Identification of Novel Drivers of Insulin Resistance and Type 2 Diabetes in the Skeletal Muscle Tissue of Non-Obese Individuals Using a Multi-Omics Approach

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Type 2 diabetes (T2D), a metabolic disorder characterized by high blood sugar and insulin resistance (IR), has serious socioeconomic ramifications. While T2D is considered a lifestyle disease, 20% of non-obese people are metabolically unhealthy and prone to developing T2D. Furthermore, mechanisms whereby these individuals develop T2D are poorly understood. The researcher was provided with gene expression profiles obtained from individuals' skeletal muscle biopsies under basal conditions and after a hyperinsulinemic-euglycemic clamp (HGC) procedure to determine each subject's insulin sensitivity. Taking two groups of non-obese subjects consisting of normoglycemic (NG) and prediabetic (PD) people, differential gene expression was measured at basal and post-HGC levels using R program packages and visualization tools. Compared to NG individuals, PD individuals showed significantly dysregulated genes at basal and post-HGC levels. Differentially expressed genes (DEG) were evaluated using pathway analysis, T2D genome-wide association data, and T2D whole-genome methylation data. Several significant DEG (FDR<0.05), namely IRS1/2, PPARG, and CDKN2A, are extant in independent T2D-related genome-wide and epigenomic data, underscoring their importance in PD pathogenesis. Twelve potential drivers of PD were identified by examining common upstream regulators of DEG. Of these drivers, FOXO1, PPARG, and CEBPB are especially involved in T2D pathogenesis. Other significant DEG include MIDN and MAOA, involved with IR and glucose metabolism respectively. These molecules, nestled in key T2D-related pathways, are attractive targets for drugs that potentially block or reverse progression of T2D. Results have important implications for clinical management of PD individuals.

Awards Won:

Qatar Foundation, Research &amp Development: Award of $1,000

Third Award of $1,000