Destabilization of β Cell FIT2 by saturated fatty acids alter lipid droplet numbers and contribute to ER stress and diabetes

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Introduction

Type 2 diabetes mellitus (T2D) is a major public health problem, for which an unhealthy diet is a major risk factor. This paper presents a novel mechanism for how saturated fat contributes to diabetes.

Saturated fatty acids (SFAs) trigger endoplasmic reticulum (ER) stress, cell dysfunction, and apoptosis of pancreatic β cells which produce insulin. Lipid droplets (LDs) sequester toxic free fatty acids (FFAs) produced in insulin resistance conditions, meaning that limitations in LD build-up results in β-cell dysfunction and hence, increased T2D susceptibility.

Methodology

Male mice were used in all experiments and housed in a 12-h light-dark cycle facility with food and water available ad libitum. MIN6 cells were cultured as previously described. Mouse pancreatic islets were isolated by perfusing the pancreas through the common bile duct with collagenase, as previously described. β cell-specific FIT2 knockout mice (βFIT2KO, KO) were generated using the Cre-lox recombination system. Mice with floxed FIT2 were bred with mice expressing Cre-recombinase, under control of rat insulin promoter.

Results

Partial restoration of FIT2 levels rescues lipid droplet biogenesis and mitigates palmitate-mediated effects in MIN6 cells. If artificially supplementing FIT2 can mitigate palmitate-mediated reduction in lipid droplet numbers in humans, this mechanism could be of great clinical value in its prevention.

References

3. https://doi.org/10.1038/nprot.2009.150

In Western diet fed mice, βFIT2KO mice displayed modest but significantly lower fasting plasma insulin levels. This significant difference is exacerbated following a glucose challenge test, showing that the loss of FIT2 in β cells significantly compromised compensatory hyperinsulinemia. This result in significantly elevated, fed state glucose levels of western diet fed βFIT2KO mice compared to the floxed control counterparts.