SUN-LB119

Hepatocyte Nuclear Factor 4α (HNF4α), the master regulator of liver-specific gene expression, is regulated by two promoters (P1 and P2) which drive expression of two groups of HNF4α isoforms referred to here as HNF4α1 and HNF4α7. HNF4α is a known regulator of gluconeogenesis and is mutated in maturity onset diabetes of the young one (MODY1). Conventionally, it was thought that HNF4α1, but not HNF4α7, is expressed in the normal adult liver, with HNF4α1 downregulated and HNF4α7 upregulated in liver cancer. Now, we identify a previously undescribed role for HNF4α7 in the normal adult mouse liver - one involved in the diurnal variations of lipid and carbohydrate metabolism. More specifically, HNF4α1 appears to be a major driver of gluconeogenesis while HNF4α7 is a driver of ketogenesis: we hypothesize that alterations in the levels of the HNF4α isoforms during the day function as a **molecular switch** between the two. Moreover, our preliminary data show that HNF4α7 is required for increased levels of circulating **ketone bodies** in female mice, suggesting interactions with the estrogen pathway. AMP-Activated Protein Kinase (**AMPK**), an energy-sensing kinase that also plays a major role in carbohydrate and lipid metabolism, has been shown to phosphorylate HNF4α1 *in vitro*, but effects *in vivo* and on HNF4α7 are not known. In order to investigate the impact of AMPK on HNF4α isoforms, we employed HNF4α isoform-specific mice α7HMZ (express only HNF4α7) and α1HMZ mice (express only HNF4α1), as well as heterozygous mice which express both. Intraperitoneal injection of the mice with AMPK activator AICAR leads to a rapid decrease in glucose. Interestingly, half the α7HMZ males and all the females began seizing 30 min post injection, while very few α1HMZ males/females and none of the heterozygous mice seized. Moreover, there were differences in the survival of the different genotypes: a third of α1HMZ mice die within 24hrs, while two thirds of α7HMZ mice die within a week, with all heterozygous mice surviving. We suspect the seizures could be due to an electrolyte imbalance exacerbated by AICAR or extremely low glucose caused by AICAR. The α7HMZ females have significantly lower potassium levels compared to α1HMZ and wildtype mice. Additionally, AMPK is known to regulate Na+/glucose transporters, and HNF4α1 is expressed in the proximal tubules in the kidney (responsible for Na+ uptake). To elucidate the cause of the seizures, AICAR injections were repeated with α1HMZ males followed by a glucose or saline gavage. Interestingly, half of the glucose-gavaged mice died within 24hrs, while all of the saline-gavaged mice survived. Our work underscores the critical role that the HNF4α isoforms play in the metabolic switch, and suggests that the kidney as well as the liver could be involved.

Neuroendocrinology and Pituitary

CASE REPORTS IN SECRETORY PITUITARY PATHOLOGIES, THEIR TREATMENTS AND OUTCOMES

Fahr's Syndrome: A Rare Neurological Disorder Unmasked by a Psychiatric Illness

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SAT-LB50

Fahr's syndrome is a rare familial disorder characterized by abnormal accumulation of calcium deposits bilaterally at basal ganglia. It commonly affects middle-aged adults and presents with a range of neuropsychiatric symptoms. The exact prevalence of Fahr's syndrome is uncertain; however, intracranial calcifications suggestive of this disorder are detected incidentally in approximately 0.3 % to 1.2 % of CT imaging of the brain with a prevalence of 1/1,000,000. It may be idiopathic or secondary to numerous causes dominated by phosphorous and calcium disorders, with the most common etiology being hypoparathyroidism. We report the case of a 27 years old female patient with a medical history of insulin-dependent Diabetes Mellitus type 1, Bipolar disorder, Autoimmune Polyglandular Syndrome Type 1, Thalassemia major, Primary Hypoparathyroidism and Bronchial Asthma who was admitted to the hospital after presenting an episode of dizziness, slurred speech and involuntary movements associated to hypoglycemia. The patient had a medical history of recurrent episodes of conscious self-induced hypoglycemia with double doses of insulin therapy and noncompliance with home medications. Upon evaluation, patient presents aggressive and defiant behavior. Physical and neurological examination was difficult to assess since she refused to be examined. Laboratories were remarkable for serum calcium of 6.2mg/dl, albumin of 3.5g/dl, with corrected calcium levels of 6.5mg/dl, suggestive of severe hypercalcemia. Head CT scan showed bilateral subcortical, basal ganglia clouded, thalamic, and cerebellar calcifications with preserved gray and white matter differentiation. Treatment was tailored to symptoms control and correction of underlying abnormalities. These case present the most critical features of the diagnostic criteria of Fahr's syndrome. Pathologically, calcifications occur in the vascular walls and in the perivascular spaces of arterioles, capillaries, and veins. Clinical findings of Fahr's syndrome vary from neurological disorder to those mimicking Bipolar disorder. In this case, there were no neurological symptoms, and this patient only presented with psychiatric manifestations suggestive of bipolar disorder. For any psychiatric condition, it is essential to rule out organic brain disorders before labeling a patient, especially one who is young and has multiple endocrinopathies which could be associated with this rare condition.

