the disease in this pedigree. By copy number variation and SNP haplotype analysis, SOX9 gene far upstream deletion of 68kb was disclosed from the 3 patients in this family, containing one of the enhancers of SOX9. Real-time PCR confirmed that the heterozygous deletion of the region result in loss of SR-XY, but not eSR-B and eALDI. Therefore, single nucleotide variation (SNV) of SRY and NR5A1 are not main causes of severe phenotype of CGD, the enhancers of SOX9 should be investigated carefully in such patients.

Adrenal

ADRENAL - HYPERTENSION

Targeting Pheochromocytoma/Paraganglioma with Polyamine Inhibitors

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Background: Pheochromocytomas (PCCs) and paragangliomas (PGLs) are neuroendocrine tumors that are mostly benign. Metastatic disease occurs in about 10% of cases, and for these patients no effective therapies are available. Patients with mutations in the succinate dehydrogenase subunit B (SDHB) gene tend to have metastatic disease with very little treatment options. To find a new treatment strategy, we utilized a metabolomics approach to identify unique metabolic pathways. A metabolomic analysis was performed on human hPheo1 cells and shRNA SDHB knockdown hPheo1 (hPheo1 SDHB KD) cells. Additional analysis of 50 human fresh frozen PCC/PGL samples was conducted. Since the polyamine pathway surfaced in the metabolomics analysis, we hypothesized that treatment with polyamine inhibitors would be an effective option for aggressive PCC/PGL tumors. In vitro studies using N1,N11-diethylnorspermine (DENSPM) and N1,N12- diethylspermine (DESPM) treatments were carried out. DENSPM efficacy was assessed in xenograft models. Results: Components of the polyamine pathway were elevated in hPheo1 SDHB KD cells compared to wild-type cells. A similar observation was noted in SDHx PCC/PGLs tumor tissues compared to their SDHB wild-type counterparts. Specifically, spermidine, and spermine were significantly elevated in SDHx-mutated PCC/PGLs, with a similar trend in hPheo1 SDHB KD cells. Polyamine pathway inhibitors DENSPM and DESPM effectively inhibited growth of hPheo1 cells in vitro as well in mouse xenografts. Conclusions: This study demonstrates overactive polyamine pathway in PCC/PGL with SDHB mutations. Treatment with polyamine inhibitors significantly inhibited hPheo1 cell growth and led to growth inhibition in xenograft mouse models treated with DENSPM. These studies strongly implicate the polyamine pathway in PCC/PGL pathophysiology and provide new foundation for exploring the role for polyamine analogue inhibitors in treating metastatic PCC/PGL.

Adipose Tissue, Appetite, and Obesity

CNS, INFLAMMATORY, AND THERMOGENIC INFLUENCES OF BODY WEIGHT

MRAP2 Regulates Energy Homeostasis by Promoting Primary Cilia Localization of MC4R

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Genetic studies in humans and mice have demonstrated that the Melanocortin 4 Receptor (MC4R) is essential for adequate regulation of food intake and body weight. MC4R is expressed in a small population of hypothalamic neurons and very little is known about its molecular and cellular dynamics *in vivo*. We have recently demonstrated that MC4R localizes to and functions at the primary cilia of select hypothalamic neurons to control energy homeostasis. The primary cilium is a solitary hair-like organelle that serves as an antenna sensing extracellular environment. Defective primary cilia lead to a series of conditions known as ciliopathies, that can manifest through a variety of clinical features, including hyperphagia and obesity.

Here we establish that the ciliary localization and the body weight regulating activity of MC4R is dependent on a single-pass transmembrane accessory protein: the Melanocortin Receptor Associated Protein 2 (MRAP2). Specifically, we show that deleting MRAP2 specifically from MC4R neurons ($MC4R^{MRAP2-/-}$) leads to early onset obesity and hyperphagia. *In vitro*, co-expression of MRAP2 in ciliated IMCD3 cells increases MC4R localization to the primary cilium. We further demonstrate that MRAP2 and MC4R colocalize specifically at the primary cilium *in vivo*, and that MC4R fails to localize to the primary cilium when MRAP2 is deleted.

These findings highlight the role of the primary cilium in the control of energy homeostasis, and the importance of accessory proteins for the localization of GPCRs to the primary cilium where they exert their function, in this case being critical for the regulation of energy homeostasis.