What You Need to Know About the Cell Based Model of Coagulation

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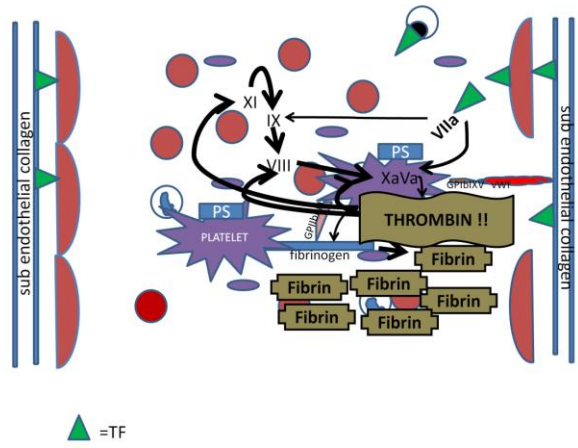
Understanding hemostasis is necessary in order to prevent and treat bleeding diatheses and thrombotic disease. Intensive research in recent years has increased understanding of this amazing and incredibly complex system. Different models to explain the process have been developed as new information is integrated with what was known previously. One well known model separates the process of blood clot formation into primary and secondary hemostasis. Primary hemostasis refers to the formation of the platelet plug, while secondary hemostasis refers to activation of the coagulation cascade and the formation of a fibrin network. Clinically it is useful to use this model and separate hemostasis into these two stages because disorders of primary and secondary hemostasis have distinct clinical presentations. Considering the clinical presentation and results of diagnostic testing with these two localizations of hemostasis in mind helps the clinician limit differential diagnoses. However, recent in vivo studies using animal models have shown that during normal hemostasis, activation of coagulation and platelets occurs simultaneously, and cells are intimately involved in initiating and sustaining the process of secondary hemostasis.

Division of secondary hemostasis using the "Y" model of the coagulation cascade is familiar to most veterinary clinicians. This model features the extrinsic and intrinsic cascade. This model is quite useful from a clinical standpoint in that the most commonly used diagnostic tests, PT and aPTT, test each "arm" of the cascade separately, with PT testing the extrinsic and common pathway and aPTT testing the intrinsic and common pathway. Looking at the pattern of prolongation of PT and/or aPTT in the context of the model can help clinicians localize and narrow differential diagnoses. For example, a pattern of marked prolongation of the aPTT and normal PT in a young dog presenting with hemarthrosis would lead the clinician to strongly suspect hemophilia A or B (Factor VIII or IX deficiency) rather than rodenticide toxicity. The structure of the Y model of coagulation also makes it easy to memorize which factors are tested by measuring PT and aPTT. For example, mnemonics passed down to generations of veterinary students include the following; the extrinsic pathway is often memorized as "lucky 7 is all by himself", the intrinsic pathway by "it's not $12.00 but $11.98, and the common pathway by the "dollar bills" X,V,II and I. The Y structure also provides some information regarding how factors can interact during coagulation and can help clinicians understand the more complex and accurate cell based model of coagulation.

The cell based model of coagulation allows for the integration of primary and secondary hemostasis and explains some clinical phenomenon that could not be explained by the "Y" model of coagulation. For example, if activation of coagulation is sequential and results in clot formation when either the extrinsic or intrinsic pathway is activated, then why couldn't deficiencies of Factor VIII or IX (hemophilia A or B respectively) simply be overcome by activation of the extrinsic cascade in vivo? The Y model also does not explain why people and cats with Factor XII deficiency do not have a bleeding disorder, or why coagulation would stay focused to a regional area of damaged endothelium and not become systemic once activation occurs.

