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Gastric Inhibitory Polypeptide Receptor (GIPR): A Future Alternative to Somatostatin Type 2 Receptor Imaging and Treatment in Neuroendocrine Tumors?

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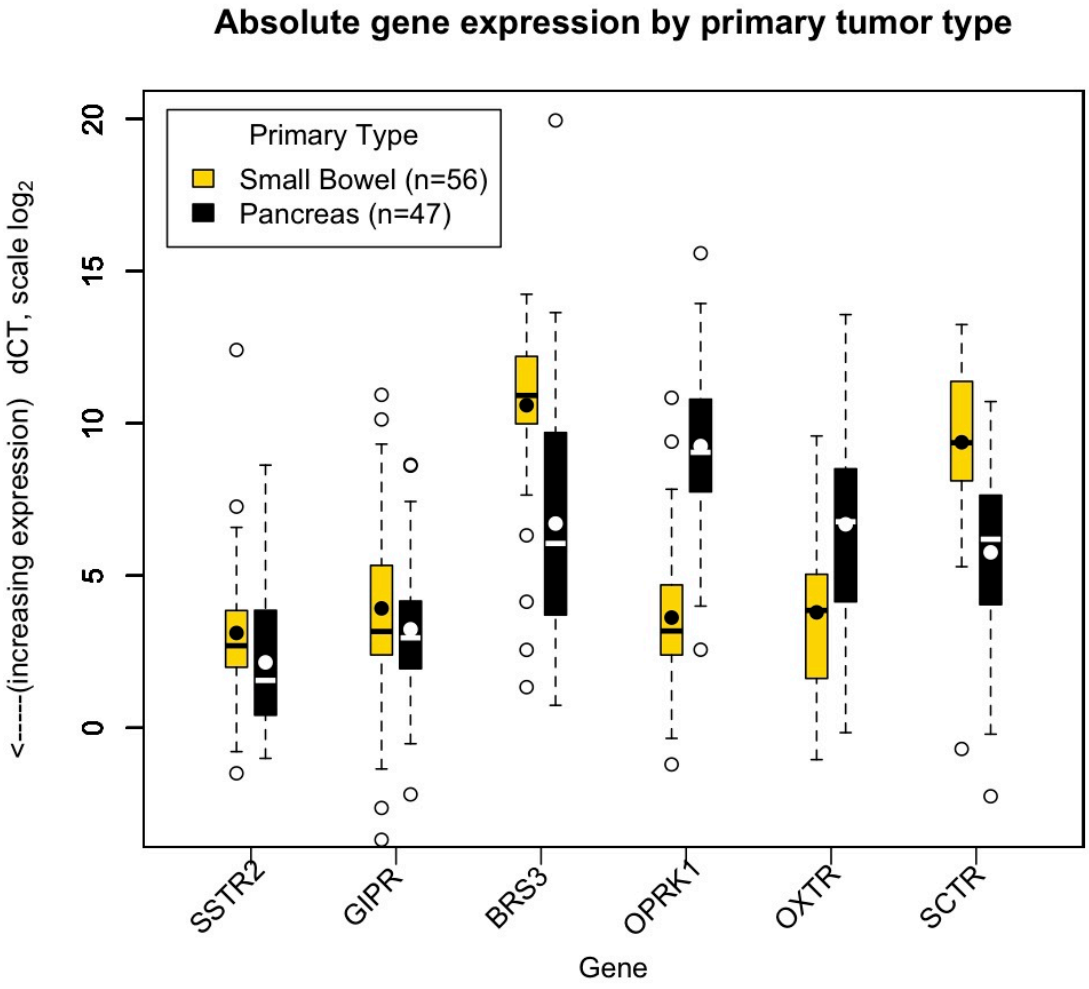
Background: Ligands binding somatostatin-type-2 receptors (SSTR2) are effective for imaging, symptom control, and radioreceptor therapy of neuroendocrine tumors (NETs). However, SSTR-directed imaging is often negative and not all patients respond to octreotide injections. This study sought to evaluate expression of new NET target genes relative to SSTR2.

Methods: RNA was extracted from primary NETs, matched normal tissue, and lymph node and liver metastases collected at surgery. Relative expression was assessed by quantitative PCR for SSTR2 and 12 genes previously found to be overexpressed in NETs (BRS3, OPRK1, DRD1, GPR98, GIPR, GRM1, SCTR, ADORA1, GPR113, OXTR, MUC13, MEP1B). Mean threshold cycles were normalized to GAPDH and POLR2A internal controls to determine expression levels (dCT). Welch's two-sample t-test compared results.

Results: Small bowel (SBNETs; 56 primaries, 32 liver, 53 nodal mets) and pancreas (PNETs; 47 primaries, 18 liver, 20 nodal mets) NETs were tested. SSTR2 expression in tumors was high (dCT=2.7, Interquartile Range (IQR) 0.9-3.9), and was 3-fold greater in tumor compared to normal tissue. Relative to normal tissue, tumor expression of GIPR, BRS3, OPRK1, GRM1, GPR113, and OXTR were increased 13, 13, 20, 17, 5, and 40-fold, respectively, with fold-increases significantly greater than those of SSTR2 ($p<0.001$). Yet compared to SSTR2, absolute expression in primaries was much lower for all of these genes except GIPR ($p<0.001$). GIPR expression was closest to SSTR2 in tumors (dCT 3.6, IQR 2.1-4.9 vs. 2.7, $p=0.01$), but had 10-fold lower expression in normal tissue than SSTR2 (ddCT -3.7, vs. -1.6, $p<0.0001$). Expression of SSTR2 and GIPR was similar in both PNET and SBNET primaries ($p=0.09$ and 0.23) and metastases ($p=0.1$ and 0.5).

Conclusions: GIPR has expression similar to SSTR2 in primary and metastatic NETs, with greater differential expression vs. normal tissues than SSTR2. Based on these favorable expression characteristics, GIPR warrants study as a target for NET imaging and therapy.

Figure 1: Absolute gene expression (dCT) by primary tumor type. Lower dCT indicates higher expression. Boxes show interquartile range, whiskers show 1.5*IQR, open circles show outliers, bar shows median, dot shows mean. GIPR shows expression in SBNETs and PNETS (mean dCT 3.9 and 3.2) similar to that of SSTR2 (mean 3.1 and 2.1, p=0.23, 0.09).



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