

refractory. With breast cancer as one of the leading causes of mortality in women, deeper understanding of lncRNAs can establish it as a potential therapeutic target. It will be determined the functional mechanisms by which lncRNAs, specifically lncRNA161, drives hormone-resistance in breast cancer. lncRNA161 was selected from a comprehensive list of lncRNAs due to it being expressed in reproductive tissue, being tamoxifen resistant, being robustly regulated by estrogen, and its association with the chromatin. It was determined that lncRNA161 was upregulated in breast cancers. When lncRNA161 was treated with estrogen, there was transcriptional activation and localization to the chromatin. Subsequent knockdown of lncRNA161 affected other genes in the estrogen signaling pathway. Overexpression of lncRNA161 demonstrated increased proliferation, and knockdown showed decreased proliferation indicating a role of lncRNA161 in tumor proliferation and progression in breast cancer. Altogether, the results suggest lncRNA161's involvement in the estrogen signaling pathway and establish it as a potential therapeutic target in hormone-refractory breast cancer. Supported by grant from the Cancer Prevention and Research Institute of Texas to S.S.G.

## Thyroid

### THYROID DISORDERS CASE REPORTS II

#### *A Severe Case of Pembrolizumab-Induced Thyroiditis*

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#### SAT-516

Pembrolizumab, a programmed death 1 (PD-1) inhibitor used for advanced malignancies, can be associated with thyroid dysfunction.<sup>1-2</sup> Specifically, thyroiditis occurs in nearly 2.3% of individuals.<sup>2</sup> The hyperthyroid phase is typically non-severe, requiring only beta blockers. Our case illustrates that conservative therapies may be ineffective in pembrolizumab-induced severe thyroiditis.

A 54-year-old woman with metastatic non-small cell lung cancer with normal baseline TSH received pembrolizumab. She was hospitalized nearly 30 days later with nausea, vomiting and tachycardia. Labs showed TSH <0.02 mcIU/mL (normal 0.3-4.7), free T4 >7 ng/dL (normal 0.8-1.7) and free T3 2105 pg/dL (normal 222-383). TSH receptor antibody was undetectable; hyperthyroidism was attributed to pembrolizumab. Metoprolol was initiated. She was re-hospitalized three days later with persistent symptoms and inability to tolerate orals. Labs again showed severe hyperthyroidism and TPO antibody 201 IU/mL (normal ≤ 20). Burch-Wartofsky score was 25. Given her symptom severity, propylthiouracil, hydrocortisone, and propranolol were initiated to reduce peripheral T4 to T3 conversion. A cortisol of 5 mcg/dL (collected 9:47AM) further supported the use of hydrocortisone. Following a normal Cosyntropin stimulation test, hydrocortisone was discontinued. Her symptoms improved but hypothyroidism developed 68 days after pembrolizumab initiation. Propylthiouracil was

discontinued; levothyroxine was started. Her TFTs ultimately normalized.

Beta blockers are the mainstay of treatment of the hyperthyroid phase of PD-1 inhibitor-related thyroiditis, though case reports have described use of glucocorticoids, anti-thyroid drugs and iodine.<sup>2-4</sup> In our patient, severe thyrotoxicosis was not responsive to beta blockers. Consideration of additional therapies is reasonable in these cases.

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## Adipose Tissue, Appetite, and Obesity CNS, INFLAMMATORY, AND THERMOGENIC INFLUENCES OF BODY WEIGHT

### *The Role of the Sympathetic Nervous System in Metabolic Disorder and Adipose Dysfunction in Obesity and Aging*

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#### OR04-02

Both obesity and aging increase susceptibility to metabolic disease and type 2 diabetes where adipose tissue dysfunction is a hallmark. In both conditions, impaired autonomic control is believed to play a key role in disrupted CNS control of metabolism. However, the role of the sympathetic nervous system (SNS) and catecholaminergic signaling in metabolic disease has not been well defined in large part due to a lack of suitable animal models(1). Surgical denervation is not specific to the SNS and chemical sympathectomy through 6-hydroxydopamine causes inflammation due to toxic effects. Abrogation of catecholamine (CA) synthesis in the whole body due to genetic deletion of the gene

for tyrosine hydroxylase (*th*), a key enzyme in CA synthesis, results in embryonic lethality likely due to the lack of dopamine and norepinephrine in the CNS where they serve as key neurotransmitters.

