Binding Of Extracellular Vesicles To Stretched Von Willebrand Factor Promotes Thrombosis

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Abstract

Background, Objective

Extracellular vesicles (EVs) released by tumor cells are being investigated as potential circulating biomarkers for cancer detection. EVs (size range 40-5000 nm) are cell-derived membrane-bound vesicles with heterogenous contents, including genetic materials, proteins, lipids and small metabolites. Tissue factor–positive (TF)-EVs are considered as biomarkers predicting tumor progression. They were also shown to enhance cancer-associated thrombosis and to be linked to elevated plasma levels of von Willebrand factor (vWF). VWF is a large multimeric glycoprotein promoting platelet aggregation. This study aimed to investigate whether circulating melanoma cells derived TF-EVs can bind to ultra-large vWF (ULvWF) to promote thrombosis.

Methods

Binding of melanoma cell-derived EVs or melanoma cells to ultra-large vWF (ULvWF) and subsequent thrombosis formation was investigated by microfluidic experiments. To this end, microfluidic channels coated with human umbilical vein endothelial cells or vWF were perfused with whole human blood supplemented with purified and fluorescently labeled EVs. EVs were characterized by nanoparticle tracking analysis, flow cytometry, and fluorescence microscopy. The expression of TF on different melanoma cells and melanoma cell-derived EVs was studied by fluorescence microscopy.

Results

VWF exhibited size-selectivity, preferentially binding EVs smaller than 400 nm, while larger EVs and intact melanoma cells failed to adhere to vWF fibers. HS expression on the EV surface was critical for vWF binding, as HS-deficient EVs exhibited significantly reduced adhesion. Functional assays revealed that TF-EVs activated platelets and facilitated microthrombus formation. Although melanoma cells did not directly interact with vWF, they became entrapped within platelet-rich microthrombi, suggesting a potential mechanism for tumor metastasis.

Conclusion

Our findings demonstrate that vWF functions as a shear-sensitive scaffold that selectively recruits small EVs and platelets, contributing to coagulation and thrombosis formation. The formation of EV-vWF-platelet aggregates may serve as a biomarker for hypercoagulation, while therapeutic disruption of this interaction could provide a novel strategy to prevent pathological thrombosis and metastasis.

Do you have any conflicts of interest?

No, I do not have a conflict of interest.