

## B-16

# RABL6A-Dependent Regulation of c-Myc Expression and Activity is Essential for Cell Cycle Progression and Survival of Pancreatic Neuroendocrine Tumor Cells

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**BACKGROUND:** Neuroendocrine tumors (NETs) are challenging, indolent malignancies whose incidence has risen significantly. New biomarkers and a greater understanding of mechanisms underlying NET pathogenesis are needed to improve patient diagnosis and therapies. We recently showed that a novel GTPase, RABL6A, is required for pancreatic NET (PNET) cell proliferation and survival but how it functions is only partly understood.

**METHODS:** Comparative gene expression analyses of PNET cells and patient specimens, RNAi-mediated knockdown of RABL6A and overexpression of Myc in PNET cell lines, and immunohistochemical (IHC) analyses of human NET tissue microarrays (TMAs).

**RESULTS:** Gene expression profiles of RABL6A-depleted PNET cells displayed remarkable overlap with dysregulated genes in patient-derived primary PNETs, with the c-Myc pathway prominently altered in both datasets. Myc is a dominant driver of many human cancers. We found that RABL6A loss in PNET cells diminished c-Myc mRNA expression 2-3 fold while dramatically reducing c-Myc protein levels and activity. We tested if re-instating c-Myc activity would rescue the growth arrest caused by RABL6A loss. Exogenous c-Myc only partially rescued the G1 phase arrest in RABL6A depleted cells. This correlated with increased S-phase entry, reduced expression of the cell cycle inhibitor, p27Kip1,

and increased levels of CKS1B, a c-Myc transcriptional target that promotes p27 degradation. However, c-Myc overexpression was unable to promote mitosis following RABL6A loss, likely due to activation of DNA damage and mitotic checkpoints. IHC stains of pancreatic and ileal NET TMAs showed that Myc expression and low nuclear p27 levels are independently associated with worse patient survival.

**CONCLUSION:** These studies reveal that RABL6A is a novel essential activator of c-Myc expression and activity, advancing our fundamental understanding of Myc regulation. Moreover, c-Myc and p27 are markers of poor NET patient survival, suggesting that their regulation by RABL6A in NETs is clinically important.