[1]Univ of Michigan Med School, Ann Arbor, MI, USA, [2]University of Michigan, Ann Arbor, MI, USA, [3]Univ of Michigan, Ann Arbor, MI, USA.

SUN-017

Prenatal exposure to excess testosterone (T) programs peripheral insulin resistance and dyslipidemia along with tissue-specific increases in ectopic lipid accumulation, oxidative stress and insulin resistance in liver and muscle of the early adult female sheep. Prenatal T increased inflammation and oxidative stress in the visceral (VAT) but not subcutaneous (SAT) adipose tissue, with no effect on insulin sensitivity in both depots. These systemic and tissue-specific metabolic changes are reminiscent of defects such as non-alcoholic fatty liver disease (NFLAD) common among aged individuals. Because it is known that gestational insults can program premature aging of reproductive organs and chronic cardiovascular abnormalities, we hypothesized that programming of premature cellular senescence is one of the ways through which gestational T induces premature aging of metabolic systems during early adulthood. To test this hypothesis, mitochondrial oxidative phosphorylation (OXPHOS) and telomere length, as measure of cellular senescence, were assessed in liver, muscle, VAT and SAT collected from control and prenatal T- (100mg T propionate twice a week from days 30-90 of gestation) -treated female sheep at 21 months of age. Genomic DNA was subjected to TeloTAGG Telomere Length Assay (Sigma-Aldrich, St Louis, MO) and whole tissue protein lysates analyzed by immunoblot using Total OXPHOS Human WB Antibody Cocktail (ab110411, Abcam, Cambridge, MA). Data were analyzed by Student's t test and Cohen's effect size analysis. Prenatal T-treatment induced 1) a trend ($p = 0.09$) towards a large magnitude increase in shorter telomere fragments (0.08 -3.6 KB) in the liver and 2) a non-significant large magnitude decrease in shorter telomere fragments in muscle and SAT without having any effect in the VAT. Prenatal T also induced a large magnitude increase in mitochondrial OXPHOS protein complexes II and IV in liver, without having an effect at the level of the muscle, VAT and SAT. These findings are suggestive that prenatal T-treatment induced hepatic defects may involve premature cellular senescence. The relevance of parallel increase in mitochondrial OXPHOS in the liver is unclear and remains to be explored. The defects observed in the muscle and SAT may occur independent of cellular senescence or alterations in mitochondrial function. The lack of change in telomere length and mitochondrial OXPHOS in spite of increased inflammation and oxidative stress in the VAT is suggestive of a potential protective function in play, consistent with maintenance of the insulin sensitivity in this tissue. This study, therefore, raises the possibility that metabolic defects programmed by gestational insults may involve premature aging of metabolic organs in a tissue-specific manner and have translational bearing in conditions associated with hyperandrogenic states.

Tumor Biology

TUMOR BIOLOGY: GENERAL, TUMORIGENESIS, PROGRESSION, AND METASTASIS

Breast Tumor Kinase (Brk/PTK6) Mediates Triple Negative Breast Cancer Cell Migration and Taxol Resistance via SH2 Domain-Dependent Activation of RhoA and AhR

Amy Renee Dwyer, PhD[1], Carlos J. Perez Kerkvliet, BS[1], Raisa Krutilina, PhD[2], Hilaire Playa, PhD[3], Deanna Park, PhD[3], Warner Thomas, BS[3], Branden Smeester, BS[1], Tiffany Nicole Seagroves, PhD[4], Carol A. Lange, PHD[5].
[1]University of Minnesota, Minneapolis, MN, USA, [2]University of Tennessee, Memphis, TN, USA, [3]University of Tennessee, Tennessee, TN, USA, [4]The University of TN Health Science Center, Memphis, TN, USA, [5]Univ of Minnesota, Minneapolis, MN, USA.

