Researchers identify muscle factor that controls fat metabolism

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Metabolic diseases, such as obesity and type 2 diabetes, have risen to epidemic proportions in the U.S. and occur in about 30 percent of the population. Skeletal muscle plays a prominent role in controlling the

body's glucose levels, which is important for the development of metabolic diseases like diabetes.

In a recent study, published in *The Journal of Clinical Investigation,* University Hospitals (UH) Cleveland Medical Center and Case Western Reserve University School of Medicine researchers have found that skeletal muscle significantly affects how the body stores and metabolizes fat.

In the study, Mukesh K. Jain, MD, senior author, Chief Academic Officer at UH, and the Ellery Sedgwick Jr. Chair & Distinguished Scientist, and his team set out to investigate the role of a gene called Kruppel-like factor 15 (KLF15) in skeletal muscle. The team utilized a mouse model with KLF15 specifically deleted in muscle.

This genetic manipulation resulted in a striking phenotype: obesity, dyslipidemia (high circulating levels of fats), glucose intolerance, insulin resistance, and a propensity to develop non-alcoholic fatty liver disease (NAFLD). Further investigation revealed that KLF15 controls skeletal muscle fat uptake and utilization. Without KLF15, fats cannot efficiently enter muscle and instead are deposited in the liver and white adipose tissue.

"We knew from prior work by our team that the role of KLF15 was critical for muscle health, because levels are increased in humans following exercise," explained Dr. Jain, who is also a Professor of Medicine and Vice Dean of University Hospitals Affairs at Case Western Reserve, and Chief Scientific Officer, Harrington Discovery Institute at UH. "Experimentally, muscle loss of KLF15 led to a reduction in exercise capacity in mice. The fact that KLF15 is also important in metabolic health is really exciting as it provides a potential molecular link between exercise and overall health."

The researchers further showed that a diet rich in short chain fatty acids (SCFAs) can improve aspects of metabolic disease. High-fiber foods, such as fruits, vegetables, beans and whole grains are rich in SCFAs. Mice given this diet showed decreased weight gain and improved glucose homeostasis (blood sugar regulation). Additionally, obese mice given this same diet demonstrated increased weight loss and improved insulin sensitivity, indicating that SCFA-rich diets can potentially serve as both a preventive and therapeutic avenue for metabolic disease.

"This predisposition to develop obesity and NAFLD both in the presence of caloric excess underscores the importance of skeletal muscle fat metabolism and organ cross-talk in the development of these serious diseases," said Liyan Fan, first author on the study. "This helps us understand the different players that contribute to metabolic disease, and consequently, identify targets for effective therapies."

Collectively, these findings identified skeletal muscle as an important regulator of fat metabolism and liver health, and SCFA-rich diets may be an effective and accessible supplemental therapy option for metabolic disease resulting from impaired fat handling.

Next steps in this research involve exploring muscle KLF15's role in different nutritional statuses (i.e. fasting and exercise), and investigating the therapeutic potential of targeting muscle KLF15.

More information: Liyan Fan et al, Muscle Krüppel-like factor 15 regulates lipid flux and systemic metabolic homeostasis, *Journal of Clinical Investigation* (2021). DOI: 10.1172/JCI139496

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