Haemostasis and Coagulation – Course notes

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Introduction

The haemostatic system involves a delicate balance between both procoagulant and anticoagulant reactions. The coagulation system can be considered a biological amplifier, whereby trace amounts of collagen, von Willebrand Factor and tissue factor exposed on the subendothelial matrix leads to the formation of large amounts of cross-linked fibrin from fibrinogen through a series of proteolytic cleavages by plasma coagulation factors.

Traditionally, haemostasis has been modelled by a “waterfall” or “cascade” model, whereby it is split up into two pathways, namely the intrinsic and extrinsic pathways. More recently, this model has been refined into a cell-based model [1] whereby the contributions of both coagulation factors and cells such as platelets play an important role in clot formation.

The cell-based model of haemostasis

The cell-based model of haemostasis can be divided into three phases, namely *initiation*, *amplification* and *propagation*. The model involves the formation of trace amounts of thrombin which in turn stimulates platelet activation, allowing for the exposure on the platelet surface for large scale thrombin generation for subsequent fibrin generation.

The *initiation* phase follows vascular insult and the exposure of active tissue factor to the circulation. Tissue factor combines with activated Factor VII to form a complex responsible for the cleavage and subsequent activation of Factor IX and Factor X. Activated Factor X combines with Factor V to stimulate the production of trace amounts of thrombin from prothrombin.

The *amplification* phase commences following the adherence of platelets to exposed von Willebrand Factor at the site of vascular injury. The trace levels of thrombin generated during the initiation phase stimulates platelet activation, leading to the surface exposure of phosphatidylserine as well as the release of procoagulant molecules such as factor V from alpha and dense granules. Thrombin also activates Factor V as well as Factor VIII and Factor XI which then further stimulate the activation of Factor X, which binds with factor V on platelet phosphatidylserine.

The *propagation* phase involves the large scale thrombin generation from prothrombin by activated Factors V and X. Thrombin then stimulates the cleavage of fibrinogen into fibrin. These fibrin monomers spontaneously form hydrogen bonds with other fibrin monomers allowing the formation of long fibrin polymers to produce a fibrin clot.

Platelets

The primary role of platelets in haemostasis is to support coagulation by the formation of a platelet plug comprised of aggregated platelets, and to provide a catalytic surface for the generation of thrombin for fibrin clot formation.

Platelet activation occurs following exposure to a number of agonists, such as thrombin, ADP, collagen and von Willebrand Factor. This instigates platelet degranulation, whereby vasoactive mediators (such as ADP) are released into the circulation assisting in the recruitment and activation of further platelets. The platelet glycoproteins IIb and IIIa undergo a conformation change which allows for the binding of fibrinogen. Further activated platelets also adhere to this fibrinogen forming large platelet aggregates. Furthermore, platelets support coagulation by providing a catalytic surface for the assembly of the prothrombinase complex between activated Factors X and V. This catalytic surface is comprised of negatively charged membrane phospholipids, in particular phosphatidylserine, which becomes exposed on the platelet surface following platelet activation. In addition, there is now increasing data to suggest that fragments of the platelet membrane (termed microparticles) are

released following platelet activation and possess a high concentration of exposed phosphatidylserine.

Fibrinolysis

Finally, fibrinolysis is concerned with the breakdown of fibrin clots. Fibrin is degraded by plasmin, derived from its precursor plasminogen. This plasminogen proteolysis is mediated by tissue-plasminogen activator (tPA), primarily located on endothelial cells. The activity of tPA is regulated by plasminogen activator inhibitor (PAI-1).

References

1. Hoffman, M. and D.M. Monroe, 3rd, *A cell-based model of hemostasis.* Thrombosis and Haemostasis, 2001. **85**(6): p. 958-65.