

# The emerging role of extracellular vesicles in clinical research inflammation, cancer progression, metastasis

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The role of extracellular vesicles (EVs) in intercellular communication is being increasingly recognized in clinical research. Being shed from cells in an evolutionarily conserved manner, EVs transfer mediators from different biomolecule categories involving them in inflammation, maintenance of homeostasis, regulation of physiological functions, and the process of horizontal gene transfer. Based on their mechanism of cellular formation, size and cargo, EVs can be subdivided into exosomes, microvesicles (MVs), and bigger vesicles, such as oncosomes and apoptotic bodies. In contrast to exosomes, MVs are released by blebbing of the outer cellular membrane, thus sharing antigenicity with their cellular origin. MVs often express tissue factor (TF) and hence, potentially activate the extrinsic pathway of the coagulation cascade. Moreover, TF+MVs induce cellular responses via the PAR2/G protein/ERK pathway, involving them in inflammation, cancer progression and metastatic spreading. In collaboration with several clinics of the UKSH, we are investigating the role of MVs in disease processes and their potential use as biomarkers, in particular (I) the characterization of MVs found in ascites of patients with ovarian carcinoma as markers for cancer progression and thrombosis (gynecology), (II) the suitability of urinary MVs from patients with bladder carcinoma as biomarkers for disease recurrence or progression (urology), (III) the importance of platelet-derived MVs from patients with head and neck tumors functioning as shuttle for clinically relevant biomolecules (e.g. PD-1, PD-L1) (otorhinolaryngology), (IV) the therapeutic and prognostic relevance of TF+MVs as PAR2/G protein activators and GPCR antibodies in rheumatic diseases (rheumatology). Purification of MVs from various body fluids is performed using sequential centrifugation steps; we have established an innovative purification method using annexin-V-coated magnetic beads. Detection, size determination and quantification of MVs are done by high-resolution flow

cytometry and electron microscopy (SEM). MVs are characterized biochemically including their exposure of PS, expression of active TF, activation of the extrinsic TENase, as well as PAR2/Gprotein/ERK signaling and, downstream, induction of tumor cell migration as surrogate parameter for their metastatic potency. We plan to establish a translational research network at the UKSH on the emerging role of EVs in various diseases including cancer, and their interaction with inflammatory processes.