Here we studied the role of the SNS and catecholaminergic signaling in metabolic control in both aging as well as high fat diet (HFD) induced obesity. We created a mouse model of inducible *th* gene deletion that is restricted to the periphery, including sympathetic fibers of the peripheral NS but spares the brain as a pharmaco-genetic model of sympathectomy(2). TH is deleted and CA levels were reduced more than 90% in peripheral tissues of TH KO mice, while intact in the CNS. TH KO mice are cold intolerant consistent with functional sympathectomy. Interestingly, TH KO mice are protected from HFD feeding induced glucose intolerance (AUC during GTT: WT 1018.8±42.0 mg/dl/hr vs. TH KO 485.0±85.8 mg/dl/hr;  $p < 0.0001$ ;  $n = 6$ ) even though food intake increased in TH KO mice. In 20 months old TH KO mice glucose tolerance was improved and fasting blood glucose levels were reduced (AUC during GTT: WT 357.3±16.2 mg/dl/hr vs. TH KO 254.5±15.6 mg/dl/hr;  $p < 0.01$ ;  $n = 12$ ) with higher insulin levels (WT 0.35±0.07 µg/l vs. TH KO 1.28±0.28 µg/l;  $p < 0.001$ ;  $n = 9$ ). Of note, insulin tolerance tests did not show marked differences. Both obesity and aging are characterized by impaired adipose tissue function with reduced lipogenic capacity. TH KO mice fed a HFD exhibit increased WAT de novo lipogenesis, lower lipolysis, and trend to exhibit decreased adipose tissue inflammation, suggesting that the SNS is a major culprit for the impaired lipogenic capacity in adipose tissue. Our data provides support for the paradigm that impaired SNS function plays an important role in the dysmetabolic states of obesity and aging.

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## Adipose Tissue, Appetite, and Obesity ADIPOSE TISSUE BIOLOGY AND OBESITY II

### *Adipocyte Specific Endothelin a Receptor Knockout Increases Adiposity in Mice*

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#### SUN-592

Obesity is associated with increased levels of Endothelin-1 (ET-1). Blockade of ET-1 type A receptors (ET<sub>A</sub>) improves lipid profile in patients with chronic kidney disease; however the mechanism is unknown.[1] In adipocytes ET<sub>A</sub> activation increases lipolysis, a potential mechanism for elevated lipids in obese individuals.[2] Therefore, the goal of

this study was to determine if adipocyte specific knockout (KO) of the ET<sub>A</sub> receptor in mice alters genes associated with lipid metabolism in adipose and improves plasma lipids. 24-week old adipocyte ET<sub>A</sub> knockout mice had significantly elevated body weight compared to floxed controls (32.6±1.0 vs. 29.5±0.7 g respectively). Echo MRI revealed that the increased body weight was due to greater adiposity (10.1±0.9 vs. 14.7±1.8 % body weight; floxed vs. KO), while no statistical difference was observed in lean weight (88.9±2.4 vs. 86.8±2.6 % body weight; floxed vs. KO). Surprisingly, there were no statistical differences in plasma total cholesterol or triglycerides. RNA sequencing indicated downregulation of 597 genes and upregulation of 444 genes in visceral adipose and downregulation of 368 and upregulation of 847 genes in subcutaneous adipose. KEGG pathway analysis revealed that most genes altered in visceral adipose were related to metabolic pathways. These data implicate a role for adipose tissue ET<sub>A</sub> receptors in regulating adiposity and promoting pathophysiology related to obesity.

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## Genetics and Development (including Gene Regulation)

### GENETICS AND DEVELOPMENT AND NON-STEROID HORMONE SIGNALING I

#### *Reciprocal Regulation of miR-375 and ICER in Pancreatic Beta Cells*

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#### SUN-718

MicroRNA-375 (miR-375) is overexpressed in people with type 2 diabetes (T2D) and has been linked to decreased insulin secretion and beta cell proliferation. Investigation into the transcription factor inducible cAMP early repressor (ICER) as an intermediate regulator of miR-375 was proposed because both are regulated by the cAMP pathway. This overexpression of miR-375 in T2D led us to hypothesize that beta cells with elevated and reduced levels of miR-375 will result in decreased and increased glucose-stimulated insulin secretion (GSIS), respectively. Results showed that when miR-375 was overexpressed, GSIS decreased by 61% when compared to a control in 25 mM glucose. Results showed that when miR-375 was inhibited, GSIS increased 6% when compared to a control in 25 mM glucose. In human islets, we found that inhibiting miR-375 led to an average 19% increase in GSIS, though due to the variability of human tissue these