B-3

Differential Gene Expression in Metastatic Pancreatic Neuroendocrine Tumors Predicts Novel Therapeutic Agents

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BACKGROUND: Pancreatic neuroendocrine tumors (PNETs) are uncommon malignancies noted for their indolent growth, propensity to metastasize, and comparatively favorable prognosis. Although both the number of treatment options and the median survival have increased in the last several decades, most patients will die of metastatic disease, and new systemic therapies are needed. We analyzed differential gene expression in PNET metastases to identify novel therapies for these tumors.

METHODS: Tissue samples were obtained from primary tumors, lymph node and liver metastases from 43 patients with sporadic, well-differentiated PNETs. RNA-Seq was performed and gene expression was compared between primary tumors and metastases. Genes which were selectively overexpressed at only one metastatic site were filtered out to reduce the influence of tissue-specific genes unrelated to metastasis. Ingenuity Pathway Analysis (IPA) and the Connectivity Map (CMap) were used to identify potentially effective drugs based upon comparisons to expression profiles from tumor cells treated with these agents. Promising drugs were tested using two PNET cell lines (BON1, QGP1).

RESULTS: A total of 841 genes were significantly differentially expressed in metastases compared to the primary tumors, 565 of which remained in the common metastatic profile after filtering. IPA predicted altered activity of several transcriptional regulators involved in cell survival, differentiation and

proliferation. Drugs targeting these regulators, including mTOR, PI3K, CDK, NF-kB, topoisomerase, and HDAC, were identified through CMap and IPA, and nine were selected for validation (Table 1). All but one compound tested demonstrated complete or near complete inhibition of proliferation in PNET cell lines.

CONCLUSION: We employed a complementary bioinformatics approach to identify novel therapeutic agents for PNETs by analyzing gene expression changes in metastatic tumors. The validity of this strategy was supported in vitro using two PNET cell lines. Additional in vivo evaluation of these compounds using PNET models of metastasis will be important for confirming their clinical utility.

Table 1: Nine compounds selected for testing in BON-1 and QGP-1. IPA analysis match score ranges from -151.046 to 0, CMap connectivity score ranges from -100 to 100; more negative scores indicate potential activity against NETs. IC50 indicates the half maximal inhibitory concentration in BON-1/QGP-1. NA = Gene expression data for this compound was not available in IPA/CMap.

Drug	Class	IPA/CMap Score	IC50 (μM)
Alvocidib	CDK inhibitor	-81.62/-96.39	0.05/0.08
Mocetinostat	HDAC Inhibitor	NA/-92.43	0.07/0.14
Entinostat	HDAC Inhibitor	-19.92/-75.58	0.19/0.17
Triptolide	NFkB inhibitor, RNA polymerase inhibitor	NA/-97.57	0.003/0.01
bisindolylmaleimide-IX	PKC inhibitor, DNA topoisomerase inhibitor	NA/-97.57	0.28/0.30
PIK-75	PI3K Inhibitor, DNA PK inhibitor	NA/-97.73	0.02/0.04
PI-103	mTOR inhibitor, PI3K inhibitor, DNA PK inhibitor	-82.28/-96.91	0.13/0.40
Apitolisib	mTOR inhibitor, PI3K inhibitor	-53.67/NA	0.19/0.31
Sirolimus	mTOR inhibitor	-31.50/-91.20	0.01/0.03