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The Beneficial Effects of Inhibition of Hepatic Adaptor Protein Phosphotyrosine Interacting with PH Domain and Leucine Zipper 2 on Glucose and Cholesterol Homeostasis

Authors : Xi Chen, King-Yip Cheng

Abstract : Hypercholesterolemia, characterized by high low-density lipoprotein cholesterol (LDL-C), raises cardiovascular events in patients with type 2 diabetes (T2D). Although several drugs, such as statin and PCSK9 inhibitors, are available for the treatment of hypercholesterolemia, they exert detrimental effects on glucose metabolism and hence increase the risk of T2D. On the other hand, the drugs used to treat T2D have minimal effect on improving the lipid profile. Therefore, there is an urgent need to develop treatments that can simultaneously improve glucose and lipid homeostasis. Adaptor protein phosphotyrosine interacting with PH domain and leucine zipper 2 (APPL2) causes insulin resistance in the liver and skeletal muscle via inhibiting insulin and adiponectin actions in animal models. Single-nucleotide polymorphisms in the APPL2 gene were associated with LDL-C, non-alcoholic fatty liver disease, and coronary artery disease in humans. The aim of this project is to investigate whether APPL2 antisense oligonucleotide (ASO) can alleviate dietary-induced T2D and hypercholesterolemia. High-fat diet (HFD) was used to induce obesity and insulin resistance in mice. GalNAc-conjugated APPL2 ASO (GalNAc-APPL2-ASO) was used to silence hepatic APPL2 expression in C57/BL6J mice selectively. Glucose, lipid, and energy metabolism were monitored. Immunoblotting and quantitative PCR analysis showed that GalNAc-APPL2-ASO treatment selectively reduced APPL2 expression in the liver instead of other tissues, like adipose tissues, kidneys, muscle, and heart. The glucose tolerance test and insulin sensitivity test revealed that GalNAc-APPL2-ASO improved glucose tolerance and insulin sensitivity progressively. Blood chemistry analysis revealed that the mice treated with GalNAc-APPL2-ASO had significantly lower circulating levels of total cholesterol and LDL cholesterol. However, there was no difference in circulating levels of high-density lipoprotein (HDL) cholesterol, triglyceride, and free fatty acid between the mice treated with GalNac-APPL2-ASO and GalNAc-Control-ASO. No obvious effect on food intake, body weight, and liver injury markers after GalNAc-APPL2-ASO treatment was found, supporting its tolerability and safety. We showed that selectively silencing hepatic APPL2 alleviated insulin resistance and hypercholesterolemia and improved energy metabolism in the dietary-induced obese mouse model, indicating APPL2 as a therapeutic target for metabolic diseases.

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