Coagulation and Inflammation

Robert A. Campbell and Elizabeth Middleton

Sir William Osler observed that "(e)xcept on few occasions, the patient appears to die from the body's response to infection rather than from it." During infection, two biological systems which are critically important in dictating the body's response are the hemostatic and inflammatory pathways. While considered separately regulated biological pathways, coagulation and inflammation are intimately connected with extensive communication between each other resulting in an optimal response to injury and infection. However, abnormal responses in either pathway can result in excessive bleeding or thrombosis or an overexaggerated immune response. Amplified coagulation and inflammatory responses occur once pathogens and inflammatory mediators reach the systemic circulation, resulting in vascular damage, microthrombi, and multiorgan failure, including sepsis. These responses can further lead to a dysregulated hemostatic system resulting in thrombotic microangiopathy (hemolytic anemia, thrombocytopenia and microthrombi), complement activation and disseminated intravascular coagulation (DIC) (1, 2). Understanding the interplay between both systems is critical to developing novel therapeutics to bring both systems back into balance. This brief review will cover three areas which greatly influence coagulation and inflammation during disease: 1) megakaryocytes and platelets, 2) coagulation and fibrinolysis, and 3) immune cells and the endothelium. Taken together, this short review will provide a global overview of dysregulated coagulation and inflammation and areas of future discovery, which could lead to the development of novel diagnostics and treatments.

The Role of Platelets and Megakaryocytes in Coagulation and Inflammation.

Anucleate, platelets have been traditionally viewed as simple cells, which participate in hemostasis and thrombosis. Platelets inherit a predictable, fixed, and relatively short-acting hemostatic toolset from their parent cell: the megakaryocyte (MK). While the hemostatic roles of platelets are well recognized, emerging data demonstrate megakaryocytes and platelets possess diverse and dynamic functions that also mediate inflammatory and immune response (3–5). In addition, platelets are thought to play critical roles in infectious diseases as many infectious processes result in thrombocytopenia due enhanced destruction of megakaryocytes and platelets (6–8).

Megakaryocytes and platelets have a relatively static transcriptome and proteome under basal conditions (9). However, recent studies have suggested the transcriptome of the megakaryocyte and subsequently the platelet, is dynamic during inflammatory processes, including viral infections and bacterial sepsis (10, 11). Changes in the transcriptome result in megakaryocytes and platelets possessing a multitude of innate immune tools, including toll-like receptors to recognize pathogens, and Fc receptors, which recognize immune complexes (3). In addition, platelets contain mRNA and proteins which act as antimicrobial agents, including antimicrobial peptides and beta-defensins, which directly act on bacterial pathogens (3, 5, 12). Platelets also release chemokines such as platelet factor 4, RANTES and β-thromboglobulin, which increase leukocyte recruitment and survival during viral infections (Figure 1). These cytokines and chemokines can reduce HIV infection by directly interacting with the viral

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envelope and inhibit *Plasmodium* parasites during malaria infection (13-16). Furthermore, certain changes in the transcriptome and proteome, including αIIb expression, have been associated with increased mortality (10).

Recently, megakaryocytes have been shown to play significant roles in fighting infections. For example, megakaryocytes possess major histocompatibility complex (MHC) I and are capable of endocytosis of endogenous antigen (17). Upon processing the antigen through the proteasome, megakaryocytes can present antigens in an MHC-I dependent manner to activate $CD8^{+}$T cells. In addition, viral infections such as influenza and dengue virus significantly alter the transcriptome of megakaryocyte and platelets, resulting in expression of novel anti-viral molecules such as interferon-induced transmembrane 3 (IFITM3) (11). Induction of IFITM3 in megakaryocytes and surrounding hemopoietic stem cells reduces viral infection and appear to be mediated through type I interferon release from the megakaryocyte.

Megakaryocytes and platelets also have toll-like receptors (TLRs) on their surface to facilitate innate immunity and interactions with other immune cells. Platelets express TLR2 (18, 19), TLR4 (20, 21), and TLR9 (22), which play a role in platelet activation, secretion of pro-inflammatory cytokines, and enable the formation of heterotypic platelet-immune cell interactions. In addition, platelets express TLR7 and TLR3, which alter platelet-leukocyte aggregates, which will be discussed more below (23, 24).

The Role of Thrombin Generation, Clot Formation and Fibrinolysis in Inflammation.

