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CDK4/6 and MEK are actionable, therapeutic targets in pancreatic and lung neuroendocrine tumors (NETs)

Koffi Amegble[1,2], Courtney Kaemmer[2,3], Shaikamjad Umesalma[2,3], Joshua Lingo[2,3], Chandra Maharjan[2,3], and Dawn Quelle[2,3].

ICARE Post-Baccalaureate Program[1], University of Iowa and Holden Comprehensive Cancer Center[2], Department of Neuroscience and Pharmacology[3].

BACKGROUND

Neuroendocrine tumors (NETs) are slow growing tumors whose incidence has risen precipitously compared to all other malignancies. These tumors develop via transformation of neuroendocrine cells throughout the body; however, they are predominantly found in the pancreas, lungs, and intestines. NETs are extremely slow-growing tumors that respond poorly to traditional anti-cancer therapies, and unfortunately patients with unresectable or partially resectable tumors will inevitably progress on the currently approved therapies. Therefore, there is a critical need to identify new drugs and/or combination therapies for treating resistant tumors. Our group has shown that pancreatic NETs (pNETs) overexpress an oncogenic Rab-like GTPase, RABL6A. RABL6A upregulates many kinases, such as CDK4/6, MEK, and AKT whose hyperactivation is a key feature of pNET and lung NET pathogenesis. Monotherapies targeting these kinases individually have not been effective when tested in pNET patients. We hypothesized that combination therapy targeting both CDK4/6 and MEK together would have synergistic antitumor activity against pNETs and lung NETs.

METHODS

Anti-tumor effects of the drugs – vehicle control, CDK4/6 inhibitor (palbociclib), MEK inhibitor (mirdametinib), or the combination – were measured *in vitro* in cultured pNET and lung NET cells via cell cycle, cell survival, and drug synergy assays. Western blotting of phosphorylated RB1 protein evaluated activity of the drugs against their target. The *in vivo* activity of the drugs, alone or combined, was measured in xenograft tumors of each NET type (BON1 and H727) in immune-deficient NSG mice.

RESULTS

Dual CDK4/6-MEK inhibitor therapy was highly synergistic *in vitro* where it caused robust pNET cell cycle arrest and cell death relative to single drug controls. The combination was also synergistic at nanomolar doses against a lung NET cell line, H727. Importantly, molecular assays showed the CDK4/6-MEK inhibitor combination effectively inactivated the targeted pathway, as measured by RB1 protein hypo-phosphorylation. In animals bearing pNET xenografts, the CDK4/6-MEK inhibitor combination significantly slowed tumor growth and yielded a 6-fold extension in average mouse survival (~120 days versus 20 days for vehicle control). Pilot drug studies of H727 lung NET xenografts showed significant anti-tumor activity of MEK inhibition alone.

CONCLUSIONS

Combination therapy targeting CDK4/6 and MEK kinases effectively inhibits NET growth *in vitro* and *in vivo*, suggesting it could be a valuable treatment option for NET patients. To date, most analyses have been conducted in pNET models; therefore, future studies will be expanded to more deeply examine the anti-tumor activities of CDK4/6 and MEK inhibitors in lung NET models.

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