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TUMOR CELL/VASCULAR CELL INTERACTIONS

VON WILLEBRAND FACTOR PREDICTS POOR OUTCOME IN PANCREATIC CANCER AND MEDIATES TUMOR-ENDOTHELIUM INTERACTIONS FACILITATING METASTASIS

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Introduction. Pancreatic ductal adenocarcinoma (PDAC) is an aggressive malignancy characterized by chemotherapy resistance, early metastatic spread and a strong prothrombotic phenotype. Previously, we reported that breast cancer cells induce endothelial cell (EC) activation and rapid von Willebrand Factor (VWF) release, thereby promoting tumor progression, we want to investigate the mechanistic role of VWF in driving PDAC metastasis. Elevated VWF levels have been associated with increased thrombotic risk and metastatic disease, and yet its role in PDAC remains poorly defined.

Aim. To elucidate the pro-tumorigenic role of VWF in PDAC progression and metastatic dissemination.

Materials and Methods. Plasma VWF antigen (VWF:Ag) levels were measured in treatment-naïve PDAC patients and correlated with survival. Interactions between VWF and PDAC cell lines (PANC1, BxPC3) were assessed by flow cytometry, immunofluorescence and microfluidic endothelial adhesion assays. VWF-induced signaling was examined using qPCR, proliferation, migration and invasion assays.

Results. PDAC patients exhibited 2.5-fold higher plasma VWF:Ag levels than healthy controls (253±147 vs 106±25 IU/dL, p<0.001), which associated with reduced survival. Crosstalk between tumor cells and ECs was evident as conditioned media from PANC1 and BxPC3 cells induced a 4-fold increase in VWF secretion from ECs. This activation was mediated by BxPC3-expressed VEGF-A, but VEGF-A-independent for PANC1. To unravel the role of VWF in metastasis under static and venous flow conditions. Under static tube-based binding conditions, PANC1 adhered to VWF, while BxPC3 showed minimal binding. Caplacizumab, a nanobody targeting the VWF A1-domain, reduced PANC1-VWF binding by 52%, indicating a role for the A1 domain in mediating PDAC adhesion. Under venous flow conditions, PANC1 adhesion to activated ECs was markedly reduced by anti-VWF treatment (38.1±23.5 vs 7.7±6.0 cells/mm[^]2[/^], p<0.01). In contrast, BxPC3 adhesion was VWF-independent but required integrin-mediated interactions. Furthermore, treatment of PANC1 with 50nM VWF significantly increased proliferation (1.25-fold), migration (2.4-fold) and invasion (2.3--fold).

Conclusions. Elevated plasma VWF levels associated with poor survival in PDAC. VWF may contribute to metastatic dissemination via tumor cells capture under flow and supporting invasive tumor cell behavior. This highlights VWF as a potential therapeutic target in PDAC.