A novel MIRO2/MYO9B/RhoA signaling axis controls tumor cell invasion and metastasis

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Background

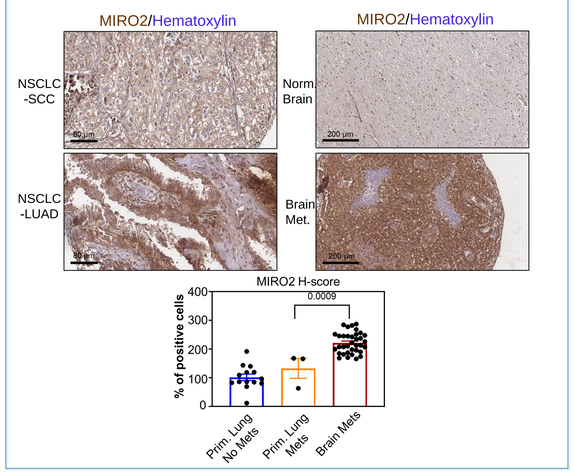
Metastasis of cancer cells to vital organs remains the leading cause of cancer related deaths, emphasizing a strong need for actionable targets in advanced stage cancer. To address this, we study novel dysregulated signaling mechanisms that cells utilize to metastasize. Here, we focus on how outer mitochondrial membrane protein—Mitochondrial Rho GTPase 2 (**MIRO2**)—promotes tumor cell invasion and metastasis through a negative regulation of RhoA. Our previous work demonstrated that MIRO2 was critical for prostate cancer cell growth and survival *in vitro* and *in vivo*. However, it remains unknown if MIRO2 only affects primary tumor growth or if this protein is important throughout tumor progression. 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. Mechanistically, we have identified a novel binding partner of MIRO2, atypical myosin IXB (**MYO9B**), and propose that this interaction is a main mechanism by which MIRO2 potentiates metastasis. MYO9B has a well-defined role in controlling cell motility via inactivation of RhoA. Excitingly, we have found 1) MIRO2 KD results in increased active RhoA, phenocopying MYO9B KD and 2) dual ablation of MIRO2 and RhoA fully rescues tumor cell invasion. Taken together, we propose a novel signaling mechanism by which MIRO2 broadly promotes invasion and metastasis through MYO9B dependent inactivation of RhoA. .

Hypothesis

MIRO2 promotes tumor cell invasion and metastasis through regulation of downstream effectors.

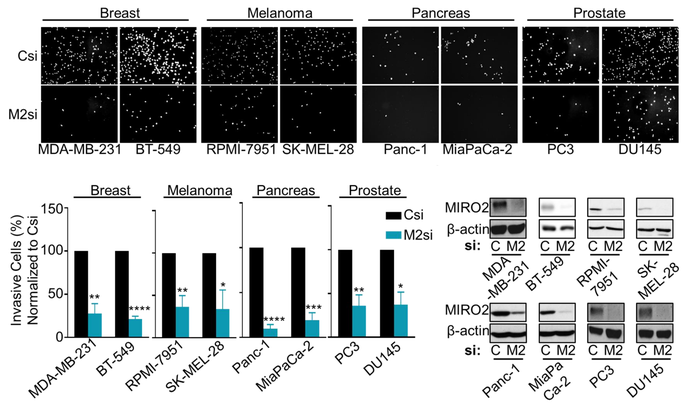
Results

Increased MIRO2 expression in metastases vs. primary tumors

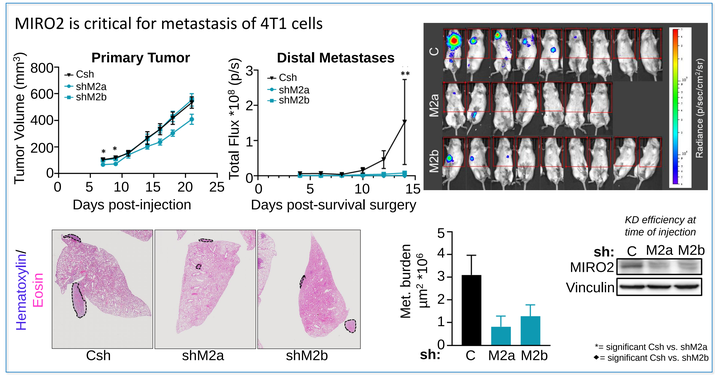


Results

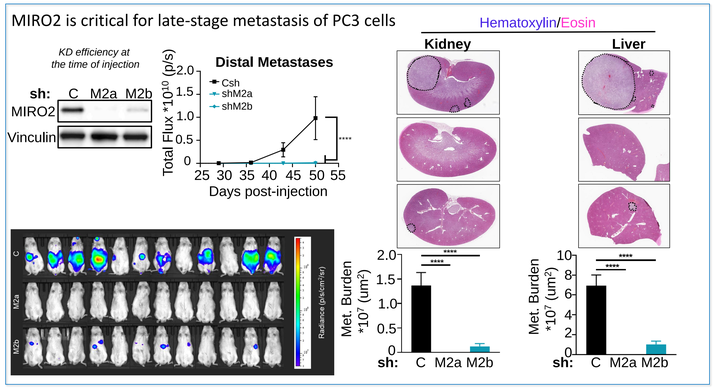
Loss of MIRO2 reduces invasive capacity across multiple tumor types



