Short title: Exosomes in pancreatic cancer evolution and metastasis

Tumor cells extensively communicate with their environment to facilitate tumor progression and to prepare metastatic niches. Recent work has established exosomes as an important means of intercellular communication. Exosomes are extracellular nanovesicles (30-150 nm) of endosomal origin secreted into all body fluids. They shuttle proteins, lipids, DNA, mRNA or microRNAs from one cell to another to modify and educate recipient cells. There is increasing evidence that tumor cells release excessive amounts of exosomes to influence carcinogenesis, growth, progression, metastasis and drug resistance. In pancreatic ductal adenocarcinoma (PDAC) exosomes have recently emerged as an important feature to shape the pre-metastatic niche in the liver. Exosomes may also represent promising biomarkers for cancer diagnosis and new targets for cancer therapy. Exosomal microRNAs are known to enhance invasiveness, drug resistance, modulate immune response and cross-talk of PDACs to pancreatic stellate cells. Thus, modulating tumor exosome secretion and exosome cargo signatures could be an interesting approach to control PDAC carcinogenesis, progression and metastasis. To this end, we have recently identified a novel major regulator of exosome secretion in PDAC (Eiseler and Seufferlein, unpublished data).

Scientific objectives: It will be the objective of the PhD student to investigate how modulation of exosome release from PDAC cells affects carcinogenesis, tumor progression and metastasis. **Aim 1: Exosomes in tumor growth and metastasis.** We will examine regulation of exosome release and content to modulate tumor growth and metastasis of PDAC cells. We will isolate exosomes from cell culture supernatants to evaluate their protein content and microRNA populations and correlate phenotypes with identified targets. **Aim 2: Exosomes in PDAC carcinogenesis and evolution.** To define the role of exosomes during PDAC carcinogenesis and progression we will use established PDAC mouse models w/wo pancreas-specific knockout of the newly identified exosome regulator to investigate whether injection of purified exosomes will accelerate carcinogenesis, tumor progression and metastasis. In a reverse approach, mice with enhanced exosome secretion will be injected with an inhibitor of exosome release (GW 4869). **Aim 3: Exosomes in the regulation of chemoresistance during palliative treatment of patients.** We will isolate exosomes from blood of PDAC patients during palliative treatment to evaluate whether exosomal microRNA content can be correlated with resistance towards chemotherapy. We will further study whether exosomes from chemorefractory PDAC cells lines transfer resistance to human pancreatic stellate cells or other tumor cells. These experiments will also be also performed with patient exosomes upon tumor progression.