SAT-133

Triple negative breast cancer (TNBC) patients have higher recurrence rates and a worse prognosis relative to patients diagnosed with other breast cancer subtypes. Protein tyrosine kinase 6 (PTK6; also called Brk), a soluble tyrosine kinase, is overexpressed in 86% of breast cancer patients, however its precise function in the context of TNBC is poorly defined. PTK6 expression is elevated in TNBC models in response to both cellular and endocrine stress, coordinated transcriptionally by the Hypoxia-Inducible Factors (HIFs) and glucocorticoid receptor (GR). We showed previously that PTK6 expression, but not its intrinsic kinase activity, is required for breast cancer cell motility. To further delineate the mechanisms of PTK6 signaling, we created kinase-intact domain structure mutants of PTK6 via in frame deletions of the N-terminal SH3 or SH2 domains. MDA-MB-231 cells expressing a PTK6 variant lacking the SH2 domain (SH2-del PTK6) were less responsive to growth factor-stimulated cell motility relative to wild type or kinase dead (KM) controls. To identify signal transduction pathways activated in TNBC cells harboring PTK6 domain mutants, we used a reverse phase protein array (RPPA), which revealed that the SH2 domain of PTK6 mediates TNBC cell motility via activation of the RhoA and/or AhR signaling pathways. Moreover, in TNBC cells, including a taxane-refractory TNBC model, addition of AhR or Rho inhibitors to paclitaxel (Taxol) enhanced cytotoxicity. Together, these studies reveal that the SH2-domain of PTK6 is an effector of advanced cancer phenotypes in GR+ TNBC cells and identify RhoA and AhR as novel therapeutic targets in PTK6+ tumors.

Diabetes Mellitus and Glucose Metabolism

TYPE 1 DIABETES MELLITUS

The Perfect Storm for Diabetic Ketoacidosis

Layla A. Abushamat, MD, MPH[1], Rajat Bhalla, MD[1], Jane E. Reusch, MD[2].
[1]University of Colorado, Denver, CO, USA, [2]Denver VAMC, Aurora, CO, USA.

SAT-670

Background

Diabetic Ketoacidosis (DKA) is a life-threatening endocrine emergency characterized by metabolic acidosis occurring in the setting of hyperglycemia due to relative insulin deficiency leading to lipolysis and production of serum ketones. Clinical circumstances can potentiate this process, such as acute infection or insulin discontinuation. Additionally, patients on SGLT2-inhibitors are at risk for euglycemic DKA. In people with type 2 diabetes, DKA is uncommon; however, a combination of precipitating factors in these patients can lead to a greater risk of DKA, particularly in the setting of SGLT2-inhibitor use.

Clinical Case
A 63 year old male with past medical history significant for uncontrolled type 2 diabetes (10 year duration, HgA1c=11.2%, on insulins detemir and aspart, metformin, and empagliflozin), coronary artery disease, and treatment refractory antibody-negative polymyositis (baseline CPK levels ~1000-2000, on a burst of prednisone for flare) presented with fever (101.2F), fatigue, myalgias, and nausea with poor oral intake and insulin cessation after recent IV zoledronic acid infusion for prevention of steroid-induced osteoporosis. He was found to be acidemic with bicarbonate=16, AG=18, Cr=1.6 (baseline 1.1), lactic acid=2.9, glucose=245, glucosuria/ketonuria, serum osmolality=295, and CPK=3613. No infectious etiology was found. Differential diagnosis of precipitating factors of DKA includes: steroid-induced hyperglycemia with lipolysis and insulin resistance; starvation ketosis from poor oral intake due to bisphosphonate-induced flu-like illness; metformin-associated lactic acidosis in setting of acute kidney injury; ketone production secondary to insulin cessation in setting of febrile illness; and SGLT2-inhibitor use with dehydration secondary to decompensated hyperglycemia. He was treated for DKA with insulin and volume resuscitation. He was discharged with discontinuation of empagliflozin.
Conclusion
In people with type 2 diabetes and multiple medical problems, a collusion of clinical factors leading to acidemia can occur simultaneously and lead to a drastically increased risk of DKA, especially in the setting of SGLT2-inhibitor use. Clinicians should have heightened awareness of minor predisposing factors that in combination can increase risk of DKA in a patient with type 2 diabetes.

Thyroid

THYROID DISORDERS CASE REPORTS I

Graves'Disease and Autoimmune Hepatitis: Management Challenges.

Maria Marta Sarquis Soares, MD,PHD[1],
Luísa Lima Castro Schutze, MD[1],
Luciana Cristian Coelho Garcia, MD[1],
Felipe Augusto Azevedo Leão felipealeao@hotmail.com, MD[1],
Lilian Mara Nunes Maia, MD[1], Nina Ramalho Alkmim, MD[1],
Maria Fernanda Marinho Saraiva, MD[1], Beatriz Santana Soares, PHD,MD[2].
[1]Univ Fed de Minas Gerais, Belo Horizonte MG, Brazil,
[2]Universidade Federal de Minas Gerais, Belo Horizonte, Brazil.