MIRO2 is critical for metastasis of 4T1 cells

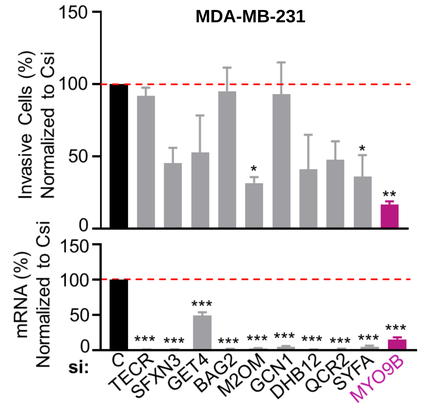


MIRO2 is critical for late-stage metastasis of PC3 cells

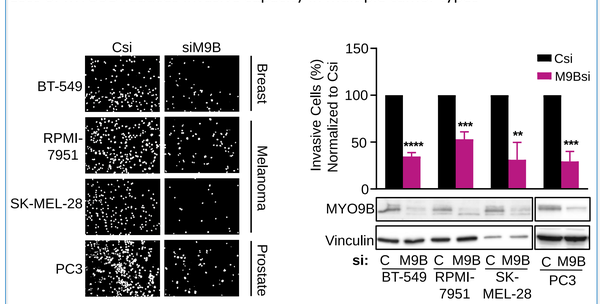


Results

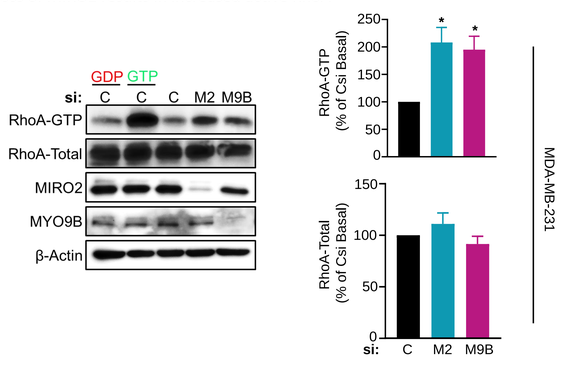
Of the top hits, MYO9B reduces invasive capacity to the greatest extent



Loss of MYO9B reduces invasive capacity in multiple tumor types

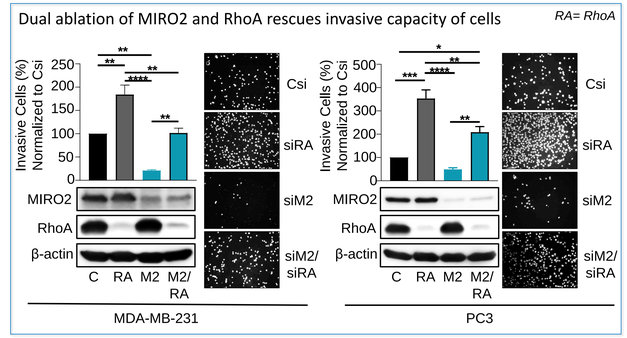


Loss of MIRO2 results in increased active RhoA

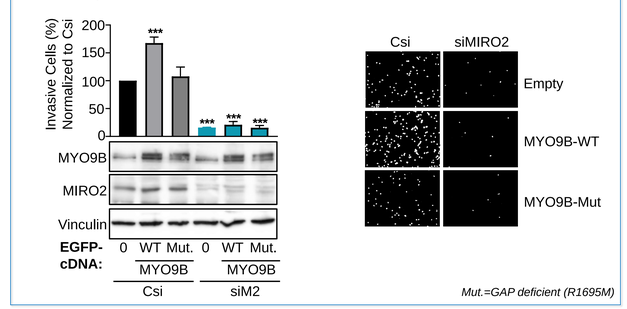


Results

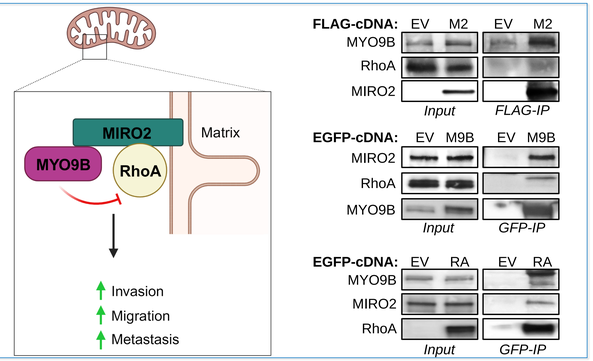
Dual ablation of MIRO2 and RhoA rescues invasive capacity of cells



MYO9B requires MIRO2 to drive tumor cell invasion



Model



Acknowledgements

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