The cell based model of coagulation integrates the role of platelets, endothelium, and the central role of tissue factor (TF) into the Y based model of coagulation and more accurately describes the sequence activation and interactions between the coagulation factors. The cell based model of coagulation was first described in the human medical literature by Hoffman in 2001, and has recently been reviewed in the veterinary literature.{Hoffman 2001; Smith 2009} The cell based model of coagulation proposes that membrane exposed TF binds circulating VIIa to generate Xa which converts prothrombin to thrombin slowly during an initiating phase. Thrombin then amplifies coagulation by activating platelets which provide a thrombogenic surface for coagulation and localize coagulation to the site of injury. Thrombin also activates Factor V and members of the intrinsic cascade, including Factor XI and VIII. The TF VIIa complex from the initiation phase also activates Factor IX of the intrinsic cascade. Thus, in the cell based model of coagulation the intrinsic cascade is activated by thrombin and TFVIIa not through contact activation. The intrinsic tenase complex consisting of FIXaVIIIa then further activates Factor X which with its cofactor Va causes a burst of thrombin production during the propagation phase. This results in fibrin clot formation.

The following description of hemostasis integrates the cell based model into the process of fibrin clot formation and is depicted below.



Hemostasis begins when endothelial damage initiates the formation of a platelet plug through binding of platelets to subendothelial collagen, which is facilitated by von Willebrand factor. The coagulation cascade is activated simultaneously during normal hemostasis because TF is exposed to blood as a result of endothelial damage. Tissue factor is normally absent from the vascular space, being expressed by cells surrounding blood vessels such as smooth muscle and subendothelial fibroblasts.TF is also expressed on activated endothelial cells, monocytes, cellular microparticles and possibly platelets. These sources of TF are believed to initiate thrombosis in pathologic states. Regardless of its source, exposure of TF to plasma Factor VII/VIIa initiates coagulation and results in the production of a small amount of thrombin.

Circulating microparticles are derived from cell membranes of RBCs, platelets, megakaryocytes, endothelial cells, neutrophils and monocytes. They express cell surface molecules that are derived from their cell of origin, and are able to interact with, and induce cell signaling in other cell types, including the endothelium. Evidence suggests that activated platelets release phosphatidylserine (PS) exposing microparticles. PS is normally present on the inside of cell membranes. Activation of platelets and microparticle formation results in PS exposure on the external surface. PS has procoagulant effects as it provides the docking site for coagulation factors during the process of coagulation. Interestingly, deficiencies in platelet exposure of PS and microvesiculation result in bleeding tendencies in people and dogs. Microparticles derived from monocytes and endothelial cells and possibly platelets also express TF. Therefore microparticles are also believed to play a role in the initiation of pathologic thrombus formation.

The amplification phase of the cell based model of coagulation occurs mainly on PS exposing activated platelets. Thrombin activates platelets, and platelet associated Factor V. Factor Va acts as a cofactor for Factor Xa. Together they form the prothrombinase complex that converts prothrombin to thrombin and this results in the production of more thrombin. Thrombin also activates Factor VIII and Factor XI of the intrinsic cascade during the amplification phase. Activation of the intrinsic pathway is downstream of Factor XII, rather than the result of contact activation would explain why Factor XII deficiency does not result in uncontrolled bleeding.

The propagation phase is driven by thrombin activation of the intrinsic pathway downstream of Factor XII, and is thought to occur primarily through thrombin induced activation and formation of the intrinsic tenase complex as described above. Formation of the tenase complex, and subsequent further activation of Factors X and V, results in further generation of thrombin.

Large amounts of thrombin are produced in the propagation phase. Thrombin catalyzes the conversion of fibrinogen to fibrin, and activates the transglutaminase Factor XIII which then cross-links fibrin and stabilizes the clot.

In summary, models of hemostasis help put large amounts of in vivo and in vivo data into an integrated and understandable context. Consideration of the models of primary and secondary hemostasis and the Y model of coagulation are useful to clinicians because diagnostic testing and patient presentations localize to divisions set forth by these models. Therefore they facilitate in making diagnostic assessments and treatment decisions. The cell based model of coagulation integrates newer information regarding coagulation into the previous models and better defines how platelets and the clotting cascade work together in the generation of a blood clot. Developing a better understanding of hemostasis will facilitate the development of diagnostic testing, prevention and treatment strategies for disorders of hemostasis and thrombosis.

References

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Smith S. The cell-based model of coagulation JVECCS 2009 19(1) 3-10.