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Basic Science

Abstract Title
Muscle-restricted SIRT3 Overexpression Protects Against Gestational Diabetes-Induced Cardiac and Metabolic Dysfunction in Offspring in a Sex-Specific Manner

Background
Intrauterine exposure to maternal gestational diabetes mellitus (GDM) increases cardiovascular risk in offspring later in life, yet the mechanisms remain unclear. In rodents, GDM induces cardiac hypertrophy and aberrant mitochondrial protein acetylation, coinciding with reduced expression of the mitochondrial deacetylase Sirtuin-3 (SIRT3).

Objective
The objective of this study is to define the role of SIRT3 in GDM-induced cardiac dysfunction and to investigate its potential as a therapeutic target.

Methods
GDM was induced by feeding female mice a HFS diet (45% fat) for 6 weeks prior to mating. Control dams were fed a low-fat (LF; 10% fat) diet. Dams were mated to transgenic (TG) male sires overexpressing SIRT3 under the muscle-creatine kinase promoter, generating litters with both SIRT3-TG and non-TG offspring. Post-weaning, offspring were placed on LF or HFS diets. At 15 weeks cardiometabolic function was assessed via echocardiography.

Results
Non-TG offspring exposed to GDM and postnatal HFS diet (GDM-HFS) displayed cardiac hypertrophy in both males (Left Ventricular (LV) mass, non-TG GDM-HFS vs non-TG Lean-LF, $p<0.001$) and females (LV wall thickness non-TG GDM-HFS vs non-TG Lean-LF, $p<0.05$), which was absent in SIRT3-TG offspring. GDM exposure altered acetylation of mitochondrial peptides in non-TG male offspring and was exacerbated by a postnatal HFS diet (GDM-HF vs Lean-LF 88 peptides, $p<0.05$). Functional classification revealed prominent representation of acetylated proteins in fatty acid oxidation, respiratory electron transport, and mitochondrial biogenesis in hearts of GDM-exposed offspring.

Conclusion
SIRT3 overexpression protects against GDM- and HFS diet-induced cardiac hypertrophy in both male and female offspring. Acetylomics also identifies cardiac mitochondrial protein acetylation as a potential mechanism that induces GDM- and HFS-induced cardiac abnormalities. These findings highlight the importance of SIRT3 in mediating the effects of GDM on the heart and support SIRT3 as a potential therapeutic target.

Authors

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