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The beneficial effects of inhibition of hepatic APPL2 on glucose and cholesterol homeostasis

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Cardiovascular disease (CVD) is the most prevalent cause of morbidity and mortality in diabetic patients. 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 inhibitor, 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 new treatments those can simultaneously improve glucose and lipid homeostasis. Adaptor protein, phosphotyrosine interacting with PH domain and leucine zipper 2 (APPL2) causes insulin resistance in liver and skeletal muscle via inhibiting insulin and adiponectin actions in animal models. Single-nucleotide polymorphisms in 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, insulin resistance, and dyslipidemia in mice. GalNAc-conjugated APPL2 ASO (GalNAc-APPL2-ASO) was used to selectively silence hepatic APPL2 expression in C57/BL6J mice fed with HFD. After the HFD feeding for 2 weeks, the animals were subjected to weekly subcutaneous injection of GalNAc-APPL2-ASO or GalNAc-Control-ASO for 16 weeks. Glucose, lipid, and energy metabolism were monitored during this treatment period.

Immunoblotting and quantitative PCR analysis showed that GalNAc-APPL2-ASO treatment selectively reduced APPL2 expression in liver instead of other tissues, like adipose tissues, kidney, muscle, and heart. 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. Metabolic cage study exhibited GalNAc-APPL2-ASO treatment increased energy expenditure suitably. 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, improve energy metabolism in dietary-induced obese mouse model, indicating APPL2 as a novel therapeutic target for metabolic diseases.

Recent Publications

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She got a master's degree in food science in Mainland China. Currently, she is a Ph.D. student at the department of health technology and informatics, The Hong Kong polytechnic university. Her research area is mechanisms and metabolic pathways of chronic diseases like obesity via metabonomics.

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