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Efficacy of Combined MEK and CDK Targeted Therapies for Pancreatic Neuroendocrine Tumors

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BACKGROUND: Combination therapies prevent acquired tumor cell resistance and are generally more effective than monotherapies. New combinations will improve the survival of patients with advanced pancreatic NETs (pNETs). RABL6A, a new oncogenic driver of pNET proliferation, acts through multiple pathways including, MEK-ERK and suppression of retinoblastoma (RB1) tumor suppressor via cyclin-dependent kinase (CDK) activation. Patient tumor analyses suggest MEK and CDK hyperactivation promote pNET pathogenesis, but clinical trials assessing CDK4/6 monotherapy have shown no benefit in progression free or survival. We hypothesize that the combination of MEK and CDK4/6 will synergistically reactivate RB1 and display greater efficacy against pNETs than CDK monotherapy.

METHODS: Quantitative kinome and phosphoproteome analyses of proliferating (RABL6A- positive) and arrested (RABL6A-silenced) pNET cells were performed to identify RABL6A targets. Effects of altered RABL6A expression and activity of targets in pNET cells were measured by immunoblotting, proliferation & survival assays, and response to drug inhibitors. Tumor suppressive effects of two MEK inhibitors (mirdametinib, binimetinib) and a CDK4/6 inhibitor (palbociclib) were measured in pNET cells and mouse xenograft tumors.

RESULTS: RABL6A depletion in pNET cells caused reprogramming of the global kinome and downregulation of 1,100 cellular phosphoproteins. IPA analyses suggested RABL6A is required for activating tumor-promoting kinases including CDKs 1/2/6 and MEK1/2. In agreement, pNET cell survival was decreased by palbociclib, mirdametinib and binimetinib in a RABL6A-dependent manner. Combined inhibitors targeting CDK4/6 and MEK was highly synergistic in promoting RB1 activation and death of pNET cells in vitro, effectively suppressed pNET xenograft growth in mice. Dual effects of MEK-CDK4/6 therapy was sustained for over 3 months in vivo, yielding a 6-fold extension of average survival (~120 days versus 20 days for vehicle control) in the model.

CONCLUSION: Combined targeting of MEK and CDK4/6 may be an effective treatment strategy to improve the survival of pNET patients whose tumors harbor activated MEK and CDK4/6.

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