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Normal Hemostasis

Alexa J. Siddon, Henry M. Rinder, and Christopher A. Tormey

INTRODUCTION

Hemostasis is the physiologic balance of procoagulant and anticoagulant forces that maintains both liquid blood flow and the structural integrity of the vasculature. Vascular damage results in initiation of clotting that produces a *localized* platelet-fibrin plug to prevent blood loss; this action is followed by processes that lead to clot containment, wound healing, clot dissolution, tissue regeneration, and remodeling. In healthy persons, all these reactions occur continuously and in a balanced fashion so that bleeding is contained while blood vessels simultaneously remain patent to deliver adequate organ blood flow. If any of these processes are disrupted because of inherited defects or acquired abnormalities, disordered hemostasis may result in either bleeding or thromboembolic complications.

Blood flow in the arterial system is different from that in the venous system and imposes different needs on the coagulation system. In the pressurized arteries, relatively minor vascular damage can rapidly result in massive blood loss; therefore, the procoagulant response in arteries must rapidly arrest bleeding. Platelets are critical to this arterial response; they initially contain the blood loss and then provide an active surface for soluble coagulation factors to both localize and accelerate formation of fibrin and, ultimately, clot formation. By contrast, the slower flow rates in the venous circulation produce slower bleeding, a feature that makes platelets less critical; instead, the balance of venous hemostasis is most dependent on the rate of thrombin generation. These differences are underscored clinically by the anticoagulant agents used in these distinct settings: antiplatelet agents such as aspirin and clopidogrel to prevent coronary and cerebral artery thrombus, whereas interventions that inhibit thrombin, including the heparins and warfarin, are used for treatment and prophylaxis of venous thromboembolic disease. Recently, new anticoagulants have been introduced, including direct thrombin inhibitors (e.g., dabigatran etexilate) and Xa inhibitors (e.g., rivaroxaban); they selectively inhibit activated coagulation factors for prophylaxis against systemic embolism from atrial fibrillation and from venous thromboembolism, respectively.

This chapter briefly details the physiologic and interdependent mechanisms of vascular hemostasis, including the normal balance of procoagulant and anticoagulant functions of the blood vessel wall, platelet physiologic factors and receptor-ligand interactions that are critical for hemostasis, and the highly complex, interwoven pathways that represent the coagulation cascade.

VASCULAR WALL PHYSIOLOGY

Vascular endothelial cells (ECs) are capable of orchestrating both procoagulant and anticoagulant events depending on circumstances. When the vasculature is intact, healthy ECs exert tonic anticoagulant activity, helping to maintain blood fluidity. In part, they provide a passive barrier function, separating the blood from subendothelial procoagulants such as collagen and tissue factor (TF). In addition, healthy ECs actively regulate the hemostatic balance of activity in their microenvironment through their secreted products (Table 50-1). These include prostacyclin and nitric oxide, both of which induce vascular smooth muscle relaxation and reduced shear when released in an abluminal direction. When secreted into the blood, they promote the generation of platelet cyclic adenosine monophosphate (cAMP), thus inhibiting platelet activation and aggregation. ECs also secrete adenosine diphosphatase, which degrades extracellular platelet-released adenosine diphosphate (ADP), thereby inhibiting platelet recruitment into the growing platelet clot. Soluble coagulation factors are also regulated by ECs in both tonic and inducible fashion. Tissue factor pathway inhibitor (TFPI) in its nascent circulating form blunts the initiation of coagulation; TFPI is subsequently primed for increased activity by exposure to small amounts of factor Xa. Quiescent thrombomodulin and tissue plasminogen activator are localized at the EC extracellular matrix, ready to be activated by local formation of thrombin and fibrin, respectively, to carry out their anticoagulant and fibrinolytic functions.

When ECs are physically damaged or become activated, their balance of coagulant properties is shifted to favor a procoagulant state. This function is mediated both by the ECs themselves and by the underlying subendothelial matrix that is exposed by vascular injury. ECs that have become activated (e.g., by toxins or

TABLE 50-1 PROPERTIES OF ENDOTHELIAL CELL COAGULANTS

PROCOAGULANT	ANTICOAGULANT
Collagen	Vasodilation
Factor VIII	Adenosine diphosphatase
Fibronectin	Heparan sulfates
Integrins	Nitric oxide
Platelet-endothelial cell adhesion molecule-1 (PECAM-1)	Prostacyclin
Selectins (E and P)	Thrombomodulin
Vasoconstriction	Tissue factor pathway inhibitor
von Willebrand factor	Tissue plasminogen activator