EDITORIAL COMMENT

Relationship Between Inflammation and Venous Thromboembolism as Studied by Microparticle Assessment in Plasma*

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Inflammation and hemostasis are coupled via common activation pathways and feedback regulation systems. During inflammation, the hemostatic balance may be disturbed, resulting in the increased production of procoagulant factors and in the down-regulation of anticoagulant mechanisms. Thus, thrombosis promotes inflammation, which in turn stimulates a prothrombotic tendency. The crosstalk between inflammation and hemostasis is complex and involves enzymatic reactions, cell receptor-mediated signaling, heterotypic cell interactions, endothelial inflammation, and the production of cell-derived microparticles, which are released into the circulation. These microparticles trigger additional cellular interactions, but their pathophysiologic effect on hemostasis remains to be elucidated.

TISSUE FACTOR IN CIRCULATING BLOOD

Venous thromboembolism results from an imbalance between procoagulant, anticoagulant, and fibrinolytic activity. Tissue factor, which is abundantly present in the adventitia of blood vessels, plays a crucial role in coagulation (1). Upon injury, such as the rupture of atherosclerotic plaques, tissue factor exposed to the circulation and associated with factor VIIa initiates formation of traces of thrombin, leading to a burst of thrombin activity and to coagulation (2). However, this model cannot explain intravascular thrombosis in the absence of vessel wall injury.

In 1999, Giesen et al. (3) demonstrated that superfusion with leukocytes of a surface consisting of activated platelets resulted in deposition of tissue factor on the platelet surface. Deposition of tissue factor on growing thrombi by (activated) circulating monocytes could explain triggering of the coagulation cascade at the surface of negatively charged platelets in the absence of vascular injury. Tissue factor is present on monocytes in a shielded manner but is exposed on transfer to activated platelets, where it triggers thrombin generation (4).

PHYSIOLOGY OF TISSUE FACTOR

Experimental animal studies with high-resolution online videomicroscopy have revealed that early accumulation of tissue factor on platelet-rich thrombi is mediated by circulating microparticles and occurs faster than expected on the basis of leukocyte recruitment on adherent platelets. Microparticles, which carry the ligand for P-selectin, PSGL-1, rapidly adhere to P-selectin expressed by activated platelets on the surface of a growing thrombus (5–8). Muller et al. (9) have reported that most of the tissue factor in plasma is associated with circulating microparticles and that it is present on the surface of activated platelets. In addition, neutrophil-secreted oxygen radicals appear to participate in tissue factor decryption.

These observations link to inflammation but do not establish a pathogenetic role of inflammation in venous thromboembolism. However, in one study (10), carotid artery ligation caused hypoxia–induced activation of vascular endothelium and rapid rosette formation of monocytes and platelets adhering to endothelium. Rosette formation was accompanied by tissue factor release and fibrin formation on the endothelium, supported activated smooth muscle cell migration, and contributed to neointima formation. Similarly, the functional interplay between endothelium, inflammatory cells, and platelets may lead to coagulation. Furthermore, inflammatory mediators, such as endotoxin, tumor necrosis factor-alpha, and interleukin 1-alpha, induce tissue factor, primarily on monocytes/macrophages, and thereby stimulate coagulation (11).

CIRCULATING MICROPARTICLES AND INFLAMMATION

Platelet–endothelial interactions depend on expression of platelet P-selectin (12), whereas it is unclear to what extent they depend on endothelial cell- and/or leukocyte-derived microparticles. Microparticles are considered to be markers of ongoing or recent endothelial cell and platelet activation (13), but it is unclear whether elevated levels constitute an enhanced risk for thrombosis. Indeed, microparticles also may express anticoagulant activity by elevating levels of activated protein C (14). Nevertheless, platelet, leukocyte, and endothelial microparticles have been shown to activate or modulate interactions between their parent cells and to contribute to tissue factor induction (13).

CAUSAL RELATIONSHIP

In this issue of the Journal, Chirinos et al. (15) investigate the relationship between established pulmonary embolism or deep vein thrombosis and inflammation, as reflected by the concentration of microparticles in plasma. These authors

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have complemented their microparticle assessment with the measurement of selected sets of conjugates between microparticles and leukocytes and between platelets and leukocytes. The strong correlation between platelet-leukocyte conjugates and the degree of leukocyte activation, measured by CD11b elevation, identifies a link between inflammation and platelet activation in venous thromboembolism patients. This link may be related to the observed increased levels of microparticles. In addition, conjugates between platelets and monocytes have a higher inflammatory potential on endothelium than free monocytes (16). To establish to what extent microparticles are markers of ongoing inflammation and contribute to venous thromboembolism by enhancing ongoing inflammation, additional relationships need to be investigated.

It remains to be shown whether increased microparticle levels in plasma during inflammation predispose to venous thromboembolism, as suggested by the demonstration by Chirinos et al. (15) that the level of microparticles, which can up-regulate tissue factor, is elevated in patients with venous thromboembolism.

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