Targeting 'lipid chaperones' may preserve lifelong metabolic health

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Researchers have found that, in a mouse model, it may be possible to achieve lifelong metabolic health. The Harvard T.H. Chan School of Public Health scientists found that mice that lack fatty acid-binding proteins (FABPs) exhibit substantial protection against obesity, inflammation, insulin resistance, type 2 diabetes, and fatty liver disease as they age compared with mice that have FABPs. However, this remarkable extension of metabolic health was not found to lengthen lifespan.

"From a public health perspective, extending the number of years that people are healthy would be a huge achievement," said Gökhan S. Hotamisligil, J.S. Simmons Professor of Genetics and Metabolism and chair of the Department of Genetics and Complex Diseases and Sabri Ülker Center at Harvard Chan School. "Our findings show that this may be possible through a mechanism that can be translated into human populations through pharmacological and nutritional interventions."

The study will appear online October 10, 2017 in *Cell Reports*.

FABPs are escort proteins or "lipid chaperones" that latch onto fat molecules, transport them within cells, and dictate their biological effects. Previous work from Hotamisligil's lab found that when FABP-deficient mice were fed high-fat or high-cholesterol-containing diets, they did not develop type 2 diabetes, fatty liver, or heart disease.

Metabolic health typically deteriorates with age, and researchers believe

that this contributes to age-associated chronic diseases and mortality. Studies have shown that high-calorie diets impair metabolism and accelerate aging; conversely, calorie restriction has been shown to prevent age-related metabolic diseases and extend lifespan.

In the new study, Hotamisligil, co-first authors Khanichi Charles, Min-Dian Li, and colleagues examined metabolic function in multiple cohorts of FABP-deficient mice throughout their life. They found that FABP deficiency markedly reduced age-related weight gain, inflammation, deterioration of glucose tolerance, insulin sensitivity, and other metabolic malfunctions. This effect was more strongly observed in female than male mice. Surprisingly however, they did not find any improvement to lifespan or preservation of muscular, cognitive, or cardiac functions with age.

The researchers saw striking similarities between the alterations in tissue gene expression and metabolite signatures in the genetic model of FABP-deficiency developed for this study and the alterations that occur due to calorie restriction. The findings suggest that it may be possible to mimic part of the metabolic benefits of calorie restriction by targeting FABPs. In addition, by examining the molecular differences between these models, it may also be possible to identify other pathways that contribute to longer life span or alternative strategies to prevent metabolic diseases.

"These simple proteins carry many fascinating mysteries that could unlock some of the greatest challenges to human health," said Hotamisligil.

More information: "Uncoupling of Metabolic Health from Longevity through Genetic Alteration of Adipose Tissue Lipid-Binding Proteins," Khanichi N. Charles, Min-Dian Li, Feyza Engin, Ana Paula Arruda, Karen Inouye, Gökhan S. Hotamisligil, *Cell Reports*, online October 10, 2017, DOI: 10.1016/j.celrep.2017.09.051

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