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MULTI-OMICS PROFILING OF RAT OFFSPRING EXPOSED TO GESTATIONAL DIABETES REVEALS CARDIOMETABOLIC DISEASE DEVELOPMENT WITH AGE

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Background:
Gestational diabetes mellitus (GDM) is the most common complication of pregnancy. Through unknown mechanisms, fetal exposure to GDM increases the risk for cardiometabolic disease development later in life.

Objective:
We hypothesize that fetal exposure to GDM alters cardiomyocyte metabolism and induces left ventricular (LV) dysfunction with age.

Methods:
To induce GDM, we fed female rats a high fat (45% kcal) and sucrose diet prior to mating and throughout pregnancy. Lean control females received a low fat (10% kcal) diet. Fetal rat ventricular cardiomyocytes (FRVC) were isolated from e20.5 offspring for U-^{13}C glucose metabolic flux analysis. The cardiac transcriptome and serum metabolites were measured in 3-month old offspring. LV morphology and function was assessed in the offspring from e18 to 12-months of age by transthoracic ultrasound.

Results:
Offspring exposed to GDM exhibited increased LV posterior wall thickness across their life course (e18 to 12-months of age; $p<0.05$) and impaired LV filling beginning at 6-months of age ($p<0.05$). When FRVC were treated with isoproterenol, U-^{13}C glucose metabolic flux through glycolysis and the citric acid cycle was reduced in GDM offspring, compared to Lean controls. In 3-month old offspring serum metabolomics revealed elevated levels of β-hydroxybutyrate (2.4-fold, $p<0.05$) and reduced citric acid cycle intermediates. These metabolic changes

corresponded to alterations in gene expression patterns identified by RNASeq associated with glucose metabolism and fatty acid transport pathways (e.g. *Irs2, Slc2a4, Pfkfb2, Pdk4 and Cpt1a*).

Conclusion:
Large-scale multi-omics profiling revealed GDM induced alterations in the cardiac gene expression profile contributing to modified serum metabolite levels in the young adult offspring. These alterations corresponded with mitochondrial dysfunction, impaired cardiomyocyte metabolic flux and contractility, in concert with LV hypertrophy and diastolic dysfunction in the GDM exposed rat offspring. Our findings identify several mechanisms that link early-life GDM exposure to the development of cardiovascular disease later in life.