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Human Cidec Transgene Improves Lipid Metabolism And Protects Against High Fat-diet Induced Glucose Intolerance In Mice

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CIDEC expression in adipose tissue positively correlates with insulin sensitivity in obese humans. Further, a single-nucleotide CIDEC variant (E186X) causes lipodystrophy, hypertriglyceridemia, and insulin resistance. To establish the unknown mechanistic link between CIDEC and maintenance of systemic glucose homeostasis, we generated
transgenic mouse models expressing CIDE\textsuperscript{C} (Ad-CIDE\textsuperscript{Ctg}) and CIDE\textsuperscript{E186X} variant (Ad-CIDE\textsuperscript{mut}) transgene specifically in the adipose tissue. Ad-CIDE\textsuperscript{Ctg} but not Ad-CIDE\textsuperscript{mut} mice were protected against high-fat diet (HFD)-induced glucose intolerance. Transcriptomics and lipidomics revealed the role of CIDE\textsuperscript{C} in lipid metabolism. Serum triglycerides, cholesterol, and low-density lipoproteins were lower in HFD-fed Ad-CIDE\textsuperscript{Ctg} mice compared to their littermate controls. Mechanistically, CIDE\textsuperscript{C} regulates the enzymatic activity of ATGL via interacting with its activator, CGI-58, to reduce free fatty acid (FFA) release and lipotoxicity. We confirmed that CIDE\textsuperscript{C} is indeed a vital regulator of lipolysis in adipose tissue of obese humans. Finally, treatment with recombinant CIDE\textsuperscript{C} decreased triglyceride breakdown in visceral human adipose tissue. Our study unravels a central pathway whereby adipocyte-specific CIDE\textsuperscript{C} plays a pivotal role in regulating adipose lipid-metabolism and whole-body glucose homeostasis. In sum, our findings identify human CIDE\textsuperscript{C} as a potential ‘drug’ or a ‘druggable’ target to reverse obesity-induced lipotoxicity and glucose intolerance.

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