incidence and significance of *CDC73* somatic mutations is largely unknown in tumors other than parathyroid tumors. **Methods/Design**: 1) Assess *CDC73* germline mutation frequency and genotypes in general population using ExAC (Exome Aggregation Consortium) and gnomAD (Genome Aggregation Database); 2) Assess *CDC73* somatic mutation frequency in various type of tumors using the Cancer Genome Atlas (TCGA) and non-TCGA datasets; 3) Examine significance of *CDC73* mutation in uterine endometrial carcinoma (UCEC). Overall survival, *CDC73* mutation signature, gene expression profile (GEP) and tumor immune microenvironment were compared between the UCEC samples with and without CDC73 mutations.
Results: In ExAC and gnomAD databases, most of *CDC73* germline mutations were mapped to the intron regions of the *CDC73* gene and nonsynonymous *CDC73* mutations are very rare, with allele frequency ranging from 8.24e-06 to 9.92e-05 and 3.97e-06 to 7.43e-05, respectively. Missense mutations accounted for more than 95% of the nonsynonymous mutations in the *CDC73* gene in both databases. 2) In 155 cancer genomics studies including both TCGA and non-TCGA datasets with no overlapping samples, *CDC73* was mutated in 0.7% cases and missense mutations comprised 78% of the *CDC73* mutations. *CDC73* somatic mutations were undetected or rarely detected in endocrine tumors except for parathyroid tumors. 3) UCEC is the tumor type that has the second highest *CDC73* somatic mutation rate (8%) after parathyroid tumors. The UCEC with *CDC73* mutations had a significantly better overall survival with a logrank p-value of 0.033 compared to the tumors with *CDC73* WT. GEP analysis revealed that the *CDC73*-mutated UCEC tumors had significant upregulation of immunological markers and enriched immunologic signature compared to the *CDC73*-WT tumors. In silico analysis of tumor immune microenvironment showed higher fractions of cytotoxic CD8 cells, T follicular helper cells and M1 macrophage in the *CDC73*-mutated UCEC tumors. The majority of the CDC73-mutated tumors were POLE ultra-mutated and microsatellite instability (MSI) subtypes, which likely account for a better survival and an increased immune-cell infiltrate of these tumors.
Conclusion: *CDC73* mutations is rare in general population and tumors except for parathyroid carcinoma and UCEC. CDC73 mutation is a marker for better prognosis in UCEC and is associated with increased immune cell infiltrate in tumor microenvironment, likely due to majority of the CDC73-mutated tumors were POLE ultra-mutated and microsatellite instability (MSI) subtypes.

Cardiovascular Endocrinology

ENDOCRINE HYPERTENSION AND ALDOSTERONE EXCESS

Angiotensin II and ACTH Receptor Expression in Aldosterone-Producing Adenomas

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SAT-LB90

Background: The mechanisms leading to elevated aldosterone synthesis in aldosterone-producing adenomas (APAs) remain an area of active research. Aldosterone-driver somatic gene mutations that allow inappropriate intracellular calcium entrance have been identified in most APAs. Cell-based studies of such mutations indicate that responses to physiologic stimuli, such as angiotensin II or ACTH, are increased. Little is known, however, regarding possible variations in response to hormonal stimuli between APAs with different aldosterone-driver mutations. Herein, we analyzed the transcript expression of the ACTH receptor (*MC2R*), the melanocortin 2 receptor accessory protein (*MRAP*) and the type 1 angiotensin II receptor (*AGTR1*) in APAs with known aldosterone-driver somatic mutations. **Methods:** RNA was isolated from normal adrenal glands (n=8), and from APAs with mutations in: *KCNJ5* (n=14), *ATP1A1* (n=14), *CACNA1D* (n=14), and *ATP2B3* (n=5). The gene expressions of *MC2R*, *MRAP, AGTR1* and aldosterone synthase (*CYP11B2*) were quantified using qPCR and normalized to β-actin. **Results:** All APA mutation groups had significantly higher transcript levels of *CYP11B2, MC2R* and *AGTR1* as compared to whole normal adrenals. While *MRAP* and *AGTR1* transcripts were comparable between tumor mutation groups, *MC2R* expression was significantly lower in *KCNJ5*-mutated APAs compared to other APAs. Overall, *CYP11B2* expression demonstrated positive correlations with *MC2R* (R=0.728, $p<0.0001$) and *AGTR1* (R=0.397, $p=0.006$) in APAs. These correlations were strongest in APAs harboring *ATP1A1* mutations, and weakest in *KCNJ5*-mutated APAs. Conversely, *CYP11B2* did not correlate with *MC2R* and *AGTR1* in the normal adrenals. **Conclusions:** ACTH and angiotensin II receptors are expressed in all APAs, regardless of the underlying aldosterone-driver somatic mutations. Further research to clarify the effects of ACTH and posture on aldosterone production from APAs could provide additional insight into developing diagnostic and subtyping tools for primary aldosteronism.

