CHRD 2024: Abstract Submission Form

Presenter Name
Khushali Trivedi

Presenter Status
PhD Student

Role in the project
Design
Perform Experiments
Analyze Data
Write Abstract

Research Category
Basic Science

Title
SIRT3 Deficiency in the Liver is Associated with Mitochondrial Dysfunction and Hepatic Steatosis in Gestational Diabetes

Background
Gestational diabetes mellitus (GDM) is the most common transient pregnancy complication that puts mothers and their children at risk for developing type-2 diabetes and obesity. GDM is characterized by glucose intolerance and insulin resistance. The mechanisms involved are poorly understood. Sirtuin 3 (SIRT3) is a mitochondrial protein deacetylase that regulates energy production in the liver.

Objective
To determine whether deficiency of SIRT3 in the liver is sufficient to induce diabetes during pregnancy.

Methods
Mice with liver-specific-deletion of SIRT3 (SIRT3-LKO) were generated by crossing Sirt3tm1.1Auw mice from Jackson Labs with loxP sites flanking exons 2-3 of the Sirt3 gene with Cre-recombinase mice with an albumin-promoter. SIRT3-LKO mice and Cre-negative controls fed either low fat diet (10% kcal fat) or high fat sucrose diet (45% kcal fat) for 6-weeks before pregnancy and throughout the 3-week mouse pregnancy to induce GDM. Glucose homeostasis was assessed by performing glucose tolerance tests (GTTs) at embryonic day e16 of pregnancy. Pregnant mice were sacrificed at e18.5 and livers were collected for histological visualization using hematoxylin and eosin and Oil Red O. Complex-1 and 2 driven mitochondrial respiration was measured using Agilent Seahorse XFe24 on isolated liver mitochondria.

Results
Genetic deletion of liver SIRT3 is sufficient to induce glucose intolerance ($p<0.01$), hepatic steatosis assessed by quantification of Oil Red O positive area ($p<0.0001$), and significantly reduced mitochondrial basal respiration ($p<0.0001$) in pregnant mice (Two-way ANOVA).

Conclusion
Our findings suggest SIRT3 plays an important role in maintaining adequate mitochondrial function during pregnancy, during an important period when maternal demands for energy production are high. SIRT3 deficiency promotes mitochondrial dysfunction which could contribute to the accumulation of lipids in the liver and glucose intolerance during pregnancy.

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No

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