Editorial

Novel Mechanism of Cancer Thrombosis Induced by Microvesicles

Keith R. McCrae

Microvesicles consist of a heterogeneous array of cell-derived vesicles of different origins. A subset of microvesicles, termed microparticles, are derived from budding from cell surfaces, whereas the smaller exosomes are released from the endosomal compartment through specific cellular transport mechanisms.[1–3] All cells, both nontransformed and malignant, release microvesicles, with increased numbers released in response to inflammatory stimuli, apoptosis, and other sources of cellular stress. Though the enumeration of microvesicles in plasma remains challenging,[4] plasma microvesicle concentrations are thought to range from 10^7 to 10^{11}/mL.

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Although microvesicles mediate many biological effects, there has been great interest in their role in thrombotic disease.[5] Because thrombosis is a common complication in patients with cancer,[6] cancer-associated thrombosis (CAT) has been a productive area in which to study the prothrombotic activity of microvesicles. Several studies have investigated the prothrombotic mechanisms of microvesicles derived from cancer cells and patients with cancer, many focusing on the role of tissue factor (TF).[7] Some studies have identified a correlation between the expression of TF by microvesicles from cancer patients and the development of clinical thrombosis.[8–10] However, though these correlations seem to be significant in the case of pancreatic cancer, they have not been confirmed in other cancer types.[11] Indeed, the mechanisms by which microvesicles promote cancer thrombosis remains incompletely understood.

In this issue of *ATVB*, Stark et al[12] examine the mechanisms by which pancreatic cancer cell–derived microvesicles (pcMV) induce thrombosis in mice. This elegant study, performed using an inferior vena cava flow restriction model and strains of genetically engineered mice lacking GP1bα (glycoprotein1bα) or expressing reduced levels of TF, suggests a novel pathway through which pcMV induce thrombosis. Importantly, the mechanism suggested by these studies differs substantially from that thought to underlie nonmalignant venous thrombosis (Figure). The key findings of this report are as follows: (1) pcMV-derived TF is not sufficient to induce robust clot formation, (2) additional TF provided by the vessel wall, presumably from activated endothelial cells, synergizes with pcMV TF to promote thrombosis, (3) neither platelets nor myeloid leukocytes are needed for thrombus formation induced by pcMV, (4) despite the requirement for host TF, pcMV drive the composition of the thrombus, which differs dramatically from that observed in nonmalignant DVT, consisting primarily of fibrin and being largely devoid of leukocytes and platelets, (5) a major contribution to the procoagulant activity of pcMV is provided by phosphatidylethanolamine, which supports robust generation of FXa; this activity is inhibited by duramycin, a tetracycline antibiotic that binds phosphatidylethanolamine with high affinity and specificity,[13] and (6) duramycin also inhibits pcMV-induced thrombus formation in vivo; enoxaparin was most effective in this regard, whereas dabigatran, a direct thrombin inhibitor, was less so.

This interesting study provides new information concerning the pathogenesis of CAT, but at the same time raises important questions. First, Stark et al[12] only studied microvesicles derived from pancreatic cancer cells; pancreatic cancer is the most prothrombotic of malignancies and, therefore, more likely to involve unique and potent mechanisms of thrombus development. Yet, the problem of CAT is not limited to pancreatic cancer. Most cancers are associated with an increased risk of thrombotic events, though some less than others, as reflected in clinical scoring systems.[14,15] Moreover, microvesicles from other cancer types have been reported to induce thrombosis through many other mechanisms; for example, prostate cancer–derived microvesicles may stimulate thrombus development, at least in part, through a Factor XII–dependent pathway.[16] Moreover, others have raised the concern that injection of exogenous microvesicles, as in the study by Stark et al,[12] may lead to peak microvesicle levels in blood that are substantially higher than those detected in tumor-bearing mice, suggesting that performing studies similar to the study by Stark et al[12] in which the source of microvesicles is an endogenous tumor should be considered.[11] Although these concerns do not detract from the important observations in this report, they illustrate the fact that additional work is needed to better understand the role of microvesicles in CAT and to define prothrombotic mechanisms of microvesicles from different types of cancers, potentially leading to customized antithrombotic approaches.

