A Novel Therapy for Resistant Pancreatic Neuroendocrine Tumors

[1]Gabriel Mpilla, [1]Amro Aboukameel, [1]Yiwei Li, [1]Philip A. Philip, and [1]Asfar S. Azmi

[1] *Department of Oncology, Wayne State University School of Medicine, Detroit MI 48201 USA;*

Pancreatic Neuroendocrine Tumors (PNETs) remain an unmet clinical problem and their incidence has significantly increased over the past two decades, likely due to improving awareness, classification, and newer diagnostic modalities. Surgery without margins is the only curative option in patients with localized tumors; however, there is no effective therapy for patients with advanced or metastatic disease. Sadly, 65% of PNETs patients die within 5 years after diagnosis. Current therapeutic approaches for advanced PNET patients include chemotherapy, targeted therapies (everolimus, and sunitinib), hormonal therapies [somatostatin analogs (octreotide or lanreotide)] and peptide receptor radionuclide therapy (PRRT). Regrettably, all these therapeutic modalities fail to show objective response in patients with PNETs in the clinic as most patients acquire resistance. Therefore, novel targets need to be identified that could improve the dismal outcome of advanced PNETs. We have recently identified p21-activated Kinase 4 (PAK4) and nicotinamide Phosphoribosyltransferase (NAMPT) as two new therapeutic targets in PNETs. PAK4 is the downstream effector of Cdc42 and Rac1 (members of the Rho family of GTPases) and is involved in critical cellular processes such as cell motility, proliferation, and survival. More importantly, PAK4 protein has been implicated in the activation of Ras/Raf/Mek/Erk and PI3K/Akt/mTOR signaling in cancers. Similarly, NAMPT is an enzyme that catalyzes the rate-limiting step in the principal salvage pathway of NAD biosynthesis in mammals. Tumor cells have highly active glycolytic, pentose and fatty acid synthesis pathways that require persistent high levels of NAD. Consequently, most cancers, rely more heavily on NAMPT for rapid NAD biosynthesis. I have demonstrated that targeted inhibition of PAK4-NAMPT signaling by a dual inhibitor (KPT-9274 a Phase I drug) can suppress PNET proliferation and reduce the growth of subcutaneous xenograft. Metabolomic analysis of KPT-9274 treated PNET cells reveals significant alterations in a series of metabolites related to NAD signaling. My new studies show that KPT-9274 could synergistically enhance the anti-tumor activity of everolimus in PNET cell lines (combination index <1). Molecular analysis of combination treatment showed down-regulation of known everolimus resistance drivers such as mTORC1, mTORC2, PI3K, ERK, FAK, RICTOR, ß-catenin. Importantly, combination of KPT-9274 (150mg/kg) and everolimus (2.5 mg/kg used at sub-optimal dose) dramatically inhibited the growth of PNET cell line derived sub-cutaneous xenograft tumors. Our investigations demonstrate that PAK4 and NAMPT are two viable therapeutic targets in the difficult to treat PNETs that warrant further clinical investigations.