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"Imaging the metastatic potential of single tumor cells in lung adenocarcinoma"

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Lung cancer is one of the leading causes of cancer-related death among men and women. Like most cancers, death in patients with lung cancer is primarily due to metastasis. Metastasis is the final step of neoplastic progression and remains the primary cause of death from lung tumors. Determining the metastatic proclivity of a tumor at the cellular level is a major challenge because of heterogeneity of the primary tumor. Molecular imaging aims to non-invasively visualize, characterize and quantify normal and pathologic processes within the living organism at the cellular and subcellular level. Although there are several technologies approved/ in the pipeline that allows for molecular imaging of metastasis, one of the most important unmet needs is whether such imaging can assess the metastatic potential of tumors. Like all predictive endeavors, the imaging of such "potential" is a daunting task, but one that only molecular imaging—rather than standard, anatomic techniques—is likely to solve. Although difficult, imaging of metastatic potential is also arguably the most important task for molecular imaging of cancer because it is generally the dissemination of malignant tissue, not its prolonged residence in an inopportune site, which kills the patient. At a molecular level, metastatic progression of lung cancer despite targeted therapy against disease-driving mutations is a complex, multireceptor driven event. Despite the advances made in the past decades, prognostication and risk stratification of patients into those who should receive chemotherapy remains challenging. Thus, the quest for the Holy Grail in biomarkers of metastatic potential continues. Recently, a multi-modular signal transducer, GIV [Gα-Interacting Vesicle-associated protein; aka Girdin] has been defined as a *bona fide* metastasis-related protein across a variety of solid tumors, including lung cancer. The molecular mechanism(s) that enables GIV to carry out its role during tumor invasion appear to be fundamental, i.e., its ability to enhance key pathways within the pro-metastatic signaling network that fuels several aspects (stem-ness, invasiveness, epithelial-messenchymal transition, anti-apoptotic signaling, chemoresistance) of the complex phenomenon of metastasis. In doing so, GIV serves as a 'total package' for supporting prometastatic phenotypes of tumor cells. Through the two aims proposed here we will evaluate the ability of GIV to predict the metastatic potential of lung cancer cells (within primary tumors or in circulation) before and during the emergence of macroscopic metastases. Our overall goal is to translate the wealth of our knowledge of GIV from the bench-top to the clinic, and unravel the potential of GIV to serve as a biomarker for assessing the metastatic potential of lung cancer at a single-cell level. Insights gained will serve as proof-of-concept that molecular imaging of GIV-dependent signaling is an effective prognostic tool for stratification of patients with lung cancer based on their metastatic potential.