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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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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