Tissue factor (TF) is a critical glycoprotein, which is located at the nexus of coagulation and inflammation (25). Expression of TF leads to the initiation of the host response against injury and pathogen invasion. TF is normally located in in the sub-endothelium to prevent aberrant exposure to blood (26). However, upon mechanical injury or inflammatory stimuli, TF expression is upregulated on perivascular cells as well as monocytes, which exposes TF to the circulating blood (Figure 2). This allows for factor VIIa (FVIIa) to complex with TF, resulting in activation of Factor IX and X, which subsequently converts a small amount of prothrombin to thrombin (26). This initial burst of thrombin acts as a positive feedback to amplify activation of the coagulation system and generate more thrombin (26). Increased thrombin generation promotes platelet activation, fibrin clot formation, and pro-inflammatory measures mediated by the activation of protease activated receptors (PARs) on endothelial and other immune cells (27). Pro-inflammatory events driven by thrombin include recruitment and activation of monocytes, neutrophils and platelets and adhesion of leukocytes to endothelial cells, and the activation of the complement systems (27-29). Furthermore, activation of PARs by thrombin and TF-FVIIa results in increased release of pro-inflammatory cytokines, which further activate endothelial and immune cells,

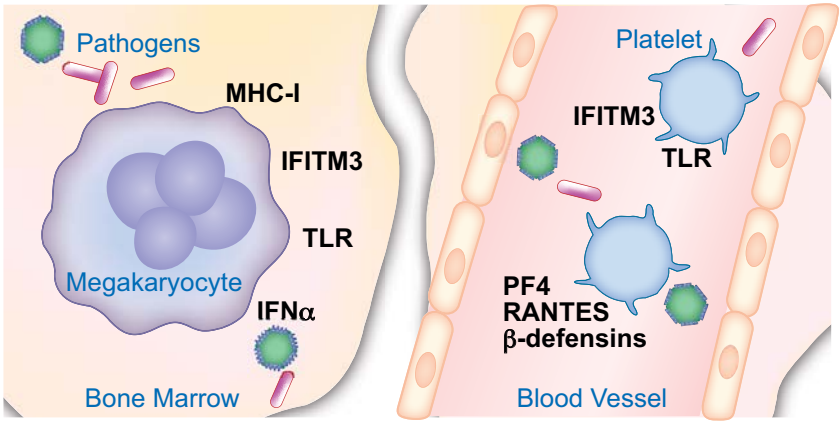

Figure 1. Megakaryocytes and platelets are key players in the inflammatory response. Pathogens and inflammatory cytokines can interact with megakaryocytes through MHC-1, toll-like receptors, and other immune receptors to alter the megakaryocyte and platelet transcriptome. Megakaryocytes can regulate viral and bacterial infections through changes in the transcriptome profile. Platelets circulate in the blood and can interact with pathogens and release inflammatory molecules to block viral and bacterial infections.

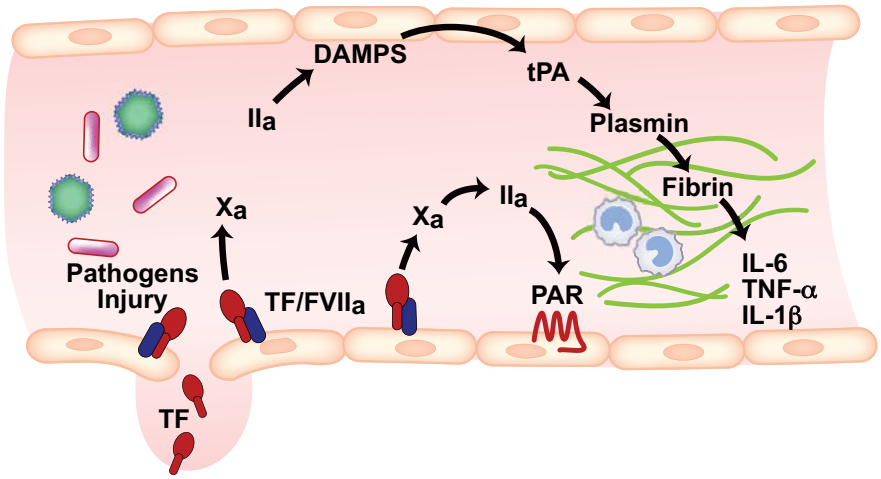

Figure 2. The coagulation pathway regulates inflammatory responses. Tissue factor (TF) is exposed upon injury and pathogen invasion and interacts with factor VIIa (FVIIa) to generate factor Xa (FXa) and thrombin (IIa). Thrombin can then cleave fibrinogen to fibrin to generate a clot, which can trap leukocytes. Fibrin and IIa will cause leukocytes to synthesize inflammatory cytokines. IIa can also active endothelial cells through PARs and other receptors to release DAMPs. Furthermore, activated endothelial cells release tissue type plasminogen activator (tPA), which can dissolve the fibrin clot.

