

# **RABL6A, A Novel Oncogene Required for Akt-mTOR and Myc Signaling in Pancreatic Neuroendocrine Tumor Cells**

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**Background:** A better understanding of pathways controlling pancreatic neuroendocrine tumor (PNET) formation and progression is needed to improve patient diagnosis and treatment. The PI3K/Akt/mTOR pathway is aberrantly activated in PNETs resulting in everolimus (mTOR inhibitor)-based therapies. However, sustained mTOR inhibition unfortunately promotes Akt hyper-activation and drug resistance. Our data suggest that RABL6A, a novel oncoprotein required for PNET cell proliferation and survival, is a key regulator of this clinically relevant pathway as well as Myc oncogenic signaling.

**Methods:** RABL6A, Akt and Myc protein levels were manipulated using viral shRNA and overexpression vectors in BON-1 PNET cells. Transcript levels were assayed by microarray and qRT-PCR, proteins assessed by western blotting, and cell proliferation / survival measured by cell counts, trypan blue exclusion, EdU incorporation and flow cytometry.

**Results:** RABL6A loss in PNET cells dramatically reduced both Akt1 and c-Myc expression and activity. Given the central role of Akt1 and Myc in promoting tumorigenesis, we hypothesized that reinstating their activity would rescue the growth arrest phenotype caused by RABL6A loss. Individual restoration of Akt or Myc in RABL6A-depleted PNET cells partially rescued the G1 phase arrest and induced S phase entry. This coincided with decreased expression of the cell cycle inhibitor, p27Kip1, and increased levels of CKS1B, a Myc transcriptional target that promotes p27 degradation. Notably, neither Akt nor Myc activation was sufficient to restore proliferation in the absence of RABL6A since cells became arrested in S-G2/M or died via apoptosis.

**Conclusion:** RABL6A controls multiple cancer pathways necessary for PNET cell cycle progression and survival. We are testing if RABL6A status in PNETs predicts responsiveness to clinical inhibitors of Akt, mTOR and Myc. These studies identify RABL6A as a new essential regulator of Akt1-mTOR and Myc pathways, suggesting its inhibition may have global anti-cancer activity and therapeutic value in PNET patients.