Reg3g Supports Mitochondrial and β-Cell Function in Female Offspring of Obese Dams

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Background and Objective

- Maternal obesity (MatOb) places offspring at a significantly higher risk for developing obesity, insulin resistance, and type 2 diabetes (T2D).
- Male offspring exhibit more severe glucose intolerance and reduced insulin secretion than females.
- Recent findings suggest a pancreatic protein, Reg3g, as a critical mediator of these sex specific differences.
- **Objective:** To test whether deletion of Reg3g eliminates sex-differences in metabolic dysfunction in MatOb offspring.

Experimental Design

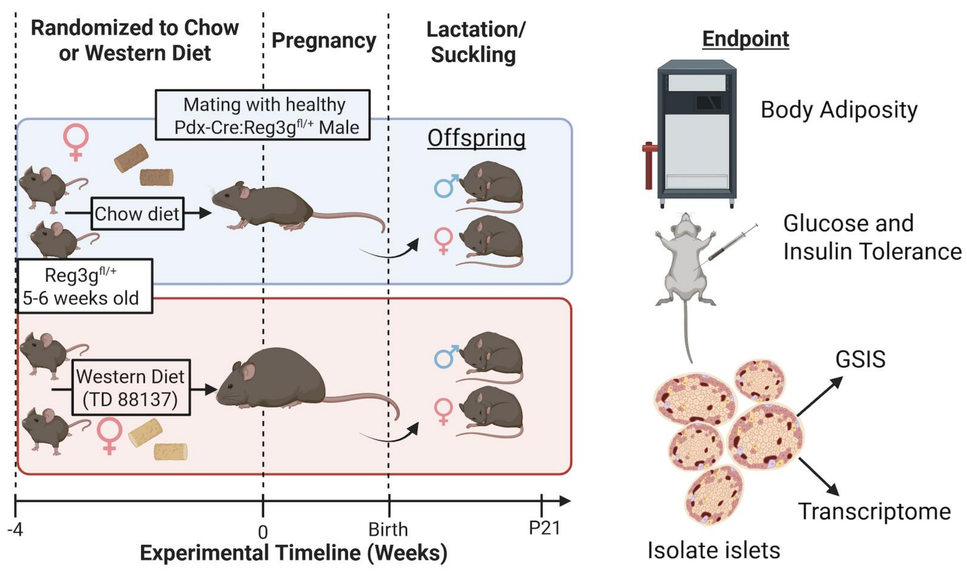

Figure 1. Generation of pancreas-specific *Reg3g* knockout offspring. Pdx1-Cre^{+} sires were crossed with Reg3g$^{fl/+}$ dams on chow (Control) or western diet (TD88137) to induce maternal obesity. Metabolic phenotyping of transgenic offspring, RNA-sequencing, and pathway enrichment analysis was also performed.