These studies also raise interesting questions on a clinical level concerning optimal methods for prediction, prevention, and treatment of CAT. Clinical scoring systems[14,17] and current guidelines[6] suggest that patients with malignancies associated with high thrombotic risk should receive prophylactic anticoagulation, particularly while undergoing therapy. However, while important, the specificity of these scoring systems needs improvement, particularly when

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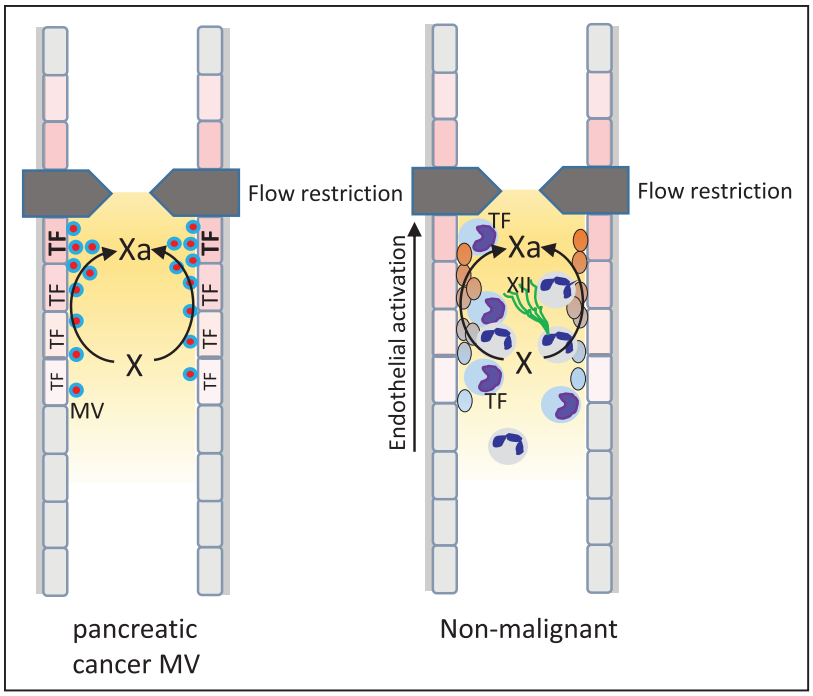

Figure. Differing mechanisms of thrombosis in pancreatic cancer and nonmalignant thrombosis. In pancreatic cancer (left image), microvesicles (MV) bind to the vessel wall, and along with stasis promote tissue factor (TF) expression. In addition to tissue factor (red), MV expose PE (phosphatidylethanolamine; represented by blue rim). Together, MV and vessel wall TF and MV PE support rapid thrombin generation and fibrin formation (represented by gold background) independently of platelets and leukocytes. In nonmalignant thrombosis (right image), endothelial activation leads to binding of platelets, which become activated (represented by color change from blue to orange). Myeloid leukocytes are then recruited to bind platelets and the vessel wall in a P-selectin and GPIbα-dependent manner. Monocytes then contribute TF to promote Factor X activation via the extrinsic pathway, whereas neutrophils release neutrophil extracellular traps (green) to promote Factor XII/intrinsic pathway activation.

applied to individuals with intermediate thrombotic risk tumors, for example, colorectal cancers. Confirmation of the mechanisms identified by Stark et al[12] in clinical samples, and correlation of these mechanisms with patient outcomes may lead to development of better biomarkers for CAT prediction. In terms of therapy for CAT, the report by Stark et al[12] confirms the observation that low–molecular weight heparins are effective for prevention and treatment of CAT.[18,19] However, although dabigatran was less effective than heparin in the model used in these studies, emerging data suggest that oral Factor Xa inhibitors such as rivaroxaban and apixaban may perhaps be even more effective and better tolerated in patients with CAT than low molecular weight heparin.[20,21] It would therefore be of interest to examine directly the efficacy of oral Factor Xa inhibitors in the model described in this article.

Finally, a role for microvesicles in other thrombotic disorders such as hemolytic anemia, heparin-induced thrombocytopenia, antiphospholipid syndrome, and others has been proposed. The properties of microvesicles that circulate in these disorders compared with those in cancer have not been defined, and whether these microvesicles induce thrombosis via a cancer versus a nonmalignant pathway would be of great interest and potentially clinical importance.

Disclosures

None.

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