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Abstract Title

SIRT3 overexpression protects against cardiometabolic dysfunction and cardiac hypertrophy in offspring exposed to gestational diabetes mellitus.

Authors

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Background

Intrauterine exposure to maternal gestational diabetes mellitus (GDM) predisposes offspring to cardiometabolic dysfunction and cardiac hypertrophy. Rodent models show GDM induces cardiomyocyte mitochondrial dysfunction. The expression of the mitochondrial protein lysine deacetylase Sirtuin-3 (SIRT3), which is a key mitochondrial regulator, is reduced in the hearts of GDM-exposed offspring.

Objective

We propose that GDM-induced reductions in SIRT3 drive cardiometabolic dysfunction in offspring, and overexpression of SIRT3 prevents systemic metabolic and cardiac alterations.

Methods

GDM was induced by feeding female mice a high-fat/high-sucrose (HFS; 45% fat) diet for 6 weeks prior to mating; control dams were fed a low-fat (LF; 10% fat) diet. Dams were mated to transgenic (TG) males expressing SIRT3 under the muscle-creatine kinase promoter, generating SIRT3-TG and non-TG offspring littermates. Offspring were weaned on to LF or HFS diets and assessed at 15 weeks of age. Cardiac

structure and function were evaluated by echocardiography, and cardiometabolic function by indirect calorimetry and glucose tolerance tests.

Results

Non-TG offspring exposed to GDM and postnatal HFS diet (GDM-HFS) displayed cardiac hypertrophy in males (Left Ventricular (LV) mass, non-TG Lean-LF vs non-TG GDM-HFS, $p < 0.001$) that was prevented by SIRT3 expression (SIRT3-TG GDM-HFS vs non-TG GDM-HFS, $p < 0.01$). Females also displayed cardiac hypertrophy (LV wall thickness, non-TG Lean-LF vs non-TG GDM-HFS, $p < 0.05$), which was prevented by SIRT3-TG. Indirect calorimetry showed GDM-HFS males had greater reliance on fatty acid oxidation at (non-TG Lean-LF vs non-TG GDM-HFS, $p < 0.0204$), which was absent in SIRT3-TG GDM-HFS offspring. GDM induced glucose intolerance in male offspring (non-TG Lean-LF vs non-TG GDM-HFS, $p < 0.0001$) and SIRT3-TG GDM-HFS were resistant to the effects of GDM on glucose tolerance. In females, SIRT3 modestly enhanced glucose tolerance at (non-TG Lean-LF vs non-TG GDM-HFS, $p < 0.0001$ and vs SIRT3-TG GDM-HFS, $p < 0.05$).

Conclusion

SIRT3 prevents GDM-induced alterations in whole-body substrate utilization and mitigates cardiac remodeling, highlighting its role as a regulator of cardiometabolic health and potential as a therapeutic target.