Editorial Focus

Tissue factor-positive microparticles in blood associated with coagulopathy in cancer

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Thrombotic events are the major complication in cancer patients, which contribute significantly to the patients' morbidity and mortality. Upregulation of tissue factor (TF), the primary initiator of blood coagulation, on malignant tumors is associated with hypercoagulability, tumor angiogenesis and progression. Blood-borne TF is mostly present on the surface of circulating microparticles (MPs) (1, 2) and has been described to increase the systemic hypercoagulability in cancer patients (3). In this issue of *Thrombosis and Haemostasis*, Hron et al. describe an approximately two-fold increase in TF-positive MPs, that was associated with a four-fold increase in D-dimer level in the blood of Duke's D colorectal cancer patients compared to tumor-free healthy age- and sex-matched controls (4). Surprisingly, the increase in TF-positive MPs seen in the circulating blood of these patients was attributed to MPs, which were mainly derived from platelets and – in trend – leukocytes.

As mentioned by the authors, the increased level of platelet-derived TF-positive MPs may relate either to TF originally synthesized by other cells and, then, transferred to platelets or to a higher proportion of TF-positive platelets that release MPs into the blood of cancer patients. Previous studies have documented TF-positive MPs obtained from monocytic cells to adhere and bind to activated platelets (5). Thus, TF present on activated platelets might be acquired from other primary cell sources by fusion of MPs with the platelet surface membrane (6) and, possibly, be re-shedded from the platelet surface in response to further platelet activation. On the other hand, platelets themselves have been demonstrated to store small amounts of TF in α -granules and to release TF-positive MPs, which can increase the blood TF activity (2). In a recent study, quiescent human platelets were reported to contain TF-pre-mRNA and, in response to platelet activation, to splice the intronic-rich message into mature mRNA, leading to de-novo synthesis of full-length TF protein in platelets (7). Whether the splicing of platelet TF-pre-mRNA is altered in patients suffering from malignant tumors is not known yet.

As discussed above, one needs to keep in mind that the mere presence of platelet antigens on TF-positive MPs circulating in blood does not allow further conclusions on the definitive primary source of TF. It is of interest whether TF-expressing tumor or epithelial cells may contribute to the pool of TF-positive MPs as here described to be present in the blood of patients with cancer. Although alternatively spliced tissue factor was reported to be expressed in human carcinoma cells (8), in-vivo experiments revealed shedding of TF-positive MPs rather than soluble alternatively spliced TF to be the main source of TF released from human cancer cells (9).

As reported by Hron et al. in this issue of *Thrombosis and Haemostasis* (see article beginning on page 119), the amount of TF-positive MPs was significantly correlated with plasma D-dimer levels (4). More interestingly, this correlation was mainly due to the TF-positive MPs derived from platelets. D-dimer is a very sensitive marker for an activation of the coagulation system and strongly predicts venous thromboembolic events in cancer patients. The positive correlation between TF-positive MPs and D-dimer levels led to the challenging assumption that TF-positive MPs, especially when derived from platelets, may have a role in the hypercoagulopathy of cancer patients. It should be stressed that the presence of TF on cellular surfaces does not necessarily mean TF to be functionally active. TF on MPs was documented to originally have a rather low procoagulant activity that becomes markedly increased when MPs interact with cells (10). Recent findings point to an allosteric disulfide bond that forms between two cysteines present in the proximal fibronectin type III domain of the extracellular part of the TF molecule. The formation of this disulfide bond seems to be involved in conformational changes of the TF molecule, possibly enabling the binding of factor X to TF followed by enzymatic activation of the TF protein (11). Nevertheless, MP-mediated coagulation can also occur via TF-independent pathways. Until TF activity has not directly been measured, further studies on the functional properties of TF-positive MPs with a focus on their respective cellular source are of great interest to gain additional insight into the pathophysiology of tumor-associated hypercoagulopathy.

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