classes. The molecular programs contributing to disease pathogenesis in CA are still poorly characterized, largely restricted to the identification of somatic mutations in *USP8* in 40-60% of CD adenomas. To more fully characterize the mutational and transcriptional landscape driving both classes of CA, we performed whole-exome sequencing and RNA-seq in 19 CD and 16 AS adenomas. We identified *USP8* mutations in 53% of CD (10/19) and 6% of AS (1/16) samples. Strikingly, in 19% of AS tumors (3/16), all exhibiting an unusually aggressive disease course, including two cases with brain metastases, we identified recurrent somatic pathogenic mutations in *TP53* and novel loss-of-function mutations in telomere maintenance genes *DAXX* and *ATRX*. Furthermore, while all tumors with *USP8* mutations (regardless of CD/AS status) exhibited no chromosomal abnormalities as measured by copy-number variation (CNV) and loss of heterozygosity (LOH) analysis, 33% of CD (4/12, including 1 tumor with a *DAXX* mutation) and 36% of AS (4/11, including all *DAXX/ATRX*-mutated cases) samples exhibited profound chromosomal instability, characterized by hyperdiploidy, widespread whole-chromosome LOH events, and arm-level breakpoints. Using transcriptome analysis (n=22), we identified three classes of tumors (C1-C3), reflecting these distinct somatic alteration profiles. C1 tumors (n=6) are characterized by chromosomal stability, includes exclusively *USP8*-mutated CD, and exhibits upregulation of genes involved in metabolic processes and protein acetylation. C2 tumors (n=10) are comprised exclusively of AS (including all *TP53*- and/or *DAXX/ATRX*-mutated cases), are characterized by chromosomal instability, and exhibits concordant upregulation of cell cycle programs. Finally, C3 (n=6) contains a mixture of AS and CD cases (including CD without mutations in *USP8*) and features an expression profile that partly overlap with C1 tumors, but also exhibit higher expression of inflammatory genes. Taken together, our data suggest that CD and AS are distinct molecular subtypes of CA, highlighting the dominant role of *USP8* mutations in driving a unique transcriptional program and illustrate for the first time that unlike most cases of CD, AS cases are characterized by profound genomic instability and cell cycle activation, features associated with a more aggressive disease course.

Diabetes Mellitus and Glucose Metabolism

DIABETES DIAGNOSIS, TREATMENT AND COMPLICATIONS

A Continuous Remote Care Intervention Utilizing Carbohydrate Restriction Including Nutritional Ketosis Improves Markers of Metabolic Risk and Reduces Diabetes Medication Use in Patients With Type 2 Diabetes Over 3.5 Years

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SUN-LB113

Novel lifestyle, pharmaceutical, and/or surgical therapies for type 2 diabetes (T2D) are under study to assess lasting impact on metabolic risk. Among them, carbohydrate restriction including nutritional ketosis (CR) has emerged as a safe and effective nutrition therapy for reducing hyperglycemia in patients with T2D[1], yet longer term effects are unknown. At the conclusion of a 2-year study assessing a continuous remote care intervention utilizing CR (CCI) among patients who selected this therapy, intervention participants were offered the opportunity to consent to participate in a 3-year extension assessing outcomes at 3.5- and 5-y following initial enrollment. 143 of 169 extension-consented participants provided data at 3.5-y follow up. Among 3.5-y completers, linear mixed effects models were used to assess change over time in diabetes-related outcomes and McNemar's tests were used to assess for a difference in the proportion of participants meeting certain criteria at baseline compared to follow-up. At enrollment, 3.5-y completers were (mean±SE) 55±1 y of age, 40.8±0.7 kg/m^2, and 8±1 y since diagnosis. Following treatment with the CCI for 3.5 y, significant improvements compared to baseline were observed in HbA1c (-0.6±0.1 from 7.4±0.1%; $P = 1.9\text{x}10^{-5}$), weight (-10.9±1.1 from 117.4 kg; $P = 6.9\text{x}10^{-17}$), nonHDL-C (-10±4 from 139±3 mg/dL; $P = 0.005$), triglycerides (-41±11 from 189±10 mg/dl; $P = 2.1\text{x}10^{-4}$), and HDL-C (+9±1 from 43±1 mg/dl; $P = 3.0\text{x}10^{-11}$); total cholesterol and LDL-C were statistically unchanged. The percentage of participants prescribed diabetes medication decreased from 84.6 to 67.1% ($P = 5.0\text{x}10^{-6}$), while 50.2% of diabetes medications and 71.4% of diabetes medications other than metformin were discontinued. The percentage of participants treated with no pharmaceuticals or monotherapy increased from 52.5 to 81.9% ($P = 1.3\text{x}10^{-8}$). 45.5% (65/143) of participants achieved HbA1c <6.5% with either no medication (34/65, 52%) or only metformin (31/65, 48%) at 3.5 y; 37.8% of participants maintained this status from 1 through 3.5 y of treatment. 22% of participants achieved diabetes remission at 3.5 y, and 17.5% of participants maintained remission status from 2 through 3.5 y of treatment. This demonstrates that clinically meaningful improvements across multiple markers of metabolic risk can be sustained in patients with T2D who selected treatment with this CCI for 3.5 y. Improvements in metabolic risk markers reduced the need for diabetes medication, allowing some patients to achieve and sustain diabetes remission. This ongoing trial will assess 5-y effects.

