

(p.Glu161fs/c.482\_491delAGGAAGAAAA) and *ADGRB2* gene (p.Leu1565Gln/c.4694T>A) were found in each of the remaining single copy of chr 1p. *ADGRB2* gene is thought to be involved in cell adhesion and angiogenesis inhibition. Copy neutral loss-of-heterozygosity were present in two (29%) of the tumour samples (chr 2 and 12q). However, no somatic mutation was found in these regions. Gene level copy number analysis identified a potential deletion in *TTI2* gene which encodes for a regulator in DNA damaging response as well as telomere length regulation.

**Conclusion** Overall, the rate of somatic variant mutations in TSHomas is low, consistent with the relative benign nature of this tumour type. No classical driver mutations were identified by this study however, chromosomal anomalies and epigenetics may play an important part in TSHoma development.

## Cardiovascular Endocrinology

### PATHOPHYSIOLOGY OF CARDIOMETABOLIC DISEASE

#### *Taurine Reverses Protein Malnutrition-Induced Endothelial Dysfunction of Pancreatic Vasculature*

Daniele Mendes Guizoni, PhD, Israelle Netto Freitas, MD, Jamaira Aparecida Victorio, PhD, Everardo Magalhaes Carneiro, PhD, Ana Paula Davel, PhD.

University of Campinas, Campinas, Brazil.

#### SUN-LB90

**Background:** Pancreatic islets are highly vascularized and there is a correlation between endocrine pancreas function and pancreas perfusion. Protein malnutrition during early stages of development predispose to cardiovascular diseases, impaired insulin secretion and, type 2 diabetes. However, it is unknown if there are alterations in the pancreatic vasculature in response to malnutrition. Taurine (TAU) supplementation has been suggested as antihypertensive and improves endothelial function and insulin secretion in cardiometabolic disorders. Here, we investigated the effect of TAU in the vasorelaxation and endothelium-derived factors of the lieno-pancreatic artery from protein malnourished mice. Because lieno-pancreatic artery provides blood supply to pancreatic splenic lobe, a protective effect of TAU may result in cardiometabolic benefits. **Methods:** Post-weaned male C57Bl/6 mice fed a normal- (14%, NP) or a low-protein (6%, LP) diet for 90 days. Concomitantly, half of LP mice received 2.5% TAU in drinking water. Lieno-pancreatic artery (internal diameter ~ 160 µm) was isolated and concentration-response relaxation curves to acetylcholine (ACh), nitric oxide (NO)-donor (SNP), or hydrogen sulfide (H<sub>2</sub>S)-donor (NaHS) were performed. The involvement of NO and endothelium-derived hyperpolarization (EDH) in ACh-induced relaxation was assessed using L-NAME (NO synthase inhibitor) or KCl (to attenuate K<sup>+</sup> efflux), respectively. Protein expression was evaluated by Western-blot; NO and H<sub>2</sub>S production by DAF-2A and WSP-1 fluorescence, respectively. **Results:** Endothelium-dependent relaxation to ACh was reduced in lieno-pancreatic artery from LP compared with NP group. Either KCl or L-NAME reduced ACh-induced relaxation, but only KCl abolished differences between LP and NP, suggesting that EDH rather than NO is involved

in the impaired endothelium-dependent relaxation of LP. In accordance, relaxation to SNP, NO production, and endothelial NO synthase (eNOS) expression were not altered in lieno-pancreatic artery of LP group compared to NP. Because H<sub>2</sub>S has been demonstrated to have EDH activity in several blood vessels we investigated this pathway. H<sub>2</sub>S production and NaHS-induced relaxation were both reduced in lieno-pancreatic artery of LP group compared with NP. TAU treatment reversed the impaired relaxation to ACh and to NaHS, as well as significantly increased H<sub>2</sub>S production in lieno-pancreatic artery of LP group. **Conclusion:** Protein malnutrition resulted in endothelial dysfunction of lieno-pancreatic artery associated with an impaired production and relaxation to H<sub>2</sub>S, which was restored by TAU. Therefore, beneficial effects of TAU on lieno-pancreatic artery vasodilatory function may result in improved pancreatic islet blood flow highlighting the potential of TAU for vasculo-metabolic protection. **Funding:** FAPESP, CAPES.

