

SAT-723

Endocrine Disrupting Chemicals (EDCs) are substances that have been increasingly implicated in many serious pathologies, such as tumor formation, metabolic, growth and reproductive disorders. The economic and health burden of exposure to these compounds has an annual predicted cost in excess of €150 billion, across the EU regions alone. Of the growing list of compounds that act as EDCs, the organohalogenated compounds (OHCs), polybrominated diphenyl ethers (PBDEs) and polychlorinated biphenyls (PCBs) have been associated with an increased risk of pituitary disease. We have previously reported that feline patients with hypersomatotropism (acromegaly) are exposed to elevated levels of PBDEs and PCBs in their environment. However, the mechanisms by which these compounds might directly influence somatotroph function have yet to be established. In this study, we use the GH3 rat somatolactotrope cell line to investigate how two PCB congeners - 138 and 153 - influence cell proliferation (using a Crystal Violet assay) and somatotrope gene expression (using a multiplex RT-qPCR approach to examine expression of *Esr1*, *Esr2*, *Sstr1*, *Sstr2*, *Sstr3*, *Sstr4*, *Sstr5*, *Insr*, *Tshr*, *Pou1f1*, *Ghrhr2*, *Gh*). GH3 cells were treated with Phenol Red-free media in the absence or presence of either PCB138 or 153 (-10 to -6 M), or in combination (-10 to -6M) for up to 72h. Treatment with either PCB alone, or in combination, caused significant concentration-dependent, biphasic changes in cell proliferation at each time point, but with a different profile of response on each day (significantly increased at high pM/low nM concentrations); there was no evidence of toxicity at maximum concentrations (-6M). Gene expression changes were determined in GH3 cells treated in the absence or presence of either -8M or -6M PCB138 or 153 for 24h. Differential effects of these compounds were seen on the expression of *Sstr3*, *Sstr4*, *Sstr5* and *Insr*; all other gene transcripts were unaffected. These findings reveal that GH3 cells exposed to physiologically relevant concentrations of PCB138 and 153, alone or in combination, show concentration-dependent increases in cell proliferation; furthermore, the expression of genes associated with therapeutic targets for the treatment of acromegaly (i.e. SSTRs) are differentially affected by exposure to PCB138 and 153. Our data indicate a potential mechanism for EDCs in the onset of acromegaly, that require further, *in vivo*, investigations.

Adipose Tissue, Appetite, and Obesity**ADIPOSE TISSUE BIOLOGY AND OBESITY II****Micronas in Brown and White Adipocytes**

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SUN-584

Two types of adipose tissue exist: white (WAT) and brown (BAT). WAT stores energy while BAT consumes fatty acids and produces heat by non-shivering thermogenesis through Uncoupling Protein 1 (UCP1). BAT and WAT cooperate in maintaining energy homeostasis balance. Understanding

their physiology is important for the development of treatments against diseases where this equilibrium is compromised, such as obesity and associated metabolic disorders. MicroRNAs (miRNAs) are potent gene regulators and an increasing body of evidence suggests their involvement in adipogenesis and adipose metabolism. MiRNAs can also be secreted into the extracellular environment and be taken up by distal cells, mediating cell-to-cell communication. However, very little is known about adipose tissue-derived circulating miRNAs. Through miRNA PCR array analysis we identified several miRNAs that are differentially secreted among undifferentiated and differentiated brown and white adipocytes, such as miR-196a, 378a-3p and miR-138-5p. Bioinformatics target prediction revealed that these miRNAs are potentially involved in important processes regulating the functioning of adipose tissue and its cross-talk with distal cells. Among the predicted targets of miR-196a, we identified ADAM10 (A Disintegrin And Metalloproteinase Domain-containing protein 10). This protein is responsible for the proteolytic release of several cell-surface proteins involved in numerous biological processes such as inflammation and its role could be of relevant importance in the physiopathology of the adipose tissues.

Adrenal**ADRENAL - TUMORS****High Prevalence Alterations on DNA Mismatch Repair Genes Related to Lynch Syndrome in Pediatric Patients with Adrenocortical Tumor Carried of the Germline Mutation on TP53**

