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The Notch1 pathway is a critical regulator of SSTR2 expression in neuroendocrine tumors

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BACKGROUND

Patients with neuroendocrine tumors (NETs) have a 5-year survival rate of 30-60%. Surgery, and newly approved 'targeted radionuclide therapy (TRT)' with [^{177}Lu]DOTATATE, are the only curative options for patients with NETs. TRT is limited to patients that have high levels of somatostatin receptor subtype 2 (SSTR2) and can improve the survival of patients with low-grade tumors, but has little effect on high-grade NETs that express low SSTR2 levels. The development and growth of neuroendocrine tumors is regulated by the Notch1 pathway. Based on our recent findings, we hypothesized that Notch1 signaling can regulate SSTR2 at both the basal level and with HDACi-induced expression in neuroendocrine tumors.

METHODS

To determine if Notch1 was upstream of SSTR2, the Notch1 gene was deleted in a pancreatic NET cell line (BON) using CRISPR/Cas9. Wild-type BON and cells lacking Notch1 (BON-N1-KO) were then treated with vehicle, 1mM, or 4mM of valproic acid (VPA; HDACi) for 48h. Total protein was isolated, and a western blot was performed to measure total SSTR2 and Notch1 expression. A functional radiopeptide uptake study was performed to determine in vitro binding of [^{68}Ga]DOTATATE to BON and BON-N1-KO cells pretreated with vehicle, 1mM or 4mM VPA for 48h.

RESULTS

Previously, we have shown that epigenetic modifiers, including histone deacetylase inhibitors (HDACi), robustly increase SSTR2 expression in NETs in vitro and in preclinical mouse NET models. The absence of the Notch1 gene resulted in lower induction of total SSTR2 comparing to wildtype pancreatic NET cells following HDACi treatment. Importantly, we observed a reduced radiopeptide [^{68}Ga]DOTATATE uptake by pancreatic NET cells lacking Notch1, even when treated with an HDACi to induce SSTR2, suggesting a decreased membrane density of SSTR2 when Notch1 was absent.

CONCLUSIONS

Our data show that Notch1 is upstream of SSTR2 and regulates its membranous expression. SSTR2 and Notch1 signaling are two critical pathways involved with the detection and progression of NETs and identifying the mechanisms which allow maximal re-expression of SSTR2 may improve NET treatment response. Moreover, Notch-induced SSTR2 activation could enhance SSTR2 targeted NET therapy.

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