ABSTRACT SUBMISSION FORM

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CHRD
CHILD HEALTH RESEARCH DAYS

CHRD 2020: Abstract Submission Form

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Title
Multi-omics Profiling of Rat Offspring Exposed to Gestational Diabetes Reveals Cardiometabolic Disease Development with Age

Background
Through unknown mechanisms, fetal exposure to gestational diabetes mellitus (GDM) increases the risk for cardiovascular disease development later in life.

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

Methods
GDM was induced in female rats with a high fat (45% kcal) and sucrose diet prior to mating, throughout pregnancy and lactation. Lean control females received a low fat (10% kcal) diet. Fetal rat ventricular cardiomyocytes (FRVC) were isolated from e20.5 offspring for U-13C glucose flux analysis and calcium handling. The cardiac transcriptome and metabolome were measured in 3-month old offspring. LV morphology and function were 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 (fetal to 12-months of age; $p<0.05$) and impaired LV filling beginning at 6-months of age ($p<0.05$). Consistent with the development of diastolic dysfunction in vivo, alterations in calcium flux and re-uptake were observed in FRVC isolated from GDM offspring compared to Lean controls ($p<0.05$). When FRVC were treated with isoproterenol, U-13C glucose metabolic flux through glycolysis and the citric acid cycle was reduced in GDM offspring. In 3-month old offspring metabolomics revealed an altered acylcarnitine profile. These metabolic changes corresponded to altered gene expression patterns associated with glucose metabolism

and fatty acid transport pathways (e.g. Irs2, Slc2a4, Pfkfb2, Pdk4 and Cpt1a) identified by RNAseq.

Conclusion
Multi-omic profiling revealed GDM-induced alterations in the cardiac gene expression profile leading to modified metabolite levels in the offspring. These alterations corresponded with mitochondrial dysfunction, impaired cardiomyocyte metabolic flux and contractility, in concert with LV hypertrophy and diastolic dysfunction in the rat offspring. Our findings identify several mechanisms that link early-life GDM exposure to the development of cardiovascular disease later in life.

Theme:
Basic Science

Do you have a table/figure to upload?
No

Are you willing to participate in Goodbear's Den?
Yes

Presenter Status:
PhD Student

What was your role in the project?
All of the above

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