1. American Diabetes Association. Standards of Medical Care in Diabetes. Diabetes Care. 2020; 43(Supplement 1): S48-S65. 2. Athinarayanan SJ, et al. Front Endocrinol. 2019; 10:348.

Genetics and Development (including Gene Regulation)

GENETICS AND DEVELOPMENT AND NON-STEROID HORMONE SIGNALING I

Association of Receptor for Advanced Glycation End Product (RAGE) Gene Polymorphisms & Serum Levels of Soluble RAGE (sRAGE) With Metabolic Syndrome (MS) in Mexican Population

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SUN-LB131

Association of Receptor for Advanced Glycation End Product (*RAGE*) Gene Polymorphisms and Serum Levels of Soluble RAGE (sRAGE) with Metabolic Syndrome (MS) in Mexican Population

Background. RAGE, a multi-ligand type 1 transmembrane glycoprotein belonging to the immunoglobulin superfamily, transduces biological signals associated with chronic cellular stress related with inflammatory responses, tissue damage, chronic and degenerative diseases (1). sRAGE is a variant of RAGE derived from cell surface cleavage mechanisms that could potentially act as endogenous inhibitors of RAGE activity (2). *RAGE* gene is highly polymorphic, with polymorphisms that could be responsible for disease development, like -374T/A (rs1800624) and -429T/C (rs1800625) polymorphisms. These are located in the promoter region and have marked effect on transcriptional activity. However, there have been conflicting findings between the potential association of RAGE polymorphisms and the development of diseases. In this work, we evaluated -374T/A (rs1800624) and -429T/C (rs1800625) polymorphisms and measured serum sRAGE levels in Mexican population with MS.
Methods. A group of healthy men without any component of the MS (n=80), and a group of men with the MS (n=80) according to the harmonized criteria for the MS were included in this study. Blood genomic DNA was isolated and genotyped by RT-PCR for the -374T/A and -429T/C polymorphisms of *RAGE* gene. sRAGE in serum was measured with an ELISA kit. **Results.** The studied population complied with the Hardy-Weinberg equilibrium (p=0.58 for -374T/A, and p=0.79 for -429T/C). Differences were observed in all the components of the MS between the two groups (MS vs. healthy subjects, p<0.000). However, there were no differences in the population according to their genotype for the -374T/A (p=0.57) and -429T/C (p=0.59) polymorphisms. There was no difference in glucose (p=0.22), triglycerides (p=0.99), and cHDL (p=0.88) levels, or waist circumference (p=0.84) according to the genotype for the -374T/A polymorphism. The same was observed for the -429T/C polymorphism (glucose p=0.57, triglycerides p=0.69, cHDL p=0.77, waist circumference p=0.99). No association of MS with the -374T/A nor 429T/C polymorphism was found. There were no differences between groups in circulating sRAGE levels (p=0.132). **Conclusion.** According to our results, the -374T/A and -429T/C polymorphisms of *RAGE* gene are not associated with the MS in Mexican population, and have no influence on serum sRAGE levels. Some other factors could be playing a role for the high prevalence of the MS, such as eating habits. Gender should be taken into consideration, for our study was performed in men exclusively. **References.** (1) Serveaux-Dancer M et al., Dis Markers. 2019 Feb 4;2019:2067353. (2) Schmidt AM. Vascul Pharmacol. 2015 Sep;72:1-8.

Adrenal

ADRENAL PHYSIOLOGY AND DISEASE

The Sexually Dimorphic Response of the Mouse Adrenal Inner Cortex to Thyroid Hormone Treatment

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SUN-LB42

The gender bias in adrenal diseases has been noticed for a long time. Mouse studies have shown that the adrenal gland is sexually dimorphic at different levels, such as transcriptome, histology, and cell renewal. However, the mechanism behind this sexual dimorphism is not fully understood. Here, we used RNA-seq to demonstrate how male and female adrenals respond differently to the same external cue, the thyroid hormone (T3) treatment, which directly elicits its function on the adrenal inner cortex by changing the cell fate of this population. Through the comparison of the adrenal gland transcriptomes from males and females with T3 or saline treatment, we found that more genes in female adrenals were responsive to the T3 treatment, whereas the fold change of the gene expressions was greater in male adrenals. Statistical analysis identified 104 sexually dimorphic T3-responsive genes. Immunostaining results showed that many of these genes were expressed in the adrenal gland inner cortex, which contains a unique cell population called X-zone (20-alpha-HSD positive). Previous studies showed that T3 treatment leads to the expansion of the 20αHSD-positive zone both in males and in females. Here we found that the top sexually dimorphic T3-responsive gene was expressed in the adrenal inner cortex partially colocalized with X-zone. Under T3 treatment, this unique cell population that surrounds the 20-alpha-HSD positive X-zone became obvious only in females but not in males. Our findings not only identified several novel marker genes for the adrenal inner cortex but also highlighted the sex-specific response of thyroid hormone action in the mouse adrenal gland.

Neuroendocrinology and Pituitary

ADVANCES IN NEUROENDOCRINOLOGY

Differential Regulation of 22 kDa and 20 kDa Growth Hormone Isoforms in Response to Acute Glucose Load and Moderate Intensity Exercise

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SUN-LB62

Differential regulation of 22 kDa and 20 kDa Growth Hormone Isoforms in response to acute glucose load and moderate intensity exercise