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TUMOR CELL/VASCULAR CELL INTERACTIONS

MELANOMA-DERIVED EXTRACELLULAR VESICLES DRIVE VON WILLEBRAND FACTOR–DEPENDENT THROMBOSIS AND METASTASIS

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Cancer-associated thrombosis (CAT) is a major complication of malignancy and is closely linked to tumor progression and metastasis. Tumor-derived extracellular vesicles (EVs), particularly those expressing tissue factor (TF), have been implicated in procoagulant activity, yet the mechanisms by which circulating EVs interact with the vascular hemostatic system remain incompletely defined. In this study, we investigated whether melanoma-derived EVs promote thrombosis through interactions with von Willebrand factor (vWF) under flow conditions. Using microfluidic assays that mimic a tumor-activated vascular environment, we demonstrate that shear-activated vWF functions as a size-selective molecular filter that preferentially captures objects smaller than ~4 µm, including platelets and tumor-derived EVs, while excluding larger cells. Although intact tumor cells do not directly bind vWF under physiological flow, the coordinated binding of EVs and platelets to extended vWF promotes platelet aggregation and the formation of platelet-rich microthrombi under flow, leading to the entrapment of circulating tumor cells within thrombi and fostering metastatic dissemination. These findings reveal a previously unrecognized mechanism by which melanoma-derived EVs couple endothelial activation, thrombosis, and metastatic dissemination via vWF-dependent interactions. Targeting ULvWF formation or EV–vWF binding may therefore represent a novel strategy to reduce cancer-associated thrombosis and limit metastatic progression.