

# Hedgehog Signaling Mediates the Dysregulation of Adrenocorticotropin Hormone Secretion and Somatostatin Receptor Expression in Cushing's Disease

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Cushing's disease (CD) is an endocrine disorder characterized by increased levels of cortisol and caused by an Adrenocorticotropin hormone (ACTH)-secreting pituitary corticotroph adenoma. The cause of these tumors is largely unknown but has been attributed to genetic mutations. Hedgehog (Hh) signaling has been implicated in corticotroph dysregulation. The somatostatin receptor subtypes (SSTR) 2 and 5 have been targets of medical therapies for CD. SSTRs are expressed on corticotrophs. Somatic mutations associated with CD including variants of USP8, USP48, and BRAF are known to lead to constitutive activation of GLI1 signaling correlated with a subsequent dysregulation of ACTH and SSTR expression. In our studies, we hypothesized that Hh signaling regulates ACTH and SSTR expression attributing to the pathophysiology of Cushing's disease. To identify the role of GLI1, we developed a human pituitary adenoma organoid model derived from human induced pluripotent stem cells (iPSCs), which were treated with glucocorticoid receptor antagonist Mifepristone, with or without GLI1 inhibitor GANT61, or Smoothed inhibitor Ketoconazole. In a separate series of experiments, cultures were treated with or without SSTR agonists Pasireotide or Octreotide to identify the role of Hh signaling in the regulation of SSTR expression. Mifepristone treatment increased ACTH secretion, POMC, SSTR2 and SSTR5 expression, which were inhibited by GANT61 and Pasireotide. Organoids generated from individual patient pituitary adenoma tissues expressed variability in SSTR expression and ACTH secretion that correlated with divergent responses to Pasireotide. Dysregulated Hh signaling led to increased ACTH secretion and SSTR expression in pituitary adenomas associated with CD.

## Awards Won:

National Anti-Vivisection Society: First Award of \$10,000