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SAT-155

Background: Adrenocortical cancer (ACC) is a rare malignant neoplasia associated with a variable clinical presentation. Pediatric patients generally have a better prognosis when compared to adults. In addition, unlike in adults where ACC which is usually sporadic, 50-80% of pediatric ACC is associated with genetic disorders such as Beckwith-Wiedemann and Li-Fraumeni syndromes. Recently, was

showed that 3-5% of adult patients with ACC presented germline variants in DNA mismatch repair genes such as *MSH2* and *MSH6*, the cause of Lynch syndrome (LS). The prevalence of these alterations in pediatric ACC is unknown. We aimed to investigate the prevalence of germline alterations in DNA mismatch repair genes among pediatric and adult patients with adrenocortical tumors (benign and malignant) carriers of the germline *TP53* p.R337H mutation. **Methods:** 35 patients selected (30 pediatric and 5 adult) with functional tumors. ACC was diagnosed in 4 pediatric and in all adult patients. NGS was performed in 35 DNA blood samples by HNPCC MASTR Plus for the identification of SNV in 4 genes (*MLH1*, *MSH2*, *MSH6*, and *PMS2*) and 3' UTR of *EPCAM*. Copy number variation (CNV) analyses were done by Copy Number Targeted Resequencing Analysis (CONTRA) and MLPA. The variants were classified, according to ACMG (American College Medical Genome) by Varsome platform. The protein expression was evaluated by Immunohistochemistry (IHC): *MLH1* (clone ES05), *MSH2* (FE11), *MSH6* (EP49), and *PMS2* (EP51). All patients were evaluated for variants in *TP53*. **Results:** NGS: 2 children presented 2 pathogenic allelic variants associated with LS (2/30, 6.6%), both patients with benign outcome and follow up of 4 years: 1 deletion in *MLH1* (c.1500_1502del) and 1 nonsense in the *MSH6* gene (c.328C>T p.Arg110X. CNV: MLPA specific for *MLH1/MSH2* showed a normal copy number. ICH: the loss of expression in *MLH1/PMS2* was identified in only one case without allelic variants. **Discussion:** Although our cohort is small, we observed 2 allelic pathogenic variants associated with LS among pediatric with adrenocortical tumors. It is higher than the prevalence of colorectal and endometrial cancer (3.2%) in LS. A personal and family history of LS tumors should be strongly considered for genetic risk assessment in pediatric patients with ACT. If the association with *TP53* alteration can influence the tumor's behavior with early clinical presentation, as seen in hereditary nonpolyposis colorectal cancer, it needs to be investigated. The patients with both alterations must be followed with surveillance, according to the US Multi-Society task force guideline for Lynch syndrome and for Li-Fraumeni syndrome.

Diabetes Mellitus and Glucose Metabolism

DIABETES COMPLICATIONS II

EDKA and MALA in the Setting of Severe Heart Failure and Acute Renal Failure, Due to SGLT2-i

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Background: EDKA is a reported potential side effect of SGLT-2i that presents a unique challenge for diagnosis and management in the setting of HF and concurrent AKI. Literature encourages wide use of SGLT-2i's, however this case demonstrates the need of proper evaluation before initiating therapy.

Case: A 53 year old male with PMH of T2DM, Atrial fibrillation, HFrEF, presented to the Emergency Dept after a week of confusion, nausea, vomiting, and diarrhea. These symptoms were presumed due to gastroenteritis and our

patient continued working on his farm in the summer heat. Following 3 days of intractable vomiting, he began to develop confusion, took his medications and presented to the ED. He was on metformin and had recently started empagliflozin following a heart failure exacerbation. Upon arrival the patient was noted to have a severe AKI with Cr of 15, hyperkalemia with potassium of 7.7, Anion gap of 45, bicarbonate of 4. Lactic acid was noted to be 7.7 and BHB was later noted to be 10.5 with a serum blood glucose of 155.

Pt was determined to have Euglycemic Diabetic Ketoacidosis with an additional Metformin associated lactic acidosis. He was started on an insulin drip with a concurrent D20 infusion to minimize fluid intake. Dextrose was titrated up to maintain a goal BG of 150-180 while on a stable insulin rate of 5u/hour, while monitoring serum ketones to resolution of DKA. Due to excess fluid intake he required intubation and later, hemodialysis due to metformin associated lactic acidosis and acute renal failure. Following 3 days of dialysis he was able to successfully wean from vent and pressors, making a complete recovery.

Conclusion:

We present a patient with EDKA likely resulting from dehydration induced AKI compounded by SGLT2i induced diuresis. As he developed his kidney injury, metformin was able to build up to toxic levels inducing lactic acidosis. Treatment in this patient was based on the underlying physiology providing glucose to allow resolution of ketosis. Treatment is not well studied, but given the origin of the pathology should resemble a standard DKA protocol with glucose repletion. SGLT2i and metformin combinations have shown an increased risk of metabolic acidosis¹ and lactic acidosis². This case highlights a potential risk of the combination in the setting of renal insufficiency and tenuous fluid states.

References:

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Diabetes Mellitus and Glucose Metabolism

LIPIDS, OBESITY AND METABOLIC DISEASE

Novel Insights into the Entero-Insular Axis in Fibrocalcific Pancreatic Diabetes: An Isoglycemic Intravenous Glucose Infusion (IIGI) Study from India

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SAT-650

Abstract: In tropical countries including India, one of the common causes for young onset diabetes mellitus (DM) is "Fibro Calcific Pancreatic Diabetes" (FCPD) characterized