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Reprint of Crosstalk between inflammation and thrombosis

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Abstract

Inflammation shifts the hemostatic mechanisms in favor of thrombosis. Multiple mechanisms are at play including up regulation of tissue factor leading to the initiation of clotting, amplification of the clotting process by augmenting exposure of cellular coagulant phospholipids, inhibition of fibrinolysis by elevating plasminogen activator inhibitor 1 (PAI-1) and decreases in natural anticoagulant pathways, particularly targeted toward down regulation of the protein C anticoagulant pathway through multiple mechanisms. The decreased function of the natural anticoagulant pathways may be particularly problematic because these appear to play a role in dampening inflammatory responses. The protein C anticoagulant pathway provides a useful model for the impact of inflammation on coagulation. This pathway plays a major role in preventing microvascular thrombosis. The pathway is initiated when thrombin binds to thrombomodulin (TM) on the surface of the endothelium. An endothelial cell protein C receptor (EPCR) augments protein C activation by the thrombin–TM complex more than 10-fold in vivo. EPCR is shed from the endothelium by inflammatory mediators and thrombin. EPCR binds to activated neutrophils in a process that involves proteinase 3 and Mac-1 and appears to inhibit leukocyte extravasation. EPCR can undergo translocation from the plasma membrane to the nucleus where it redirects gene expression. During translocation it can carry activated protein C (APC) to the nucleus, possibly accounting for the ability of APC to modulate inflammatory mediator responses in the endothelium. TNF α and other inflammatory mediators can down-regulate EPCR and TM and IL-6 can depress levels of protein S in experimental animals. Inhibition of protein C pathway function increases cytokine elaboration, endothelial cell injury and leukocyte extravasation in response to endotoxin, processes that are decreased by infusion of APC. In vitro, APC inhibits TNF α elaboration from monocytes and to block leukocyte adhesion to selectins. Since thrombin can elicit many inflammatory responses in microvascular endothelium, loss of control of microvascular thrombin generation due to impaired protein C pathway function probably contributes to microvascular dysfunction in sepsis.

Keywords: Endotoxin; Macrophages; Fibrinogen

1. The impact of inflammation on procoagulant reactions

A simplified version of blood coagulation and some of the control mechanisms are shown in Fig. 1. Inflammatory mediators such as endotoxin and the

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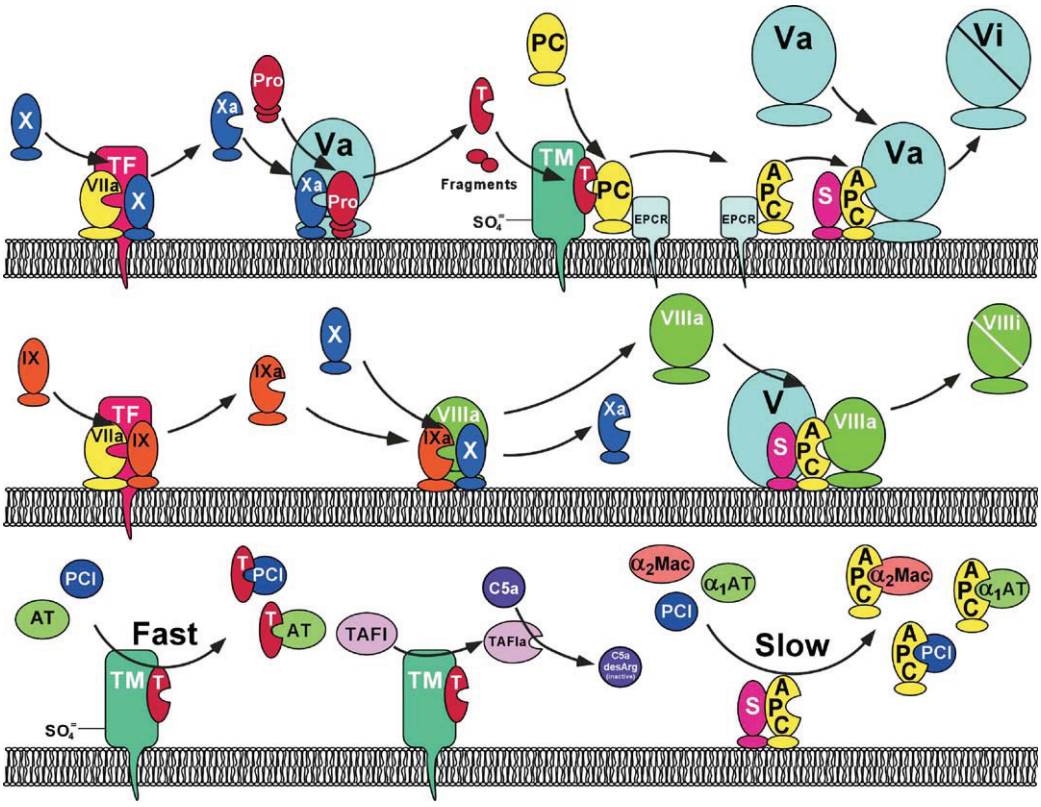

Fig. 1. A simplified view of the regulation of blood coagulation by the protein C pathway. Factor VIIa (VIIa) binds to tissue factor (TF) to activate factor X (X), generating factor Xa (Xa). Factor Xa then finds to factor Va. The complex of factors Xa–V converts prothrombin (pro) to thrombin (T). Thrombin can then either bind to TM or carry out procoagulant reactions like fibrin formation or platelet activation. When bound to TM, thrombin can activate protein C (PC) to activated protein C (APC). This process is enhanced when protein C is bound to the endothelial cell protein C receptor (EPCR). Activated protein C bound to EPCR cleaves substrates other than factor Va. Activated protein C dissociates from EPCR and can then interact with protein S to inactivate factor Va. The middle row shows inactivation of the factor IXa (Ixa)–factor VIIIa (VIIIa) complex by APC. In this case, factor V participates with APC and protein S in the inactivation of factor VIIIa. In the bottom row, the plasma proteinase inhibitors that regulate the protein C activation complex and the anticoagulant complex of APC and protein S are illustrated. *Abbreviations*: α_1-AT, α1-antitrypsin; α_2-Mac, α_2-macroglobulin; PCI, protein C inhibitor; AT, antithrombin. The thrombin activatable fibrinolysis inhibitor (TAFI) is activated (TAFIa) by the thrombin–TM complex. TAFIa then inactivates C5a (C5a). For simplicity, the activation of factors VII, V, and VIII are not shown. (Figure modified with permission from Esmon CT. Thromb Haemost 1999;82:251–8, copyright F.K. Schattauer.)

inflammatory cytokines initiate coagulation through the induction of tissue factor expression, primarily on monocyte/macrophages [1,2]. Tissue factor is not normally present in the circulation at anything more than trace levels [3]. Thus, normal hemostasis arises when the blood vessels are breached causing the blood to contact tissue factor bearing extravascular cells [4]. Complement activation generates the C5b9 complex, which, if deposited on cells causes exposure of phosphatidylserine on the surface of the cells by flipping this lipid from the inner to the outer membrane leaflet [5]. Phosphatidylserine on the outside of the cell is critical for the initiation and amplification stages of the coagulation cascade to function effectively. This lipid flip-flop is often a limiting process in coagulation. To achieve maximal phosphatidylserine expression, very potent platelet agonists like C5b9 or the combination of thrombin plus collagen are needed [5–7]. Inflammation will also elevate fibrinogen synthesis. Fibrinogen levels rise under theses