Regulation of Platelet Activation and Coagulation and Its Role in Vascular Injury and Arterial Thrombosis

Maurizio Tomaiuolo, PhD, Lawrence F. Brass, MD, PhD, Timothy J. Stalker, PhD*

KEYWORDS

• Platelet activation • Coagulation • Vascular injury • Arterial thrombosis • Antithrombotic agents • Hemostasis

KEY POINTS

- The platelet response to vascular injury involves multiple cell signaling pathways that are coordinated in both time and space.
- Local conditions within the evolving platelet plug microenvironment result in the development of platelet agonist gradients.
- Antiplatelet therapeutics targeting specific platelet activation pathways have disparate effects on platelet mass architecture depending on the spatiotemporal regulation of the target pathway.

INTRODUCTION

The hemostatic response to vascular injury is a complex process requiring regulated activation of coagulation proteins, platelets, and components of the vascular wall to form a localized hemostatic plug that prevents bleeding. Many aspects of this process have been well-characterized at the molecular and cellular levels in vitro, and the major biochemical pathways responsible for coagulation and platelet activation have been reviewed extensively elsewhere.[1–5]

This review focuses primarily on how the multiple components of the hemostatic system are integrated in time and space to generate an optimal response, including how fluid dynamics and the physical architecture of platelet plugs contribute to the formation of complex biochemical gradients at a site of vascular injury. Although presented in the context of hemostasis, all of the players and processes discussed have an important role in pathologic thrombosis as well, as indicated by the clinical usefulness of multiple therapeutics directed against platelet and coagulation targets as antithrombotics. As we continue to gain a better understanding of how coagulation and various cellular signaling pathways are coordinated in time and space during hemostasis, we are more likely to uncover differences that may exist between hemostasis and thrombosis that could be targeted for safer antithrombotic treatments.

THE HEMOSTATIC RESPONSE TO VASCULAR INJURY

In a fairly simplified view, the hemostatic response can be considered as a sequence of cellular and molecular events delineated into the overlapping phases of initiation, extension and stabilization. Each of these phases involves prohemostatic molecular processes that result

Department of Medicine, Perelman School of Medicine, University of Pennsylvania, 421 Curie Boulevard, Philadelphia, PA, 19104, USA
* Corresponding author.
E-mail address: tstalker@mail.med.upenn.edu

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in the rapid plugging of a hole in the vessel wall to stem bleeding, balanced with antihemostatic processes that limit the response to the site of injury and prevent unwarranted vascular occlusion. The molecular players involved include adhesion molecules and their ligands, platelet surface receptors that initiate intracellular signaling pathways, and the coagulation cascade to generate thrombin and fibrin, among others.

Initiation

Hemostasis is triggered by the exposure of blood to a breach in the vessel wall. During the initiation phase, circulating platelets are recruited to the injury site via adhesive interactions between von Willebrand factor (vWf) bound to collagen fibers in the vessel wall and the platelet glycoprotein Ib (GPIb)–IX-V receptor complex. VWf is normally found circulating in the plasma in an inactive form, is secreted constitutively from endothelial cells as part of the extracellular matrix, and is also secreted from Weibel-Palade bodies of activated endothelial cells.[6,7] After a breach in the vessel wall, circulating vWf is deposited on collagen fibers exposed at the injury site.[8] Unfolding of the protein as a result of shear forces exposes binding sites for platelet surface GPIb to rapidly recruit platelets from the circulation.[6,7,9] Because the vWf–GPIb complex interaction is relatively weak, additional adhesive interactions mediated by integrin family adhesion molecules on the platelet surface are also required for firm platelet attachment at the site of injury. These include $\alpha_2\beta_1$ integrin binding to collagen and $\alpha_{IIb}\beta_3$ binding to vWf and other ligands. For platelet integrins to bind their ligands, they must undergo a conformational change from a resting to active state that requires platelet activation. Platelet activation during the initiation phase is likely mediated via multiple platelet signaling pathways, including activation of the GPVI collagen receptor, activation of platelet ATP and ADP receptors via release of these molecules from damaged cells and by signaling downstream of the GPIb–IX-V complex. In addition, escaping blood at the site of injury encounters tissue factor expressed by cells in the vessel wall and extravascular tissue initiating the generation of thrombin, which is a potent platelet activator.

Extension

After initial platelet adhesion and activation, additional platelets are recruited from the circulation to form a platelet aggregate via platelet–platelet cohesion during the extension phase. This cohesion is mediated primarily by binding of the plasma protein fibrinogen to $\alpha_{IIb}\beta_3$ integrin (aka GPIIbIIIa). Each fibrinogen molecule has 2 $\alpha_{IIb}\beta_3$ binding sites and can therefore mediate platelet–platelet interactions by binding to receptors on 2 adjacent platelets. Platelet recruitment and $\alpha_{IIb}\beta_3$–mediated cohesion require platelet activation by ADP released from platelet dense granules and thromboxane A_2 (TxA_2) generated by platelets already adherent at the site of injury. Thrombin activity also continues to contribute to platelet activation. The importance of $\alpha_{IIb}\beta_3$ in mediating platelet aggregation is demonstrated by the lack of aggregation of platelets from Glanzmann's thrombasthenia patients, which results in a bleeding diathesis. Inhibition of platelet aggregation using $\alpha_{IIb}\beta_3$ antagonists is effective to prevent thrombosis in the setting of percutaneous coronary intervention.[10,11]

Stabilization

Once formed, the nascent hemostatic plug must condense and become firmly anchored at the injury site to resist the force of flowing blood and prevent rebleeding. In addition to activating platelets, thrombin converts fibrinogen to fibrin, forming a network of fibrin fibers that helps to stabilize the platelet plug. Stabilization is also facilitated by consolidation of the platelet mass via actin-myosin–mediated platelet retraction. Platelet activation is reinforced by positive feedback from soluble agonists (thrombin, ADP, TxA_2), as well as contact-dependent signaling pathways that are initiated once platelets come in close proximity to one another such that receptor/ligand pairs on adjacent platelets become engaged. Again, $\alpha_{IIb}\beta_3$ integrin has an important role in this stage, now acting as a signaling molecule regulating platelet retractile processes.[12]

An Updated Model of Hierarchical Hemostatic Plug Architecture

This description of the hemostatic response provides a general sequence of events. It is consistent with, and in large part derived from, clinical experience regarding the importance of the various molecular players involved as defined by bleeding diatheses that result from either genetic or acquired deficiencies of specific molecular components. However, recent studies examining hemostasis and thrombosis in vivo show that this model is overly simplistic. Rather than a mass of uniformly activated