resulting in secretion of damage-associated molecular patterns (DAMPs) (30). DAMPs will bind to TLRs on endothelial cells, immune cells, and platelets to further amplify inflammation (30).

Thrombin activates PARs on platelets and endothelial cells and generates fibrin. Thrombin activation of platelets results in release of chemokines and cytokines to reduce the spread of infection, while fibrin formation allows pathogens to be trapped and cleared by leukocytes (27-29).

Besides activating PARs on platelets and endothelial cells, thrombin will cleave soluble fibrinogen into insoluble fibrin. Fibrin plays a significant role in preventing blood loss by sealing damaged vessels (31). However, fibrin formation also recruits monocytes and macrophages to limit pathogens from spreading (32). Furthermore, fibrin directly regulates the production of inflammatory cytokines and chemokines, including tumor necrosis factor alpha (TNFα), interleukin 1-beta and monocyte chemoattractant protein-1(33). Inflammatory cytokine production is thought to be mediated by TLR4 (34). Fibrin(ogen) appears critical to regulating host immune responses as fibrinogen-deficient mice have less macrophage adhesion and recruitment as well as reduced thrombin-mediated cytokine production (35).

Generation of fibrin to reduce blood loss and prevent systemic bacterial spreading also activates the fibrinolytic system to break down the fibrin matrix and promote wound healing (35). Thrombin activates the endothelium to generate and secrete tissue-type plasminogen activator as well as urokinase type plasminogen activator. Both enzymes cleave plasminogen to plasmin, which ultimately degrades fibrin (36). While the fibrinolytic system is beneficial enhanced activation of the system can lead to increased inflammation. Plasmin generation can induce activation of NF-ϰB to drive expression of TNF-α, IL-1, and IL-6 (37). Plasmin can also activate parts of the complement pathway leading to the generation of inflammatory anaphylatoxins and the formation of the membrane attack complex (38). The importance of thrombin generation, fibrin formation, and fibrinolysis has been demonstrated in mouse models where reduced thrombin generation and enhanced fibrinolysis increases susceptibility to bacterial infections, suggesting thrombin, platelets and megakaryocytes play critical roles in stemming the spread of infection, while maintaining hemostasis (35).

The Role of Immune Cells and the Endothelium in Coagulation and Inflammation.

Immune cells, including monocytes, macrophages, and neutrophils are key regulators of the interface between coagulation and inflammation. Monocytes are innate immune cells

responsible for phagocytosis of pathogens and the development of tissue macrophages and dendritic cells (39). Monocytes are a significant source of TF, which can drive aberrant thrombin generation and cytokine production from surrounding immune cells (26). In addition, activated platelets bind to monocytes through their surface receptor P-selectin, adhering to PSGL-1 on the monocyte surface (40). Engagement of these two receptors and the formation of platelet-monocyte aggregates (PMAs) induces proinflammatory cytokine production by the monocytes, resulting in increased inflammatory and altered coagulation pathways (Figure 3) (41). Increased PMA formation has been associated with inflammatory diseases such as diabetes, sepsis, and cardiovascular disease (42-44).

Neutrophils also play a significant role in altering inflammation and coagulation. During inflammation, activated neutrophils release web-like structure called neutrophil extracellular traps (NETs), which are made up of DNA, histones, and enzymes, such as neutrophil elastase and myeloperoxidase (MPO), to prevent the spread of pathogens (45). While NETs are responsible for entrapping and eliminating bacteria, they are also known to promote inflammation and thrombosis (45). NETs can be found inside thrombi and promote resistance to fibrinolysis (46). Furthermore, NETs can activate platelets and endothelial cells, and promote the formation of more NETs from surrounding neutrophils. Histones associated with NETs also propagate increased coagulation and platelet activation. In vivo evidence has recently demonstrated a significant role for NETs in thrombosis (46). Increased markers of NETs, including MPO-DNA complexes and circulating free DNA have been observed to increase after experimental deep vein thrombosis in baboons (47) while systematic DNase treatment to degrade NETs protects mice from thrombosis (48).

