Collateral Amplification of the PTHrP Gene Drives Pancreatic Cancer Growth and Metastasis and Reveals a New Therapeutic Vulnerability

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Background: Metastasis is the leading cause of cancer-related death in PDAC, yet very little is understood regarding the underlying biology. As a result, targeted therapies to inhibit metastasis are lacking. Whole-genome sequencing has established that the squamous/quasi-mesenchymal/basal-like PDAC subtype, which is characterized by its high metastatic proclivity, is annotated by *KRAS* gene amplification. Here, we report that the squamous lineage gene parathyroid hormone-related protein (PTHrP encoded by *PTHLH*) is located directly adjacent to *KRAS* and is co-amplified in metastatic PDAC patients.

Methods: We generated a novel mouse model whereby we deleted the cytokine *Pthlh* in KPCY tumor model. We further employed genetic deletion and pharmacological inhibition in orthotopic injection, tail vein metastasis assays, mouse hospital pre-clinical trials, and patient-derived 3D organoid models.

Results: *PTHLH* is co-amplified along with *KRAS* in TCGA, is enriched in metastatic patients from the COMPASS trial and correlates with significantly decreased survival in both cohorts. We generated KPCY-Pthlh^{CKO} mice and showed that they have significantly reduced primary and metastatic tumor burden and dramatically increased survival relative to KPCY controls. In parallel experiments, we treated mice with an anti-PTHrP monoclonal antibody, which similarly reduced primary and metastatic tumor growth. Finally, RNA-seq revealed a downstream mechanism whereby PTHrP facilitates entry into the metastatic cascade by inducing EMT. PTHrP loss abrogated EMT, resulting in a nearly complete elimination of disseminating cells. Thus, KPCY-Pthlh^{CKO} tumors are locked in a well-differentiated epithelial state and are unable to initiate the metastatic process.

Conclusions: This work demonstrates the importance of PTHrP signaling in PDAC metastasis, and future studies will look to translate anti-PTHrP antibodies into clinical trials. In a broader sense, we establish a new paradigm of collateral amplification, where an assumed passenger gene (*PTHLH*) is co-amplified along with an oncogene (*KRAS*) and endows the evolving tumor with an oncogenic and pro-metastatic phenotype.

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