Adrenal

ADRENAL - TUMORS

Repressive Epigenetic Programs Reinforce Steroidogenic Differentiation and Wnt/β-Catenin Signaling in Aggressive Adrenocortical Carcinoma

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SAT-LB34

Adrenocortical carcinoma (ACC) is a rare, aggressive cancer. Up to 75% of patients develop incurable metastatic disease, highlighting an urgent need for novel medical therapies. We recently identified a rapidly progressive ACC subtype characterized by CpG island hypermethylation (CIMP-high), sustained Wnt/β-catenin signaling, steroidogenic differentiation, and cell cycle activation. CIMP-high status alone accounts for 40% of ACC, but predicts 70% of recurrences and >50% of deaths. Intriguingly, hypermethylated CpG islands in CIMP-high ACC are unmethylated in fetal and adult adrenal cortex, suggesting DNA methylation is supported by cancer-specific mechanisms. We therefore sought to investigate how aberrant epigenetic programming contributes to ACC biology. In embryonic stem cells, the Polycomb repressive complex 2 (PRC2) represses differentiation programs through EZH2-mediated histone H3 lysine 27 trimethylation (H3K27me3) deposition in promoter CpG islands free of DNA methylation. Gain or loss of EZH2/PRC2 function prevails in a variety of human cancers, enabling proliferation in a tissue-specific manner. Here, we identify that CIMP-high ACC exhibit high expression of EZH2/H3K27me3, but paradoxically bear DNA hypermethylation in annotated PRC2 target regions. To determine if DNA methylation of PRC2 targets disrupts or is controlled by EZH2, we characterized EZH2's role in CIMP-high ACC cell line NCI-H295R at baseline and in response to EZH2 inhibition (EZH2i). EZH2-directed IP-MS revealed EZH2 interacts with PRC2 members and DNA methylation-sensitive accessory proteins, but no DNA methyltransferase machinery. ChIP-seq revealed EZH2 and H3K27me3 colocalize in repressive domains genome-wide, but DNA methylation and H3K27me3 are mutually exclusive. EZH2i induced H3K27 demethylation and loss of viability, but with no effect on CIMP-high DNA methylation. These data suggest PRC2 target DNA methylation in CIMP-high ACC is maintained independently of EZH2, enabling EZH2/PRC2 to coordinate alternative programs required for cell survival. We then measured the consequences of EZH2i on the NCI-H295R transcriptome (RNA-seq), EZH2/H3K27me3 deposition genome-wide (ChIP-seq), and chromatin accessibility landscape (ATAC-seq). EZH2i led to global downregulation of cell cycle, Wnt/β-catenin transcriptional programming, and steroidogenic differentiation, partially explained by EZH2i-induced offloading of EZH2 from H3K27me3 domains to accessible promoters genome-wide. Taken together, our studies illustrate how aberrant CpG island hypermethylation in CIMP-high ACC participates in a targetable repressive epigenetic cascade that reinforces oncogenic adrenocortical transcriptional programs. Ultimately, we hope to illuminate novel strategies for tissue-specific disruption of the aberrant epigenetic wiring that defines CIMP-high ACC.

Adipose Tissue, Appetite, and Obesity

ADIPOSE TISSUE BIOLOGY AND OBESITY II

The Transcriptomic Evidences on Role of Abdominal Visceral vs. Subcutaneous Adipose Tissue in the Pathophysiology of Diabetes in Asian Indian Indicates the Involvement of Both

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SUN-LB106

Introduction: Asian Indians show "thin fat phenotype" characterized by higher visceral adipose tissue(VAT) and lower subcutaneous adipose tissue(SAT) mass and their higher cardio-metabolic risk has been attributed to this fat distribution. However, the underlying molecular pathology and role of these adipose depots in the pathogenesis of T2D in them remains unknown.**Hypothesis:** The comparison of transcription profiles of abdominal VAT and SAT and their correlation with diabetes related intermediate phenotypic traits could shed some light on their role in the pathophysiology of diabetes.**Methodology** *Subjects*: 19 diabetics (*M: F* ratio, 8:11) and 16 age and BMI matched controls (*M: F* ratio 5:11) undergoing abdominal surgery (non-malignant and non-infective conditions).*Clinical Parameters*: Anthropometry, Serum glucose, insulin, HOMA-R, HbA1c, lipid profile, FFA, adipocytokines. Abdominal VAT, SAT and liver fat were estimated by MRI.*Adipose tissue biopsy*: SAT and VAT samples were taken during surgery. *Genome-wide gene expression profiling* of these biopsies was performed using Affymetrix GeneChipPrimeView® arrays. The data was submitted to NCBI-GEO (Accession # GSE78721). Selected genes were validated by qPCR. Gene set enrichment analysis (GSEA) for functional and Weighted Gene Correlation Analysis (WGCNA) for statistical comparison was done.**Results:**Diabetics had higher waist circumference (*p=0.05*), HOMA-R (*p=0.0002*), Visceral fat content (*p=0.02*) and adipocyte size (*p=0.02*)*GSEA: diabetics vs. controls*: In VAT 16 gene sets were upregulated (*FDR < 25%*) enriching various immune system and inflammation-related pathways. In SAT too, various inflammatory genes were upregulated however they were statistically non-significant (FDR > 25%). Moreover, 12 out of 16 significantly enriched pathways in VAT were among the top 20 pathways in SAT. *GSEA in diabetics: VAT vs SAT:* None of the gene sets were found significant at FDR < 25% which substantiated our hypothesis that overall pathophysioloigcal alteration in both depots are similar. *WGCNA for statistical comparison of VAT and SAT depots* The correlation between measures of average gene expression and overall connectivity between both depots was significantly positive. Several modules of co-expressed genes in both VAT and SAT showed positive as well as negative correlation with various intermediate phenotypic traits of diabetes. In both depots they enriched several pathways otherwise known to be associated with pathological adipose tissue like inflammation, adipogenesis etc.

Conclusions

In Asian Indians, diabetes pathology inflicts similar molecular alternations in VAT and SAT, which are more intense in the former. The role of both adipose depots in the pathophysiology of diabetes is along similar lines and they enrich several molecular pathways which are otherwise known to be implicated in pathological adipose tissue.