## Tumor Biology

### TUMOR BIOLOGY: GENERAL, TUMORIGENESIS, PROGRESSION, AND METASTASIS

#### *Paraneoplastic Hypercalcemia in a PTH Producing Adrenocortical Carcinoma - a Rare and Deadly Condition*

Sven Gruber, MD<sup>1</sup>, Cong Tang, PhD<sup>1</sup>, Mesut Berber, PhD candidate<sup>2</sup>, Stefan Fischli, MD<sup>3</sup>, David Penton-Ribas, PhD<sup>2</sup>, Daniela Mihic-Probst, MD<sup>1</sup>, Felix Beuschlein, MD<sup>1</sup>.

<sup>1</sup>University Hospital Zurich, Zurich, Switzerland, <sup>2</sup>University of Zurich, Zurich, Switzerland, <sup>3</sup>Luzerner Kantonsspital, Luzern, Switzerland.

#### SAT-LB23

**Background:** Hypercalcemia is a commonly encountered paraneoplastic manifestation of certain cancers with or without endocrine differentiation. However, the association between adrenocortical carcinoma (ACC) with paraneoplastic hypercalcemia is very rare, and therefore little is known about the cause and its relevance in the disease. **Clinical Case:** A 40-year-old woman presented in the hospital with a 5-month history of progressive flank pain with unintentional weight loss of 6 kg. MRI revealed a mass of 9x8.1x4.8 cm of the right adrenal gland with inhomogeneous contrast enhancement. Biochemical investigations provided evidence of endogenous hypercortisolism (24-hour urinary cortisol excretion [490 µg, n<236 µg/l], 1mg dexamethasone suppression test [199 nmol/l, n<50 nmol/l], ACTH [28 ng/l, n<61 ng/l]) although the patient did not show any specific clinical sign of overt hypercortisolism. In addition, laboratory testing revealed an exceptionally high plasma level of calcium [max 3.67 mmol/l (albumin-corrected)] and low phosphate [min 0.26 mmol/l] in the setting of low PTH [6.4 ng/l, n>15 ng/l] and PTHrP levels [<0.50 pmol/l]. However, subsequent dilution unmasked a highly elevated PTH concentration of 2171.5 ng/l with persistent low PTHrP levels, indicating false low values due to a hook effect in the initial measurement. Levels of 1,25-dihydroxy vitamin D and 25-hydroxy vitamin D were in the normal range. A PET-CT provided no indications of metabolically active (osseous) metastases. After correction

of the serum calcium towards tolerable values, the tumor was removed by open en bloc adrenalectomy. Histologic evaluation confirmed an ACC (TNM pT4 pN1 (2/3), L1, V1, high grade) despite missing immunohistochemically expression of classical adrenal markers (diagnosis of exclusion). Supplemental quantitative RT-PCR studies support the diagnosis of ACC by detecting significant SF-1 and CYP11B2 expression in the tumor cells. Further analyses provided evidence that the mRNA expression of PTH, but not PTHrP, was moderately increased in the ACC sample compared to NCI H295R cells. Upon tumor resection, serum calcium levels swiftly normalized indicating the tumor as the sole source of PTH secretion. Despite initiation of adjuvant mitotane- and salvage chemo-therapy, the patient died 3 months later upon of a massive tumor relapse with a recurrence of severe hypercalcemia. **Conclusion:** This case demonstrates paraneoplastic hypercalcemia in a PTH producing ACC. PTH may induce hypercalcemia, impair adrenal steroid synthesis and act as an autocrine growth factor in ACC, as described in few individual cases for PTHrP producing ACC [1]. This suggests a poor prognosis for this rare entity.

1. Rizk-Rabin, M., et al., Differential Expression of Parathyroid Hormone-Related Protein in Adrenocortical Tumors: Autocrine/Paracrine Effects on the Growth and Signaling Pathways in H295R Cells. 2008.

## Thyroid

### HPT-AXIS AND THYROID HORMONE ACTION

#### *TSH Is a Negative Modulator of Hippo Transcriptional Effectors*

Celia Fernández-Méndez, PhD Student, Pilar Santisteban, PhD. Biomedical Research Institute 'Alberto Sols', Madrid, Spain.