The endothelium also plays a critical role in crosstalk between inflammation and coagulation (49, 50). Activated endothelial cells can express TF and initiate thrombin generation and fibrin formation (51). Endothelial cells also constitutively secrete vWF, and vWF-size cleaving and controlling ADAMTS-13 enzyme to maintain vWF homeostasis (52, 53). Infections can consume ADAMTS-13 or lead to antibody formation to exhaust or inactivate its capacity (49, 50). Decreased ADAMTS-13 activity may lead to the development of thrombotic thrombocytopenic purpura (TTP), or hemolytic uremic syndrome (HUS) or atypical, aHUS, resulting in thrombosis formation in the microvasculature (brain, kidneys) due to platelet- and vWF-rich deposition and complement activation (54). Platelets can also bind to endothelial derived-vWF and generated fibrin on the endothelium (thrombocytopenia, “consumption”).

The endothelium also contains natural anticoagulants that prevent abnormal

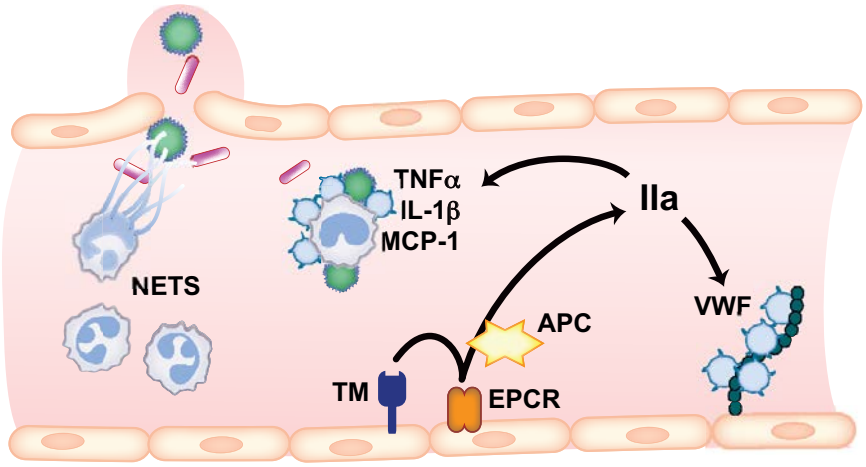

Figure 3. Inflammation activates immune cells to regulate infection. Pathogens and inflammatory cytokines can activate neutrophils to release neutrophil extracellular traps, which kill bacterial pathogens. Activated platelets will interact with monocytes to induce pro-inflammatory cytokines. Activated platelets will also adhere to vWF secreted by activated endothelial cells. Finally, thrombomodulin (TM) and the endothelial protein C receptor (EPCR) interact to generate activated protein C (APC) to inactivated thrombin (IIa), which downregulates coagulation.

thrombin generation and fibrin formation. During inflammation, these glycosaminoglycans are downregulated due to release of proinflammatory cytokines. The reduction of glycosaminoglycans can reduce the activity of antithrombin and tissue factor pathway inhibitor, two critical anticoagulants which regulate thrombin and TF/FVIIa, respectively (55, 56). Reduced glycosaminoglycans also impact leukocyte adhesion and transmigration (55, 56). Other polysaccharides involved in the glycocalyx formation on the endothelial cell surface regulate coagulation and vascular function besides glycosaminoglycans. Disruption of the glycocalyx leads to increase thrombin generation, platelet adhesion and vascular edema within minutes of the loss of the glycocalyx.

Endothelial cells also express thrombomodulin (TM) and endothelial cell protein C receptor (EPCR), which are responsible for the generation of activated protein C (APC) (57). APC is a critical regulator of coagulation and inflammation and deficiency of APC or EPCR significantly augment the risk of deep vein thrombosis and thromboembolism (57, 58). APC downregulates thrombin and fibrin formation by cleaving coagulation factors such as factor VIIIa and Va. In addition, thrombin becomes inactivated when bound to TM; therefore, APC and TM are critical anticoagulant and anti-inflammatory mediators (57, 58). Besides, regulating thrombin generation, APC inhibits NF-κB translocation to the nucleus and reduces release of pro-inflammatory cytokines, expression of TF, and inhibits recruitment of neutrophils (59).

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