Researchers identify the metabolic signaling pathway responsible for dyslipidemia

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Researchers from Boston University School of Medicine (BUSM), including Yu Li, PhD, and other colleagues, have demonstrated that a nutrient sensing pathway is involved in the disruption of cellular lipid homeostasis in obese and insulin resistant mice fed a diet high in fat and sucrose. This nutrient sensing pathway, which is described in the current on-line issue of *Cell Metabolism*, may also have implications for the health benefits of polyphenols containing foods against fatty liver, hyperlipidemia, and atherosclerosis associated with obesity and type 2 diabetes.

Although it is well known that elevated serum cholesterol and triglyceride levels and fatty liver are caused by increased hepatic lipid synthesis and/or decreased lipid clearance in patients with obesity and diabetes, the underlying mechanistic pathways of these changes remains unknown.

The master regulators of lipid metabolism that were studied are called AMPK and SREBP. The researchers used a molecular biology approach, cell culture system and animal models to indicate that dysregulation of AMPK, an energy sensor, and SREBP, a protein that is important regulator for lipid biosynthesis, are affected in obesity. Mice fed a diet with high fat and high sucrose became obese and had insulin resistance and elevated circulating levels of cholesterol and triglyceride which led to accelerated atherosclerosis. In contrast, dietary supplementation with S17834, a polyphenol, significantly improved the metabolic disorder, lipid levels and atherosclerosis.

"Our findings suggest that AMPK suppression and SREBP activation are a root cause of fatty liver and hyperlipidemia in type 2 diabetes and its associated vascular complications such as atherosclerosis," said senior author Mengwei Zang, MD, PhD, an assistant professor of medicine at BUSM.

According to the researchers the potential health benefits of polyphenols have been gaining increasing interest. "In our studies, AMPK is potently and persistently activated by polyphenols including the natural compound resveratrol, which is present in red wine, grapes and green tea, as well as the synthetic polyphenol S17834, which is a drug candidate provided by Servier Pharmaceutical Company," explained Zang. "AMPK directly suppresses SREBP via its phosphorylation, inhibiting the activity of its target lipogenic enzymes in the liver, and accounting for the protective effects of the polyphenols on fatty liver, blood lipids and diabetic atherosclerosis," she added.

The researchers believe these findings may lead to the development of new drugs that could stop or slow diabetes progression or improve current treatments.

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