A novel role for MIRO2 in tumor cell invasion and metastasis. DP Boulton (Ph.D, GS), M Furnish, and MC Caino, Department of Pharmacology, University of Colorado | AMC.

Metastasis of cancer cells to distal 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 focus on how a mitochondrial protein—Mitochondrial Rho GTPase 2 (MIRO2)—promotes tumor cell invasion and metastasis through a negative regulation of RhoA. Our previous work identified higher MIRO2 mRNA expression in cancer vs. normal patient samples, which correlated with worse patient outcomes. Furthermore, in the context of prostate cancer we demonstrated that MIRO2 was critical for tumor growth *in vitro* and *in vivo*. However, it remains unknown if MIRO2 affects primary tumor growth or if this protein is important throughout tumor progression. Using siRNA-mediated knockdown (KD) of MIRO2 we clearly show that MIRO2 KD ubiquitously reduces tumor cell invasion in breast, melanoma, pancreatic, and prostate cancer cell lines. Preliminary experiments modeling late-stage metastasis showed that tail vein injection of PC3 cells stably expressing MIRO2 targeting shRNA had reduced kidney and liver metastatic burden. In further mechanistic studies, we identified novel MIRO2 binding partners and used siRNA to KD the top hits and observe changes in invasive capacity. We found that atypical myosin IX B (MYO9B) reduced the invasion of cells to the largest extent. MYO9B is known to control cell motility through spatially inactivating RhoA at the leading edge of migrating cells. Excitingly, MIRO2 KD showed an increase in active RhoA, phenocopying MYO9B KD. Lastly, in pilot experiments we found that dual KD of MIRO2 and RhoA rescued invasive capacity in comparison to MIRO2 KD alone. Overall, we propose a novel mechanism by which MIRO2 broadly promotes invasion and metastasis through MYO9B dependent inactivation of RhoA.