Title: Exosomes released by highly migratory premalignant lung epithelial cells facilitate epithelial-mesenchymal transition and migration of unselected slow migratory cells

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Abstract:

Non-small cell lung cancer (NSCLC) recurs in 30%-55% of patients, and the metastatic process occurs early in the development of the disease. Exosomes are cell-derived nanovesicles that have the ability to induce a process called epithelial-mesenchymal transition (EMT), which may be involved in the development of field cancerization. Thus, we propose that using exosome-based liquid biopsy has the potential to identify early metastases in NSCLC.

We used human bronchial epithelial cells (HBEC) that exhibit activated Kras-G12D and p53 knockdown, representing a state of premalignancy. Using a novel "constricted migration"-based selection method, we have identified a distinct subgroup of premalignant, high-risk HBECs (highly motile or HM) that exhibit exceptional mobility both in vitro and in vivo. Thereby providing a distinctive platform for investigating premalignant cell migration and early metastasis. Exosomes derived from HM-HBECs have unique molecular characteristics and induce the unselected (UN or low migratory)-HBECs to acquire an HM phenotype characterized by heightened EMT, accelerated migration, and augmented invasive potential in vitro.

We used Surface-enhanced Raman spectroscopy (SERS) to derive exosomal spectroscopic signals to distinguish between HM-HBEC and UN-HBEC exosomal signatures. Then, we used machine learning (ML)-based approaches to differentiate the Raman fingerprints of HM and UN exosomes. These fingerprints were then integrated into a training dataset and evaluated using ML to assess their distinguishability, resulting in a high accuracy of over 85% for separating the two datasets. We are now in the process of enlarging our training dataset and optimizing the hyperparameters to train the ML model using human pleural effusion (metastatic)-derived exosomes. ML-based spectroscopic analysis has the potential to aid in the early detection and interception of metastatic lung cancer.