RABL6A Promotes PNET Angiogenesis and Development in Vivo

Chandra Kumar Maharjan¹; Courtney Kaemmer¹; Casey Bauchle¹; Samuel Stephens¹; David Meyerholz¹; Dawn Quelle¹

¹The University of Iowa

BACKGROUND: Pancreatic neuroendocrine tumors (PNETs) progress slowly but relentlessly, invariably resulting in untreatable metastatic disease. A better understanding of mechanisms driving PNET pathogenesis will guide more effective and more targeted therapies. We recently discovered a novel oncogenic driver of tumor cell survival and proliferation, named RABL6A, that promotes clinically relevant pathways (AKT-mTOR and VEGFR) in PNET cells. Genetic and proteomic tumor analyses show RABL6A is highly expressed and activated in patient PNETs. Here, we use genetically altered mouse models to test the hypothesis that RABL6A drives PNET formation and angiogenesis in vivo.

METHODS: RIP/Tag2 (RT2) mice express oncogenic SV40 large T-antigen (Tag) under the rat insulin promoter (RIP), resulting in islet β cell transformation and development of hyperplastic islets, angiogenic islets, and insulinomas in a time-dependent fashion. RT2 mice were crossed with RABL6A knockout (KO) mice to generate four cohorts: WT, RT2, RABL6A KO, and dual targeted RT2-RABL6A KO. Tumor formation was tracked via weekly assessment of plasma insulin by ELISA. Pancreata of euthanized mice were either perfused with collagenase to isolate islets for molecular analyses or fixed in paraformaldehyde for histopathological studies at specific time points.

RESULTS: RT2 mice developed high-grade angiogenic PNETs whose development was effectively tracked by increases in plasma insulin levels. We are still expanding the RT2-RABL6A KO cohort of animals, but initial results for female RT2 vs RT2-RABL6A KO mice are compelling. RABL6A loss led to significant reductions in PNET tumor number and size (endocrine area), number
of angiogenic islets, and number of mitoses within islets. Those changes correlated with extended survival in RT2 females lacking RABL6A.

**CONCLUSION:** Studies are ongoing. However, early data suggest RABL6A promotes PNET development in vivo by increasing tumor cell proliferation and promoting the angiogenic switch.