conferenceseries.com

Dawn E Quelle, Pancreat Disord Ther 2016, 6:4(Suppl)
http://dx.doi.org/10.4172/2165-7092.C1.002

International Conference on
Pancreatic Disorders and Treatment
October 17-19, 2016 Chicago, USA

RABL6A, a novel oncogene required for Akt-mTOR and Myc signaling in pancreatic neuroendocrine tumor cells

Dawn E Quelle
University of Iowa, USA

A better molecular understanding of pancreatic (neuroendocrine tumors PNETs) 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 has the unintended consequence of hyper-activating Akt, thereby promoting drug resistance. Our data suggests that *RABL6A*, a novel oncoprotein amplified in PNETs, is a key regulator of this clinically relevant pathway. We found that *RABL6A* is essential for PNET cell proliferation and survival, and its loss dramatically reduces both Akt1 and Myc expression and activity. Given the central role of Akt1 and Myc in promoting tumorigenesis, we hypothesized that reinstating their activity would rescue the arrest phenotype caused by *RABL6A* loss. Individual restoration of Akt1 or c-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. Thus, RABL6A controls multiple pathways essential for PNET cell cycle progression and survival. We are currently 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 signaling pathways, providing compelling mechanistic insight into the oncogenic function of *RABL6A* in PNETs.

Biography

Dawn E Quelle has obtained her PhD in Biochemistry and Molecular Biology from the Pennsylvania State University. In her Post-doctoral work with Dr. Charles Sherr at St Jude Children's Research Hospital, she studied cell cycle control and discovered the ARF tumor suppressor. She is an Associate Professor of Pharmacology at the University of Iowa and Leader of the Cancer Genes and Pathways Program in the Holden Comprehensive Cancer Center. Her research explores mechanisms of tumor suppression with a focus on the molecular and in vivo functions of ARF*RABL6A*s binding partners, such as *RABL6A*, in cancer.

dawn-quelle@uiowa.edu

Notes: