Thrombin’s role in hemostasis

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Introduction

Thrombin is a serine protease thrombin that plays pivotal roles in hemostasis and coagulation pathways. When thrombin is activated from prothrombin, it converts soluble fibrinogen to fibrin, activates Factors V, VIII, and XI (which generate more thrombin), and activates platelets. 

Understanding the in vivo regulatory mechanisms and pharmacologic modulation of thrombin activation and effects is important. This presentation will focus on regulatory mechanisms of hemostasis and critical role of thrombin in these processes.

Thrombin’s role in the initial hemostatic response

The initial hemostatic response following vascular injury is triggered by expression of tissue factor (TF) on subendothelial vascular membranes. TF will bind activated factor VII (fVIIa), present in low concentrations, to activate factor X to fXa, a critical step in hemostatic activation. Subsequently, fXa generates trace amounts (0.1–1 nM) of thrombin. Factor Xa and also thrombin are major targets of anticoagulation agents, including the new oral anticoagulants. Other physiologic inhibitors that regulate TF-triggered procoagulant responses include tissue factor pathway inhibitor (TFPI) neutralizes fXa when it is in a complex with TF-fVIIa. The other regulator of TF-trigger procoagulant response is antithrombin (AT, formerly called antithrombin III; a serine protease inhibitor; SERPIN) which circulates at a high concentration (150 µg/ml~2.7 µM) and neutralizes the initially formed fXa and thrombin. Thus, the procoagulant triggering reaction only proceeds when TF is exposed at a high enough level to overcome inhibition by TFPI and AT.

Propagation of coagulation and role of thrombin

Circulating platelets further contribute to localized thrombin generation and clot formation at the site of vascular injury. Platelets initially adhere to subendothelial collagen-von Willebrand factor (vWF) via their glycoprotein (GP) Ib receptors. Thrombin generated by TF-fVIIa/fXa (the ‘extrinsic pathway’) is capable of activating adherent platelets in its vicinity via protease activated receptors 1 and 4 (PAR1 and PAR4). Thrombin-activated platelets play a pivotal role in subsequent coagulation processes by multiple mechanisms including release of additional factors including activated factor V released from platelet α-granules upon platelet activation. Factors XI, VIII, and V are involved in sustaining procoagulant responses (the ‘intrinsic pathway’) after thrombin-mediated activation.

Thrombin also causes the activation of additional serine protease zymogens (inactive enzymatic precursors), cofactors, and cell-surface receptors including expression of GPIIb/IIIa receptors that bind fibrinogen. Factor XIII is also activated by
thrombin to FXIIIa, a transglutaminase. Fibrin monomers are rapidly cross-linked by FXIIIa. Thus fibrinogen and factor XIII are final thrombin substrates that play pivotal roles in stabilizing the primary hemostatic plug.

Endothelial regulation of thrombin and coagulation

The intact endothelium has critical anticoagulant functions that maintain blood in a fluid state. The endothelium attenuates platelet activity by releasing nitric oxide, prostacyclin, and tissue plasminogen activation (tPA). Endothelial cells also secrete heparan sulfate, a glycosaminoglycan which catalyzes anticoagulant activity of AT. Plasma AT binds to heparan sulfate located on the luminal surface, and in the basement membrane of the endothelium. Thrombomodulin is another endothelium-bound protein with anticoagulant and anti-inflammatory functions. In response to systemic procoagulant stimuli, tissue-type plasminogen activator (t-PA) is transiently released from the Weibel-Palade bodies of endothelial cells to promote fibrinolysis. During inflammation, activated endothelium modulates procoagulant responses by synthesizing tissue factor, von Willebrand factor (vWF), plasminogen activator inhibitor (PAI)-1, and PARs (protease activated receptors).

Thrombin generation and the hemostatic response are generally limited to the site of vascular injury because key serine proteases are membrane-bound on activated platelet surfaces and systemic responses attempt to limit thrombin generation. Plasma (free) FXa and thrombin are rapidly neutralized by heparan-bound AT. Thrombin is also taken up by endothelial surface-bound thrombomodulin. The binding of thrombomodulin to exosite I of thrombin optimizes the catalytic activity of thrombin toward generation of the natural anticoagulant protein C and TAFI (thrombin-activatable fibrinolysis inhibitor). In the systemic circulation, activated protein C (APC) has been shown to exert multiple anti-inflammatory and cytoprotective functions by modulating endothelial protein C receptor (EPCR) and protease activated receptor-1 (PAR-1, thrombin receptor) via mechanisms still under investigation. TAFI also exerts anti-inflammatory effects by cleaving bradykinin and C5a. Multimers of vWF are also increased during inflammation, and they are down-regulated by ADAMTS-13 (A Disintegrin and Metalloprotease with a ThromboSpondin type 1 motif, member 13), which is also synthesized by endothelial cells.

The inability to locally regulate thrombin production creates a systemic activation state known as disseminated intravascular coagulation or DIC. Studies suggest AT therapy may be effective in reversing adverse effects of DIC, and recombinant thrombomodulin is approved in Japan for this purpose.

Summary

Thrombin is a key hemostatic molecule that in many ways is the center of the hemostatic universe. Many drugs have been designed around this molecule specifically to either inhibit its activation as anticoagulation agents, or to promote its activation in bleeding patients as procoagulants. Thrombin in addition to hemostatic activation has major inflammatory effects, and undergoes a complex series of processes to regulate its activation including membrane bound and systemic protease inhibitors. We have used thrombin generation also as a tool to help better understand its activation and requirement in critically bleeding patients, and have been used to determine effectiveness of reversal
of the new oral anticoagulation agents. Understanding its complex role in critically ill patients is important in managing these patients perioperatively.¹


