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CDK4/6-MEK Targeted Therapy Causes Regression and Reduced Metastatic Colonization of Pancreatic Neuroendocrine Tumors

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BACKGROUND

New therapeutics and combinations are needed to improve the survival of patients with advanced, metastatic pancreatic NETs (pNETs). RABL6A is a novel oncogenic driver of pNET pathogenesis that acts through multiple oncogenic pathways. Kinome and phosphoproteome analyses of proliferating (RABL6A-positive) pNET cells, versus arrested (RABL6A-knockdown) controls, demonstrated that druggable cyclin-dependent kinase 4 and 6 (CDK4/6) and MEK kinases are activated in growing pNET cells. Consistent with those findings, published studies of patient pNETs by immunohistochemistry (IHC) and RNAseq have identified robust activation of CDK4/6 and MEK in the tumors. Studies in other tumor types show CDK4/6 and MEK inhibitors have synergistic antitumor activity linked with heightened CD8 T cell and/or natural killer cell activation. This drug combination has not yet been evaluated in pNETs.

METHODS

Synergistic effects of MEK inhibitor (Mirdametinib) and CDK4/6 inhibitor (Palbociclib) were measured by cell proliferation & survival assays, colony formation and immunoblotting. Tumor suppressive effects of drug inhibitors were measured *in vivo* using 3 pNET mouse models: 1) flank xenografts in immunodeficient mice, 2) tail vein metastasis xenografts in immunodeficient mice, and 3) immune competent, *Pdx1-Cre;Men1$^{fl/fl}$;Pten$^{fl/fl}$* knockout mice that develop insulinoma by 5-6 months of age.

RESULTS

Dual CDK4/6-MEK inhibitor therapy was highly synergistic *in vitro* in causing pNET cell death and pathway inactivation, as measured by retinoblastoma protein (RB1) hypo-phosphorylation. *In vivo*, the CDK4/6-MEK combination significantly slowed the growth of flank pNET xenografts, yielding a 6-fold extension of average survival (~120 days versus 20 days for vehicle control). This combination likewise suppressed (but did not eliminate) pNET growth in a bioluminescence metastasis model and effectively reduced the number of colonized tissues relative to monotherapy controls. Most impressively, dual CDK4/6-MEK inhibition caused dramatic tumor regression associated with a unique B/plasma cell infiltration phenotype in our *Pdx1-Cre;Men1$^{fl/fl}$;Pten$^{fl/fl}$* mouse model of insulinoma.

CONCLUSIONS

Combination therapy targeting CDK4/6 and MEK effectively inhibits pNET growth and metastatic colonization. Monotherapies were not effective, in agreement with failed CDK4/6 monotherapy trials in pNET patients. In immune competent *Pdx1-Cre;Men1$^{fl/fl}$;Pten$^{fl/fl}$* mice, CDK4/6-MEK inhibition causes significant tumor regression linked with tumor infiltration of B and plasma cells. These data suggest that the increased efficacy of CDK4/6-MEK targeted therapy against pNETs in immune competent mice is due to activation of an anti-tumor immune response, which we propose may sensitize tumors to immune checkpoint inhibitor therapy.

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