Diabetes Mellitus and Glucose Metabolism

LIPIDS, OBESITY AND METABOLIC DISEASE

Broad Spectrum Effects of a Ketogenic Diet Delivered by Remote Continuous Care on Inflammation and Immune Modulators in Type 2 Diabetes and Prediabetes

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SAT-LB125

Type 2 diabetes (T2D) is associated with, and often preceded by, increased levels of circulating c-reactive protein (CRP)

and WBC count that mediate the body's inflammatory and immune responses (inflammatory mediators [IMs]). This relationship between inflammation and diabetes is complex, as statins have anti-inflammatory properties but paradoxically promote or exacerbate T2D. Recently it has been reported that beta-hydroxybutyrate levels characteristic of nutritional ketosis enhance cellular defenses against oxidative stress and block the assembly of the NLRP3 inflammasome. As part of an ongoing study of the effects of a well-formulated ketogenic diet (WFKD) delivered via a web-based continuous care intervention (CCI) on 262 patients with T2D[1] and 116 with prediabetes (PreD), we determined plasma levels of 16 IMs at baseline, 1 yr, and 2 yrs. These same IMs were concurrently monitored in 87 patients with T2D recruited as usual care controls (UC). At baseline, a statin was prescribed for 50% of the T2D/CCI patients, 27% of PreD/CCI patients, and 59% of the T2D/UC patients; at which time statin use was associated with reduced plasma CRP ($P=7 \times 10^{-5}$) compared to non-statin users in the T2D/CCI group only. There were no other significant baseline differences between statin users and non-users for any IMs (WBC, TNFa, IL-1b, IL-6, IL-8, IL-18, IFN-g, E- L-, and P-selectins, EGF, VEGF-A, MCP-1, ICAM-1 and VCAM-1). After 1 yr and 2 yrs of the CCI, mean weight losses in T2D were 12% and 10%, HbA1c reductions were 1.3% and 0.9%, and diabetes medication use was reduced by 51% and 53%, respectively. Linear mixed effects models were used to assess change in IMs over the 2 yrs, facilitating intent-to-treat analyses. Fourteen of the 16 IMs (excluding ICAM-1 and VCAM-1) were reduced compared to baseline in T2D/CCI ($P<0.001$), with none showing significant increases between yrs 1 and 2. A similar pattern albeit at lower magnitudes was seen in patients with PreD/CCI. Despite lower CRP values at baseline, T2D/CCI patients prescribed a statin experienced further reductions with the WFKD over the 2 years ($P=3 \times 10^{-5}$). In the T2D/UC group, no significant changes in any of the IMs were observed at 1 yr or 2 yrs. These observations suggest that a WFKD delivered via the CCI has broad-spectrum anti-inflammatory and immune modulatory effects in patients with T2D and PreD. Consistent with prior reports, statin use was associated with reduced CRP at baseline in the T2D/CCI group, but this effect was not significant in PreD/CCI and T2D/UC groups. CRP reductions were nonetheless significant in T2D/CCI statin users, suggesting added benefit of the WFKD. We conclude that improvements in IMs induced by a combination of nutritional ketosis and weight loss contribute to the beneficial effects of the CCI in the management of T2D.

1. Athinarayanan SJ, et al. Front Endocrinol. 2019. 5;10:348

Diabetes Mellitus and Glucose Metabolism

METABOLIC INTERACTIONS IN DIABETES

Mice With Skeletal Muscle-Specific DRP1 Deficiency Are Resistant to Obesity and Diabetes Induced by a High Fat Diet

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SUN-LB118

The skeletal muscle of type 2 diabetics exhibits mitochondrial dysfunction associated with increased mitochondrial fission. Dynamin-related protein 1 (DRP1) is responsible for mitochondrial division, whereas mitochondrial-endoplasmic reticulum contacts (MERCs) mark mitochondrial sites where fission occurs. Here, we have shown that skeletal muscle-specific DRP1 knock out (KO) mice are partly protected from high fat diet-induced obesity and diabetes, and exhibit increased insulin and glucose tolerance along with lower insulinemia. We also found that KO mice exhibit increased energy expenditure per unit of lean mass. Isolated DRP1-deficient skeletal muscle fibers from KO mice fed high fat diet have reduced respiratory capacity when exposed to ADP and palmitoylcarnitine, but not when exposed to ADP, pyruvate, and malate. Additionally, the skeletal muscle of KO mice fed normal chow exhibited altered expression of genes associated with MERCs and increased expression of genes linked to ER stress. We observed substantial increases in gene expression of FGF21, a downstream signal of the ER stress response, in KO mice. However, FGF21 plasma concentration in KO mice was not elevated. Additionally, changes in MERC gene expression could potentially alter calcium signaling between the mitochondria and endoplasmic reticulum, changing insulin sensitivity in KO mice. In conclusion, we have shown that skeletal muscle-specific DRP1 KO mice are resistant to high fat diet-induced obesity and diabetes, perhaps due to elevated energy expenditure and differential mitochondrial respiratory adaptations to different substrates. Although FGF21 does not appear to contribute to this effect, it is possible that other ER-stress signals might help explain the observed phenotype in KO mice.

Healthcare Delivery and Education

EXPANDING CLINICAL CONSIDERATIONS FOR PATIENT TESTING AND CARE

The "Normal" Hormonal Levels in Athletes: Should Reference Ranges Be Adapted for the Physically Active Population?

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MON-LB305

Background: Despite the growing number of physically active subjects, including elite and amateur athletes, little is known regarding metabolic and hormonal chronic adaptations to exercises. While the elucidation of the hormonal and metabolic physiological adaptations to physical activity is of emerging importance, the Endocrine and Metabolic Responses on Overtraining Syndrome (EROS) study have serendipitously unveiled the existence of multiple metabolic and endocrine physiological changes in male athletes, including chronic increase of testosterone with concurrent physiological increase of estradiol, enhanced GH and cortisol responses to stimulations,andincreased catecholamines, basal metabolic rate, fat oxidation, and hydration status. These findings were uncovered due to a novel methodological design in which athletes affected