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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

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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

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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.