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Inhibition of Serotonin Biosynthesis Suppresses Tumor Growth

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BACKGROUND: Small bowel neuroendocrine tumors (SBNETs) are a subgroup of NETs originating from enterochromaffin cells in the intestine. SBNETs express high level of Tryptophan Hydroxylase 1 (TPH1), a key enzyme involved in serotonin biosynthesis. High levels of serotonin cause carcinoid syndrome which can be treated with somatostatin analogs and the TPH1 inhibitor telotristat ethyl (TE). Although somatostatin analogs have been demonstrated to have anti-tumor properties, the effects of TE on tumor growth remains inconclusive. Several groups have found that TE has no growth inhibitory activity on NET cells in vitro but one recent study showed inhibition of tumor growth in patients. To investigate this discrepancy, we studied the effect of TPH1 inhibition both in vitro and in vivo using genetic and pharmacologic approaches, and whether serotonin biosynthesis can be further suppressed using inhibitors targeting the nicotinamide dinucleotide (NAD) pathway.

METHODS: We generated stable TPH1 knockdown BON-1 cells using specific shRNAs, assessed their growth rate and angiogenesis potential in vitro and in vivo by measuring cell division, serotonin level, endothelial cell tube formation, tumor weight, and tumor vascularity staining. We treated mice harboring BON-1 tumors with a vehicle control, TE, NAD inhibitor, and both drugs.

RESULTS: TPH1 knockdown cells and TE treated cells showed similar growth rate as control cells in vitro. However, TPH1 knockdown cells formed smaller tumors in vivoand tumors were less vascularized. The combination of TE and NAD inhibitor reduces serotonin biosynthesis and resulted in improved anti-tumor effect.

CONCLUSION: Although TPH1 inhibition showed no effect on tumor cell

growth in vitro, TPH1 inhibition reduced tumor formation in vivo. Pairing TE with NAD inhibitor represents an efficient strategy to metabolically target NETs.

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Effect of telotristat ethyl and NAD inhibitor on neuroendocrine tumors.

Biological Effects	Telotristat Ethyl (TE)	NAD inhibitor	Combo TE & NAD inhibitor
Anti-tumor cell growth *in vitro*	none	++	++
Anti-tumor growth *in vivo*	+	++	+++
Anti-angiogenic properties	+	++	+++
Serotonin biosynthesis inhibition	++	+	+++