ImmunoTools *special* Award 2015

Julia Gross, PhD

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Signaling mechanisms of Extracellular vesicles in tumor progression

During tumor progression malignant cells undergo several steps of transformation, which enable them to detach from tumor site, invade and colonize distinct tissues. This also involves the crosstalk between tumor cells, with the immune system, their source and target tissues. Most cell types secrete extracellular vesicles (EVs), a heterogenous population of membrane particles, named according to their size and origin, as microvesicles (MVs) (250-1000 nm) or exosomes (50-100 nm).

Exosomes are derived from endosomal compartments, namely multivesicular bodies, while microvesicles are considered to stem from the plasma membrane by outward budding. These membrane particles carry a wide range of structural proteins on their surface and have been shown to contain mRNA, miRNA and bioactive lipids. Functionally, they have been described as a specific form of inter/extracellular communication: (1) Tumor cell-derived EVs prime metastatic sites for incoming tumor stem cells (*Peinado et al. 2012*). (2) EVs are modulators of the immune system by communicating between dendritic cells and B-cells (*Zeelenberg et al. 2008*). Specific protein markers for MVs (CD147) and exosomes (CD9, CD63) have been identified. We have shown recently that one type of small EVs (50-100 nm), called exosomes, carry Wnt proteins on their surface, which enables them to induce Wnt signaling activity on target cells. Together with its cargo-receptor Evi, Wnt proteins are sorted via endosomal compartments onto exosomes, a process that depends on ESCRT proteins (HGS and TSG101) and the R-SNARE Ykt6 (*Gross et al. 2012*). In addition, more and more evidences is emerging that a variety of different signaling molecules are secreted on EVs from their sending cells, such as proteins from the Delta-like, TGFbeta and Hedgehog family (*Webber et al. 2015, Vyas et al. 2014*).

In addition, we found that tumor-derived EVs induce Wnt5a expression in macrophages and subsequently the protein itself is sorted and secreted in a feedback loop onto EVs, enhancing migration and invasiveness of tumor cells (*Menck et al. 2013*). Functionally, the divers effects that EVs have on their neigbouring cells are only beginning to emerge and the mechanisms regulating EV release and trafficking of signaling molecules onto EVs are insufficently understood. Is the same machinery responsible for MV and exosomes packging?

We want to understand how tumor cells crosstalk with their microenvironment and release signaling molecules on EVs leading to increased migration and invasion. We will use the ImmunoTools antibodies to analyze different EV populations by direct cell sorting (MV) or a bead-based sorting approach (Exosomes). ImmunoTools ELISA reagents will be used to monitor and quantify release of EV and cytokines from tumor cells and the recombinant proteins will be used to trigger EV release from tumor cells and to functionally test different signaling reporters.

ImmunoTools *special* AWARD for **Julia Gross** includes 25 reagents

FITC - conjugated anti-human CD9, CD18, CD29, CD63, CD147, Control-IgG1

APC - conjugated anti-human CD9, CD63, CD147, Control-IgG1

recombinant human cytokines: rh BMP-2, rh EGF, rh HGF, rh IL-6, rh MCP-1 / CCL2, rh MIP-3a / CCL20, rh PDGF-AA, rh PF4 / CXCL4, rh SHH, rh TGF-beta3, rh TNFα

human ELISA-set for 96 wells, human IL-6, human sCD147 (sEMMPRIN), (each 3 reagents)

DETAILS more AWARDS