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Basic Science

Abstract Title
Sirtuin-3 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 metabolic disorder during pregnancy. GDM significantly increases the post-pregnancy risk of type 2 diabetes and obesity. GDM is marked by insulin resistance and glucose intolerance, the underlying mechanisms remain poorly understood. Sirtuin-3 (SIRT3) is a mitochondrial NAD+-dependent deacetylase that regulates oxidative metabolism in the liver. We have previously observed reduced liver SIRT3 expression in GDM rodents.

Objective
The objective is to determine whether liver-specific SIRT3 deficiency disrupts mitochondrial function and lipid metabolism during pregnancy, driving glucose intolerance, characteristic of GDM.

Methods
Liver-specific SIRT3 knockout mice (SIRT3-LKO) were generated by crossing Sirt3tm1.1Auwmice from Jackson Labs with albumin-promoter driven cre-recombinase mice. SIRT3-LKO mice and controls were fed either a low-fat diet (10% kilocalorie fat) or high-fat-sucrose diet (45% kilocalorie fat) for 6-weeks before pregnancy and throughout the 3-week mouse pregnancy to induce GDM. Glucose tolerance tests were performed at gestational day 16 (GD16). Pregnant mice were sacrificed at GD18, and maternal livers were collected for histological visualization of steatosis and mitochondrial function was assessed using SeahorseXFe24 to measure complex I-and fatty acid–driven respiration in isolated liver mitochondria.

Results
Pregnant SIRT3-LKO mice exhibited glucose intolerance (1.3-fold, $p<0.01$) and serum insulin levels elevated by 1.5-fold ($p<0.01$) compared to controls. Histological analysis of the liver showed marked hepatic steatosis, with 1.8-fold elevated hepatic triglyceride levels ($p<0.05$). Mitochondrial respiration was significantly impaired with 2.5-fold reduced fat oxidation ($p<0.001$) and 1.4-fold reduced complex I–linked basal respiration ($p<0.0001$) in SIRT3-LKO liver mitochondria.

Conclusion
SIRT3 is a key regulator of hepatic mitochondrial function and lipid metabolism during pregnancy, at a stage when maternal demands of energy production are high. Liver-specific SIRT3 deficiency disrupts fat oxidation and promotes steatosis, leading to hyperinsulinemia and glucose intolerance—metabolic hallmarks of GDM. Future work will assess whether activation of SIRT3 reverses hyperglycaemia and hepatic steatosis during pregnancy.

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