Perilipin 5 Deletion Unmasks an Endoplasmic Reticulum Stress-Fibroblast Growth Factor 21 Axis in Skeletal Muscle.

Abstract

Lipid droplets (LDs) are critical for the regulation of lipid metabolism, and dysregulated lipid metabolism contributes to the pathogenesis of several diseases, including type 2 diabetes. We generated mice with muscle-specific deletion of the LD-associated protein perilipin 5 (PLIN5, Plin5MKO) and investigated PLIN5's role in regulating skeletal muscle lipid metabolism, intracellular signaling, and whole-body metabolic homeostasis. High-fat feeding induced changes in muscle lipid metabolism of Plin5MKO mice, which included increased fatty acid oxidation and oxidative stress but, surprisingly, a reduction in inflammation and endoplasmic reticulum (ER) stress. These muscle-specific effects were accompanied by whole-body glucose intolerance, adipose tissue insulin resistance, and reduced circulating insulin and C-peptide levels in Plin5MKO mice. This coincided with reduced secretion of fibroblast growth factor 21 (FGF21) from skeletal muscle and liver, resulting in reduced circulating FGF21. Intriguingly, muscle-secreted factors from Plin5MKO , but not wild-type mice, reduced hepatocyte FGF21 secretion. Exogenous correction of FGF21 levels restored glycemic control and insulin secretion in Plin5MKO mice. These results show that changes in lipid metabolism resulting from PLIN5 deletion reduce ER stress in muscle, decrease FGF21 production by muscle and liver, and impair glycemic control. Further, these studies highlight the importance for muscle-liver cross talk in metabolic regulation.