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Neuroendocrinology and Pituitary
PITUITARY TUMORS I

METTL3 Promotes Sparsely Granulated GH-Secreting Pituitary Adenomas to Behavior as Densely Granulated Adenomas

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SAT-LB61

Background: Growth hormone (GH)-secreting pituitary adenomas can be divided into densely and sparsely granulated subtypes, based on electron microscopic studies. The latter are frequently associated with more invasive behavior, and respond worse to somatostatin analogues. The underlining mechanisms are largely unknown. Increasing evidence showed that N6-methyladenosine (m6A) of messenger RNAs (mRNAs) participated in the development of various tumors. We aimed to investigate the role of RNA m6A modification in the classification of GH-secreting pituitary adenomas. **Methods:** The main components of m6A methyltransferase complex, demethylase, and RNA m6A levels were compared between sparsely and densely GH-secreting tumors. The role of METTL3 was functionally studied. **Results:** The level of m6A methyltransferases (METTL3, WTAP and METTL14) and demethylase (FTO and ALKBH5) were significantly downregulated in GH adenomas, comparing to the normal pituitary tissues. However, only METTL3 and METTL14 were shown to significantly higher in densely granulated tumors than those in sparsely ones. Consistently, the level of RNA m6A was markedly increased in densely granulated GH adenomas. In addition, the expression of METTL3 was positively correlated with the level of RNA m6A among tumor samples, and METTL3 silencing decreased RNA m6A of GH3 cells. METTL3 was demonstrated to function as a tumor suppressor based on *in vivo* and *in vitro* evidence, using patient-derived and GH3 cells. Moreover, the sensitivity of GH3 cells to pasireotide was increased with METTL3 overexpression, but decreased when METTL3 was silenced. Consistently, METTL3 silencing inhibited GH secretory, and decreased the expression of SSTR2 and SSTR5. **Conclusions:** METTL3 functions as a tumor suppressor in GH secreting adenomas, and enhance tumor cells sensitivity to medical treatment. Our work uncovers the critical roles of METTL3 in the pathogenesis of GH adenomas, since it potentially promotes the transition from sparsely to densely granulated subtypes.

Neuroendocrinology and Pituitary
PITUITARY TUMORS II

Title: The Genomic Landscape of Sporadic Thyrotrophinomas

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MON-LB48

Title: The genomic landscape of sporadic thyrotrophinomas

Background: Thyrotrophinoma (TSHoma) is rare and knowledge on the genomic landscape of this tumour type is very limited.

Aim: To perform whole-exome sequencing (WES) in a population of TSHomas to identify recurrent somatic genetic events

Method: WES was performed on paired tumour and germline DNA of 7 patients with TSHomas. Three tissue samples were formalin-fixed paraffin-embedded and 4 fresh frozen tumour samples. Fresh blood samples were also collected from each patient. The average of mean depth of coverage amongst all samples was 129X, and 97% of target bases were covered ≥20X.

Results: Four (57%) of the seven patients were male and median age at diagnosis was 52 years. (IQR 46, 60) Six patients (86%) had macroadenomas. Four patients (57%) had central thyrotoxicosis at diagnosis and three patients' tumour stained positive for TSH on histology examination. Two patients (29%) had growth hormone co-secreting tumours. In total, 69 somatic variants were identified to be of potential interest, averaging 1.4 variants per million base-pair of DNA read. No variants were observed in more than one individual. According to the GTEx database, 9 of 69 genes (*DRC3, HDAC5, KDM1A, POLR21, TCF25, THAP7, TTC13, UNC5D, UNC13A)* were highly expressed in the pituitary (top 10%). Four of these genes appear to contribute to tumour development via epigenetic pathway. Specifically, three of these genes (*HDAC5, KDM1A, THAP7*) either interact with or form part of histone deacetylases whilst POLR21 encodes a subunit of RNA polymerase II which is responsible for mRNA synthesis. On the other hand, *TCF25* gene is thought to act as transcriptional repressor and UNC5D plays a role in cell-cell adhesion.

Large scale copy number variations involving gain or loss of whole chromosome or chromosome (chr) arm were observed in six (86%) tumour samples. Chr 5, 9, 13 and 19 were most commonly affected by chromosomal gains. Deletion of chr 1p was seen in two cases and mutations in *KDM1A*

(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.
ConclusionOverall, 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

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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_2S)-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^+ efflux), respectively. Protein expression was evaluated by Western-blot; NO and H_2S 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_2S has been demonstrated to have EDH activity in several blood vessels we investigated this pathway. H_2S 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_2S 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_2S, 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

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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