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# Examining Pancreatic Islet Lipotoxicity by Two-Photon NAD(P)H Imaging in a Microfluidic Device

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Pancreatic islet beta-cells maintain blood glucose through the regulated secretion of insulin. A rise in blood glucose stimulates production of NAD(P)H resulting in a cascade of increased ATP/ADP ratio, closure of ATP-sensitive potassium channels, membrane depolarization, $Ca^{2+}$-influx, and insulin secretion. During the course of Type II diabetes, the glucose-stimulated insulin response is dampened by glucose and lipid toxicity. To measure glucose-stimulated metabolism in this tissue, we use microfluidic devices to hold the tissue stationary while imaging NAD(P)H autofluorescence using two-photon microscopy. This setup provides sufficient spatiotemporal resolution to measure cytoplasmic and mitochondrial NAD(P)H responses.

It has recently been shown that the novel endocrine factor, FGF21, protects metabolically active tissues such as liver and white adipose tissue (WAT) by regulating fatty acid metabolism. To test the effects of FGF21 on islet beta-cells, we measured the levels of Acetyl-CoA carboxylase (ACC) in response to FGF21. ACC is an enzyme involved in the synthesis of malonyl-CoA, a substrate used in fatty acid synthesis and a regulator of fatty acid oxidation. Reducing ACC expression is critical to the normal compensation of beta-cells to lipid toxicity. We show that FGF21 decreases ACC protein levels in mouse pancreatic islets.

To determine whether decreased ACC protein level acts as a protective mechanism in maintaining β-cell sensitivity to glucose, we examined changes in NAD(P)H by two photon microscopy of living islets held in a microfluidic device as a direct measure of changes in the metabolism. Our data reveals that compared to control islets, FGF21-treated islets retain the glucose-stimulated NAD(P)H response in a high fat environment. We will further examine the kinetics of the glucose-stimulated response in microfluidic flow. Overall, these studies will determine the metabolic changes that occur during the β-cell response to FGF21, and enhance understanding of how this effect can protect beta-cells from high fatty acid stress.

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