Islet Reg3g Expression is Elevated in Female MatOb Offspring

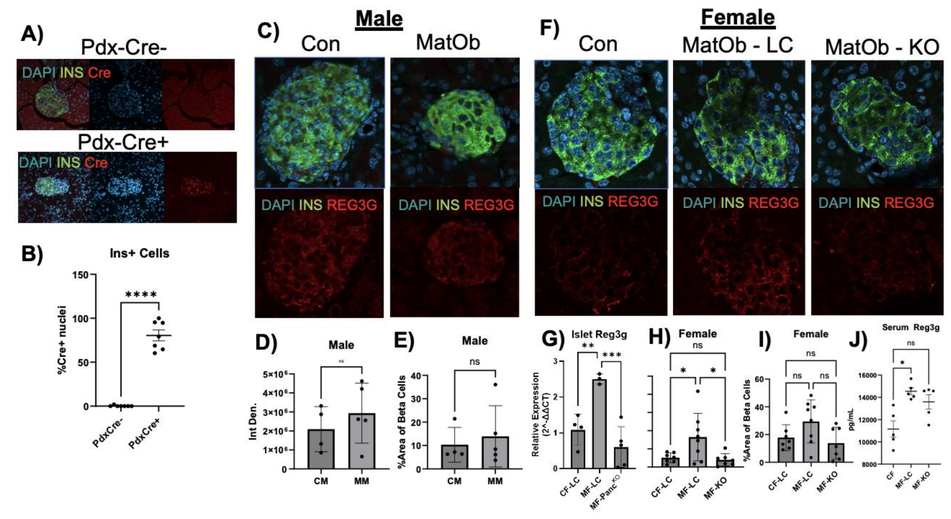

Figure 2. (A) Immunofluorescence staining of Pdx-Cre- and Pdx-Cre+ mice pancreata illustrating (B) 60-100% of β-cell nuclei with Cre recombinase expression at P21. (C-E) Male MatOb offspring did not exhibit an increase in β-cell Reg3g protein while female MatOb (F-I) exhibited (G) higher expression of Islet Reg3g in the littermate control group (MF-LC). This increase was abolished in pancreas specific knockout offspring (MF-KO). (J) Serum Reg3g was elevated in MF-LC, but not significantly changed in MF-KO.

Loss of Reg3g Impairs Glucose Tolerance and Insulin Secretion in Female Offspring of Obese Dams

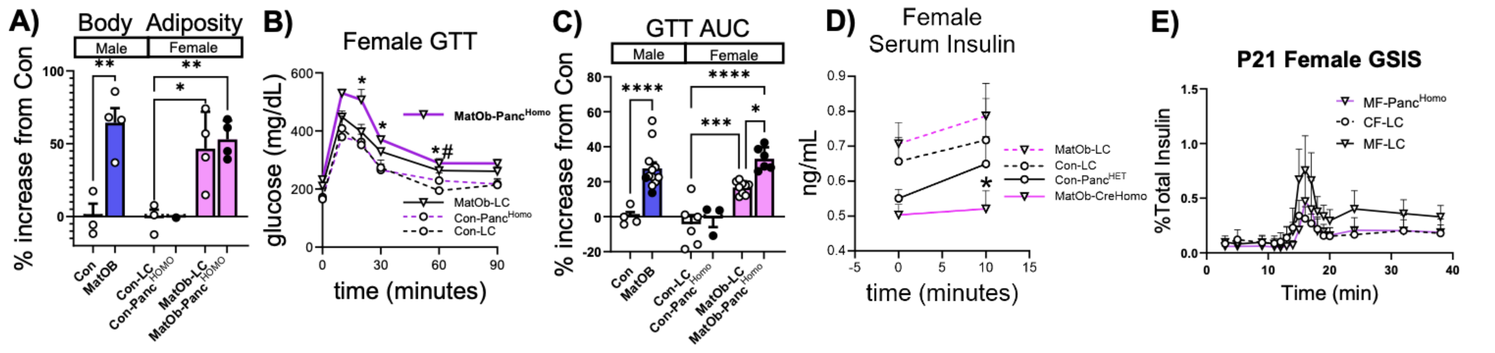

Figure 3. (A) Body Adiposity of P21 offspring. (B) Glucose tolerance illustrating MatOb-Panc^{Homo} with the highest glucose excursion and (B) GTT AUC. (D) Measured serum insulin with 1g/kg glucose challenge. (E) Ex-vivo glucose stimulated insulin secretion (GSIS) revealing enhanced insulin secretion from MF-LC offspring.

Enriched Pathways in MF-LC Islets

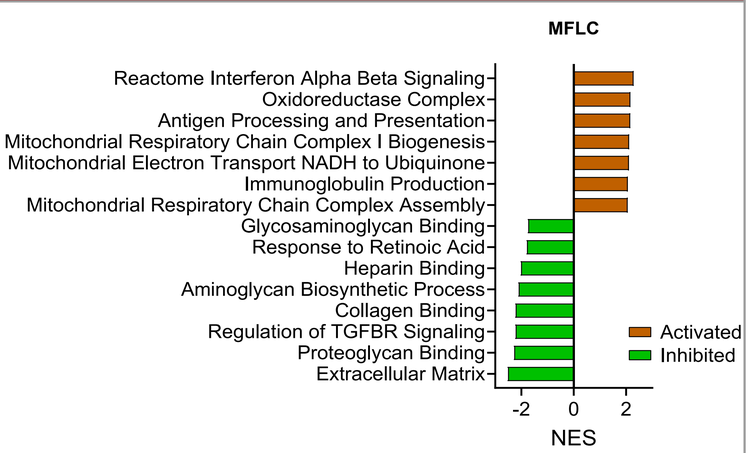

Figure 4. Pathways that are exclusively enriched in MF-LC groups. Data highlight upregulation of mitochondrial pathways central to energy metabolism and insulin secretion in β-cells of MF-LC offspring.

