Soluble Tissue Factor Emerges From Inflammation
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Inflammation and coagulation play crucial roles in the pathogenesis of vascular disease. Growing evidence reveals a tight mutual network in which inflammation not only activates coagulation, but coagulation also feeds back to inflammatory activity. Tissue factor (TF), as the cellular initiator of the extrinsic coagulation pathway, plays a key role in this cross-talk. The activation of coagulation and the deposition of fibrin are well characterized consequences of inflammation and can be viewed as an essential part of the host defense reaction. Under certain conditions, however, coagulation may contribute to excessive thrombus formation, and the recruitment of inflammatory cells to a ruptured atherosclerotic plaque may provoke subsequent myocardial infarction. Expression of TF by inflammatory cells in the unstable plaque can initiate the extrinsic coagulation cascade, and the thrombin thus generated can activate platelets and lead to the formation of a platelet–fibrin thrombus. Systemic inflammatory changes that occur in severe sepsis also induce TF expression in monocytes and increase the number of circulating procoagulant microparticles. The subsequent intravascular coagulation may contribute to multiple organ dysfunctions. In addition, coagulation can markedly increase the inflammatory cell activity and, thereby, aggravate organ damage even further. Coagulation factors activate protease-activated receptors (PARs) on mononuclear or endothelial cells and thereby contribute to cytokine generation or inflammatory cell apoptosis. Elegant experiments in genetically modified mice identified the key role of TF and PARs in coagulation-induced inflammation during endotoxemia. A decrease in TF activity in low TF or a PAR-2 deficiency in combination with thrombin inhibition abrogated systemic inflammatory changes.

The TF gene encodes 2 proteins that arise from alternative splicing of its transcript. A transmembrane protein consisting of a 219-amino acid extracellular domain, a 23-residue transmembrane domain, and a 21-residue intracellular domain is constitutively expressed in a number of extravascular cells and is induced by various stimuli in vascular cells. A soluble protein of 206 amino acids lacks the C-terminal transmembrane and cytoplasmic domains. Upon exposure to blood, the transmembrane protein binds and allosterically activates factor VIIa (FVIIa). The TF–VIIa complex cleaves factor FX, leading to thrombin generation. Independently of cellular TF, blood-borne soluble TF may play a role in the propagation of thrombosis, but its precise role and regulation have remained obscure. TF antigen in plasma is found to be elevated in a number of disease states associated with increased activation of the coagulation. However, this circulating extracellular TF consists of 2 forms in addition to soluble secreted TF: truncated forms and procoagulant microparticles (MP). MPs are small membrane vesicles, released from blood cells or endothelial cells on activation by cytokines, shear stress, or apoptosis. They support coagulation by exposure of negatively charged phospholipids and TF. Recent studies suggest that blood-borne TF contributes to thrombogenesis after vascular injury via hematopoietic and endothelial cell–derived microparticles. In contrast, blood of healthy individuals lacks detectable functional TF. Even though soluble TF was identified 2 years ago, its expression and contribution to the procoagulant potential under inflammatory conditions has remained dubious.

Now, Szotowski et al show in the current issue of Circulation Research that proinflammatory cytokines induce expression of soluble TF in endothelial cells. As early as 10 minutes after stimulation with TNF-α, mRNA expression and subsequent release of soluble TF was induced. In contrast, induced mRNA expression of transmembrane TF was observed after 60 minutes, and most of this full-length TF remained within the cellular fraction. This suggests that increased TF detected in the supernatant should result from soluble TF. Concurrently, tissue factor pathway inhibitor was decreased in the cellular fraction, whereas it increased in the supernatant after stimulation with proinflammatory cytokines. Most importantly, TNF-α induced TF activity in MP-free supernatants after addition of phospholipids. To confirm that soluble TF was responsible for the increased TF activity, the authors applied inhibitory antibodies that specifically precipitate the soluble isoform. These antibodies abolished TF activity. Thus, soluble TF released under inflammatory conditions may not only serve as an early marker for endothelial activation but may also contribute to the procoagulant potential of endothelial cells.

Szotowski et al have clearly demonstrated that proinflammatory cytokines can induce expression of soluble TF. To further assess the physiological importance of this interesting observation, the concentration of soluble TF under inflammatory conditions like sepsis or myocardial infarction should be determined. This may be particularly important as earlier studies have suggested that physiologic concentrations of FVIIa and soluble TF exhibit negligible activity and thus may not likely trigger blood coagulation by themselves. As 20-fold higher concentrations of FVIIa were used by Szotowski et al, it is possible that the soluble form of TF is reinforced to bind FVIIa. Although previous studies reported that blood-borne TF is recruited into developing thrombi, the specific contributions...
of soluble TF and MP-derived TF to thrombus propagation remains to be determined.

The identification of soluble TF as a potentially important player in inflammation and coagulation may allow developing novel therapeutic strategies to abrogate the pathological feedback loop between inflammation and coagulation.

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References

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