SUN-502
Graves' disease (GD) is the most common etiology of hyperthyroidism and may be associated with other autoimmune disorders. Case report: A.J.M.N., 27 years old, previously healthy, presented with abdominal discomfort, nausea and headache. She used paracetamol 750mg t.i.d for seven days. After that, she noticed jaundice and sought medical care. On admission, patient was icteric, oriented, afebrile, without signs of heart failure or alterations in the intestinal habit. Admission laboratory tests: AST 1287 U/L (RR<46), ALT 1090 U/L (RR < 50), total bilirubin (TB) 45.66mg/dL (RR<1.3), direct bilirubin 42.22mg/dL (RR<0.8), TSH 0.04 mcUI/ml, FT4 > 6.99 ng/dL (RR< 2.19). Serology for infectious diseases (A, B and C viral hepatitis; cytomegalovirus; Epstein-Bar Virus, syphilis; Dengue virus) were negative. Available antibodies for autoimmune hepatitis (anti-LKM1, anti-mitochondria, anti-smooth muscle, anti-SSB, anti-SSA, anti-Rnp / Sm, anti-DNA) were non-reactive. Ceruloplasmin and serum copper were normal. TRAB 3 IU/L (RR<1.75 IU /L); Thyroid scintigraphy showed homogeneous distribution of parenchymal contrast and regular contours of the gland; 15-minute uptake was 9.19% (RR: 1%-6%). Propranolol (40mg q.i.d) was prescribed. Burch and Wartofsky score was 30 (possible previous infection episode as precipitation factor = 10 points and unexplained jaundice = 20 points). Since the patient did not have diagnostic criteria for thyroid storm and since liver function was greatly altered, we opted to treat the thyroid disease with 12mCi of radioiodine, instead of antithyroid drugs (ATD). Differential diagnosis of the liver disease, whether due to autoimmunity or due to hyperthyroidism itself or both, were considered. Corticosteroid therapy (prednisone 40mg) was added due to the possibility of the coexistence of GD and autoimmune hepatitis previously reported as been 1.8% of the autoimmune hepatitis cases. Liver biopsy was performed 4 days later, and the findings were compatible with this condition. Ten days after prednisone and 20 days after radioiodine, we noticed a drop in TB (45 to 20mg/dL) and liver enzymes (AST= 69 and ALT 106) and she was discharged with normal FT4. Autoimmune hepatitis and GD presents a management challenge because sometimes it is not possible to confirm the etiology before treatment. The abnormalities could have been due to hyperthyroidism itself, since all autoantibodies to autoimmune hepatitis have been ruled out, but liver biopsy was very suggestive of the autoimmune cause. Initiating ATD for rapid improvement of hyperthyroidism could represent a risk due to hepatotoxicity of these drugs. On the other hand, withholding the treatment in cases of hepatic insufficiency due to hyperthyroidism, can have disastrous consequences. The option with beta-blocker, radioiodine and corticosteroid was successful and might be considered in similar cases.

Thyroid

BENIGN THYROID DISEASE AND HEALTH DISPARITIES IN THYROID I

Insulin Resistance, Lipid Profile and High-Sensitivity C-Reactive Protein in Patients with Autoimmune Thyroiditis

Celestino Neves, MD[1], João Sérgio Neves, MD[2], Miguel Pereira, MD[2], Ana Oliveira, MD[2], José Luís Medina, MD, PhD[3], Luís Delgado, MD, PhD[4], Davide Carvalho, MD, PhD[1].
[1]Department of Endocrinology, Diabetes and Metabolism, São João Hospital Center, Faculty of Medicine of University of Porto; Institute for Research and Innovation in Health (i[3]S), University of Porto, Porto, Portugal, [2]Department of Endocrinology, Diabetes and Metabolism, São João Hospital Center, Faculty of Medicine of University of Porto, Porto, Portugal, [3]Faculty of Medicine of University of Porto, Porto, Portugal, [4]Department of Immunology, São João Hospital Center, Faculty of Medicine of University of Porto, Porto, Portugal.

SAT-431
Introduction: Thyroid function and autoimmunity has been associated with cardiovascular events in patients with