADP-degrading enzyme called ectoADPase (CD39). After injury or in disease states, the constitutive anticoagulant nature of the vessel wall can turn and be procoagulant.

In the platelet plug hypothesis that has been around for decades, at sites of developing injury, platelets under shear are slowed by adherence to von Willebrand factor (vWF) (see Chap. 12) and activated after their interaction with exposed collagen through the platelet receptor GPVI [1]. This initial platelet event at a site of vessel injury is called primary hemostasis. Exposed collagen, aggregated protein, cellular polyphosphates (polyP), or extracellular RNA also has the ability to bind plasma factor XII (XII) to support its autoactivation to factor XIIa (XIIa). Factor XIIa formed in such a manner leads to a cascade of activation of blood coagulation protein leading to thrombin formation. This pathway is not essential for hemostasis but may be important for pathologic thrombosis. Simultaneously or alternatively, injured subendothelium results in the expression of tissue factor which complexes with factor VII/VIIa to activate factor IX and leads to thrombin formation. This latter mechanism for thrombin formation is essential for hemostasis and is an alternative process for thrombosis. Formed thrombin by any mechanism leads to more fibrin clot and platelet activation through the platelet thrombin receptors, protease-activated receptors 1 and 4 (PAR1 and PAR4). These events additionally activate platelets and expose surface phospholipids like phosphatidylserine (PS) which itself is a

procoagulant, i.e., a thrombin-generating surface. Activated platelets also release ADP and serotonin to recruit more platelets and polyP, a lipid material that can support factor XII activation. Finally, most probably, different stimuli lead to different mechanisms for thrombin formation. These additional processes leading to thrombin formation are termed secondary hemostases.

In recent years, another understanding for the initiation of hemostasis has been demonstrated at least in the experimental model situation. For example, a laser injury to a small arterial blood vessel results in tissue factor, factor VIIa, and thrombin formation before platelets adhere and aggregate. The formed thrombin recruits platelets for a dense platelet thrombus, and additional platelet activation releases platelet ADP to recruit another layer of the platelet thrombus [6]. These secondary mechanisms lead to either vessel occlusion or thrombus dissolution depending upon the strength of the initial thrombin formation or secondary platelet response.

The complexity of these mechanisms is magnified by arteries versus veins, high shear versus low shear, large vessels versus small vessels, and healthy tissue versus atherosclerotic diseased vasculature. All of these processes are occurring variably simultaneously and contribute to bleeding cessation or hemostasis or unchecked occlusive thrombosis. Even though these systems are interacting, overlapping, and redundant, they function in an elegant balance. The remarkable thing is that the absence of only one factor alters the balance that leads to a bleeding or thrombotic state.

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