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Extracellular Vesicles as biomarkers for cancer progression and cancer associated VTE

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Microvesicles (MVs) represent a subgroup of extracellular vesicles (EVs) emerging from various cells by blebbing of their outer membrane. Therefore, they share features such as membrane composition and antigenicity with their parental cells. Released by many immune and tumor cells, MVs act as intercellular messengers, account for horizontal gene transfer and can activate the coagulation system. With the aim to investigate their relevance for tumor cell biology, we characterized MVs released by human tumor cell lines of various origins in the absence or presence of TNF-a. After stimulation, we used the combination of low and high-speed centrifugation to enrich MVs from cell culture supernatants. We analyzed the presentation of phosphatidylserine (PS) and tissue factor (TF) activity on the cell surface and investigated their potency to induce tumor cell migration. In all tumor cell lines, TNF-a stimulation enhanced the release of MVs.

While the expression of PS was universally increased, an elevated activity of procoagulant TF could be detected on MVs from lung, pancreatic, and colon carcinoma, but not from breast and ovarian cancer cell lines. Functionally, TNF-a stimulation significantly increased the potency of MVs to induce tumor cell migration. In conclusion, inflammatory conditions promote the release of MVs with increased procoagulant activity from tumor cell lines in vitro. PS-containing and TF-expressing MVs may account for systemic activation of the coagulation system as seen in cancer patients and, since they induce tumor cell migration, they may serve as biomarkers for tumor progression. Publication: Cell Biology International 2018

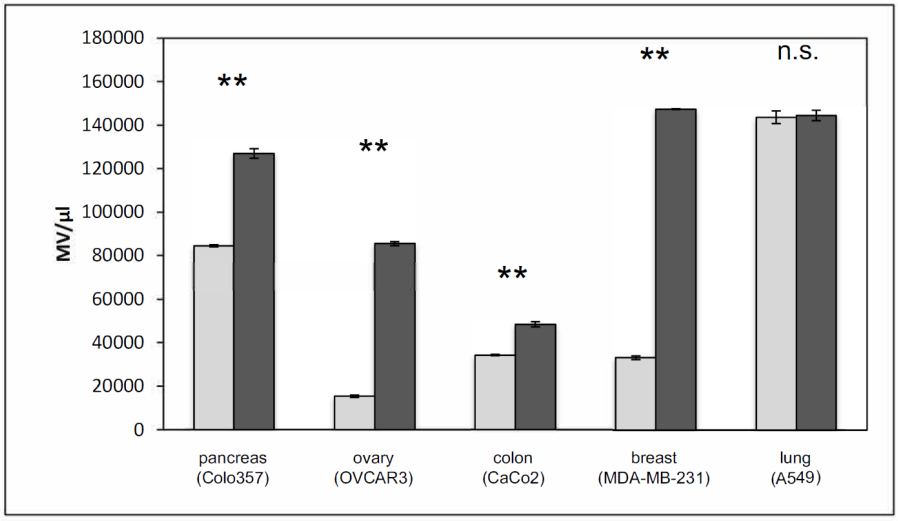

Figure 1: TF activity of tumor cell-derived MVs: With the Zymuphen MP-TF activity assay with the purified MVs, we measured the procoagulant activity of the MVs exposing TF on their surface. The substrate turnover of factor Xa is directly correlated to the amount of active TF present on the MVs, derived from unstimulated (light gray columns) or TNF-a-stimulated (dark gray columns) tumor cell lines. The amount of active TF is expressed in pg per 106 MVs. Values shown are the mean SD; n 1⁄4 4 per group; indicates significant differences between unstimulated and stimulated treatment groups, P < 0.01, P < 0.001.