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Distinct mTOR Pathway Activity in Neuroendocrine Tumors of the Pancreas and Small Intestine Revealed by Immunohistochemical Analysis

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Background: Neuroendocrine tumors (NETs) of the pancreas and small intestine frequently metastasize; however, no standard therapy exists for patients with unresectable, progressive disease. Components of the mTOR signaling pathway have been identified as potential therapeutic targets in NETs, and inhibitors of the pathway are being investigated in clinical trials. We evaluated the expression and activity of mTOR pathway components in NETs of the pancreas (PNET), small bowel (SINET), and normal tissues.

Methods: Archived formalin-fixed, paraffin-embedded tissues were obtained from 28 patients: 16 PNETs and 12 SINETs. Expression and phosphorylation of mTOR and its downstream effectors S6K and 4E-BP1 were assessed by immunohistochemistry.

Results: Distinct activation (phosphorylation) of mTOR, 4E-BP1 and S6K was observed in PNETs, SINETs, and normal tissues. We observed p-mTOR in 12/16 (75.0%), p-4E-BP1 in 0/16 (0.0%), and p-S6K in 2/16 (12.5 %) PNETs. In normal islets, we detected p-mTOR in 0/11 (0%), p-4E-BP1 in 5/12 (41.7%), and p-S6K in 3/12 (25%). We observed p-mTOR in 12/12 (100%), p-4E-BP1 in 1/12 (8.3%), and p-S6K in 3/12 (25%) SINETs. Phospho-mTOR was detected in 6/6 (100%), p-4E-BP in 5/6 (83.3%), and p-S6K in 3/6 (50%) normal SI.

Conclusions: We show that activated components of the mTOR signaling pathway are present in PNETs and SINETs. Our analysis reveals distinct profiles of active mTOR pathway components in PNETs and SINETs compared with each other and with their respective normal tissues. Our results suggest a lack of concordance among p-mTOR and p-4E-BP1 and p-S6K; this may result from the actions of other signaling pathways that affect S6K and/or 4E-BP1, non-coordinate dephosphorylation of S6K and 4E-BP1 in tissue sections, or variances in the efficacies of the antibodies employed. The work herein provides important information for the evaluation of potential predictive biomarkers that could be validated in future clinical trials.