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Mitochondria engage the Integrated Stress Response and RhoA GTPase signaling to support tumor progression

Metastasis of cancer cells to vital organs remains the leading cause of cancer related deaths, emphasizing a strong need for actionable targets in advanced stage cancer. To address this, we study novel dysregulated mitochondrial signaling mechanisms that cells utilize to metastasize. In this seminar, I will discuss the mechanisms by which the outer mitochondrial membrane protein Mitochondrial Rho GTPase 2 (MIRO2) promotes tumor cell invasion and metastasis. Our previous work identified higher MIRO2 mRNA expression in cancer vs. normal patient samples in a multitude of cancer types, which correlated with worse patient outcomes. Furthermore, we demonstrated that MIRO2 was critical for prostate cancer cell growth and survival in vitro and in vivo. Furthermore, using siRNA mediated knockdown (KD) of MIRO2 we find MIRO2 KD ubiquitously reduces tumor cell invasion in breast, melanoma, pancreatic, and prostate cancer cells. Utilizing metastatic prostate and breast cancer models, we demonstrate that mice injected with MIRO2 shRNA cells have significantly lower metastatic burden compared to mice injected with control shRNA cells. Network analysis of MIRO2's binding partners identified metabolism, cell cycle, and cellular responses to extracellular stimuli amongst the top over-represented pathways. At the mechanistic level, we identified 2 independent MIRO2 protein complexes that control either tumor growth or tumor cell invasion. These include the general control of amino acid synthesis (GCN1)-dependent integrated stress response, and the atypical myosin IXB (MYO9B) which inactivaties RhoA GTPase signaling. Taken together, we propose a novel signaling mechanism by which MIRO2 broadly promotes invasion and metastasis through GCN1 or MYO9B signaling pathways.