Enriched Pathways in MF-KO Islets

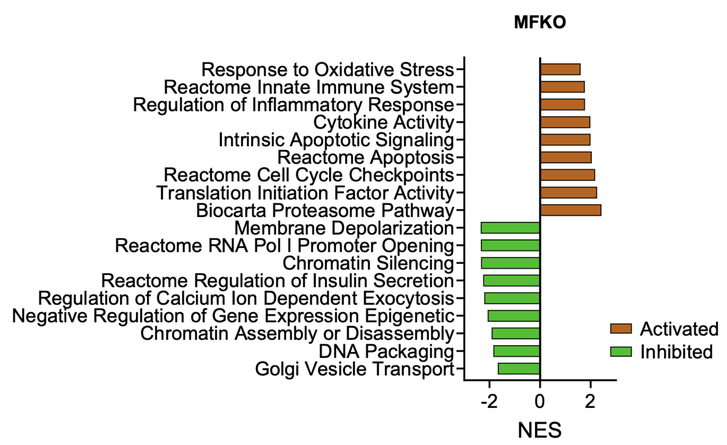

Figure 5. Pathways that are exclusively enriched in MF-KO groups. Data revealed upregulation of stress and immune-related pathways, and downregulation of key functional pathways, including those involved in insulin secretion.

Differentially expressed (DE) genes in enriched pathways

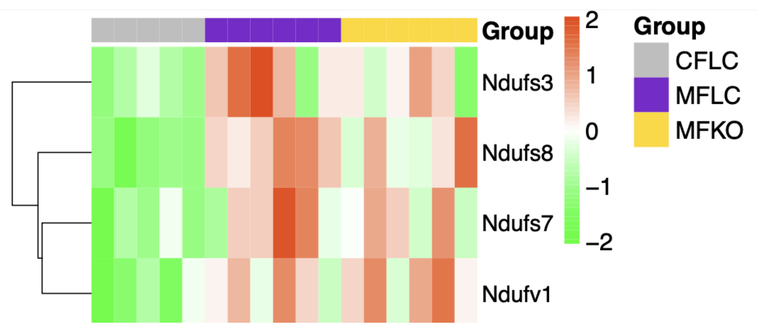

Figure 6. Increased expression of gene sets associated with mitochondrial Complex I genes in islets from both MatOb groups, with a greater upregulation in MF-LC offspring. The data suggest enhanced mitochondrial adaptation and insulin secretion potential in Reg3g^{+} islets.

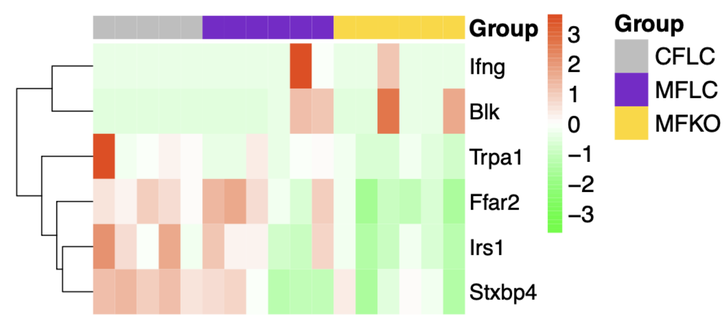

Figure 7. Decreased expression of genes associated with insulin secretion in islets from both MatOb groups, with a greater downregulation in MF-KO offspring. The data suggest impaired β-cell stress responsiveness, signaling, and secretory function in Reg3g^{-} islets.

Conclusion

- Loss of Reg3g impairs glucose tolerance and insulin secretion.
- Female MatOb offspring exhibit higher islet and serum Reg3g expression.
- Reg3g may support mitochondrial metabolic reprogramming in response to maternal obesity, facilitating ATP production and GSIS.

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