#### SAT-LB78

Hippo signaling pathway regulation by hormonal signals acting through G-coupled receptors has been widely described. Modulation of processes such as tissue growth or differentiation by this pathway critically relies on the location and levels of its major effectors: the cofactors YAP/TAZ and the family TEAD of transcription factors. Despite this well-defined regulatory mechanism, little is known about the Hippo pathway in the thyroid gland. Thyrotropin (TSH), main factor for thyroid follicular cells differentiation, plays its role by interacting with its G-protein-coupled receptor (TSHR). High serum TSH levels are associated with hypothyroidism, characterized by a change in thyroid follicle morphology and inflammation of the thyroid gland. This led us to study if TSH could modulate the Hippo pathway. Rat thyroid follicular cells (PCC13) were treated with TSH and forskolin, an adenylyl cyclase activator. By immunofluorescence and western blot, levels and subcellular location of the Hippo Pathway components were assessed in different conditions. An increase of the Hippo kinase MST1/2 and LATS1/2 was observed after TSH and forskolin treatments, corresponding to a downregulation of the transcriptional mediators of the pathway TAZ, YAP and Tead1. Especially remarkable is the translocation of YAP/TAZ from the nucleus, which involves a decrease in their activity. Next, we validated the results in an *in vivo* model generating hypothyroidism in 3-month-old male C57BL/6J by adding MMI

(2-Mercapto-1-Methylimidazole) and perchlorate (KClO<sub>4</sub>) to their drinking water. After 2 weeks of treatment, we euthanized the animals, validated higher TSH serum levels and performed analysis of the Hippo components in the thyroid by immunohistochemistry. A reduction in the levels of the Hippo effectors TAZ, YAP and Tead1 was found in the thyroid slices from hypothyroid mice, confirming the *in vitro* results. In addition, evaluation of a human thyroid tissue microarray, including Hashimoto disease samples, led to a validation of the previously described TSH role. Hereby, we report a crosstalk by which TSH is increasing the kinase axis of the Hippo pathway thus decreasing the activity of its main transcriptional effectors in the nuclei. Future research of the role of these transcriptional effectors will be carry out to discern if their decrease could be associated with the morphology changes linked to hypothyroidism.

## Diabetes Mellitus and Glucose Metabolism

### DIABETES COMPLICATIONS II

#### *Euglycemic Diabetic Ketoacidosis on Initiation of Ertugliflozin in a Patient With Type 2 Diabetes Mellitus Precipitated by a Ketogenic Diet*

Ryan Richstein, D.O., Christopher Palmeiro, D.O., M.Sc.

AtlantiCare Regional Medical Center, Atlantic City, NJ, USA.

#### MON-LB124

**Background:** Diabetic ketoacidosis (DKA) is defined by metabolic acidosis, ketosis and hyperglycemia. It is considered to be a consequence of significant insulin deficiency and/or insulin resistance and is usually precipitated by the presence of hyperglucagonemia or other counterregulatory hormones. In patients on oral sodium-glucose cotransporter 2 (SGLT2) inhibitors, decreased carbohydrate availability through renal glucose excretion can cause serum glucose levels to be lower than what is normally seen (< 200 mg/dL) in DKA cases, masking the diagnosis. This phenomenon is termed euglycemic DKA (EuDKA). Existing evidence suggests that EuDKA in the setting of SGLT2 inhibitor use is rare and occurs mostly in patients with type I diabetes mellitus (T1D) and seldom in type 2 diabetes mellitus (T2D). Most published reports of EuDKA in patients with T2D describe patients on SGLT2 inhibitors with clear inciting events such as decreased insulin doses, surgery, or severe acute illness. To our knowledge, none have reported EuDKA precipitated by ertugliflozin. This is also the first report of EuDKA of a patient in the United States with T2D initiating SGLT-2 inhibitor use while on a low carbohydrate diet. **Clinical Case:** A 53-year-old female with a history of poorly controlled T2D was admitted to the hospital with EuDKA within seven days of starting ertugliflozin and alogliptin. Patient admitted to strict adherence to a low-carbohydrate diet for one week prior to admission. On admission, the patient was afebrile. Initial labs showed blood glucose 104 mg/dL, serum bicarbonate 8 mmol/L, anion gap 22, pH 7.100, beta-hydroxybutyrate 66.94 ng/mL (0.20-2.81), and a hemoglobin A1c of 11.2%. Urinalysis revealed glucosuria ≥500 mg/dL, ketonuria 80 mg/dL, hyaline cast 20/lpf, no nitrites or leukocyte esterase, WBC 1/hpf. Flu PCR negative. WBC count was 17.4 x10<sup>3</sup>/uL initially, though all CBC cell lines decreased with