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RABL6A-Myc Signaling Promotes Pancreatic Neuroendocrine Tumor Cell Proliferation and Survival

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BACKGROUND: New targeted therapies are needed for treating advanced pancreatic NETs (pNETs). RABL6A is required for pNET cell proliferation and survival, but how it functions is incompletely understood. We recently found RABL6A is required for Myc expression in islets and pNET cells, but the importance of Myc in mediating RABL6A oncogenic activity is unknown.

METHODS: The metastatic gene signature of patient pNETs and small bowel (sb) NETs was examined by RNAseq and Ingenuity Pathway Analysis. Molecular and biological effects of altered RABL6A expression was determined in cultured pNET cells. Exogenous Myc-ER was expressed to test Myc's ability to rescue the RABL6A loss phenotype. Tumor suppressive effects of inhibitors targeting Myc (JQ1, CPI203) and CDK4/6 (palbociclib), individually or combined, were measured in pNET cells and xenograft tumors.

RESULTS: Myc pathway activation was found to be the primary, unifying feature of increased RABL6A signaling in pNET and sbNET patient metastases. We explored the RABL6A dependency of Myc transcriptional activity and observed marked reduction of Myc target gene expression in RABL6A-deficient pNET cells. Expression of an estrogen receptor Myc fusion protein (Myc-ER) partially rescued the RABL6A knockdown phenotype by pushing G1 arrested cells into S phase, but it was not enough to enable mitosis and sustained proliferation in the absence of RABL6A. Notably, drugs targeting Myc (Bromodomain inhibitors, JQ1 and CPI203), suppressed pNET cell viability in a RABL6A dependent manner. The bromodomain inhibitors synergized with CDK4/6 inhibitors to effectively kill

pNET cells, diminish migration in vitro and reduce pNET xenograft growth in vivo.

CONCLUSION: Our findings demonstrate RABL6A is a new essential regulator of Myc signaling in pNETs whose expression is required for responsiveness to bromodomain inhibitors. Combined targeting of Myc and CDK4/6 kinases enhances RB1 tumor suppressor activity and may be a useful approach for treating pNETs that harbor activated Myc and CDK4/6.

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