Gene associated with obesity and type 2 diabetes is connected to how cells regulate fat

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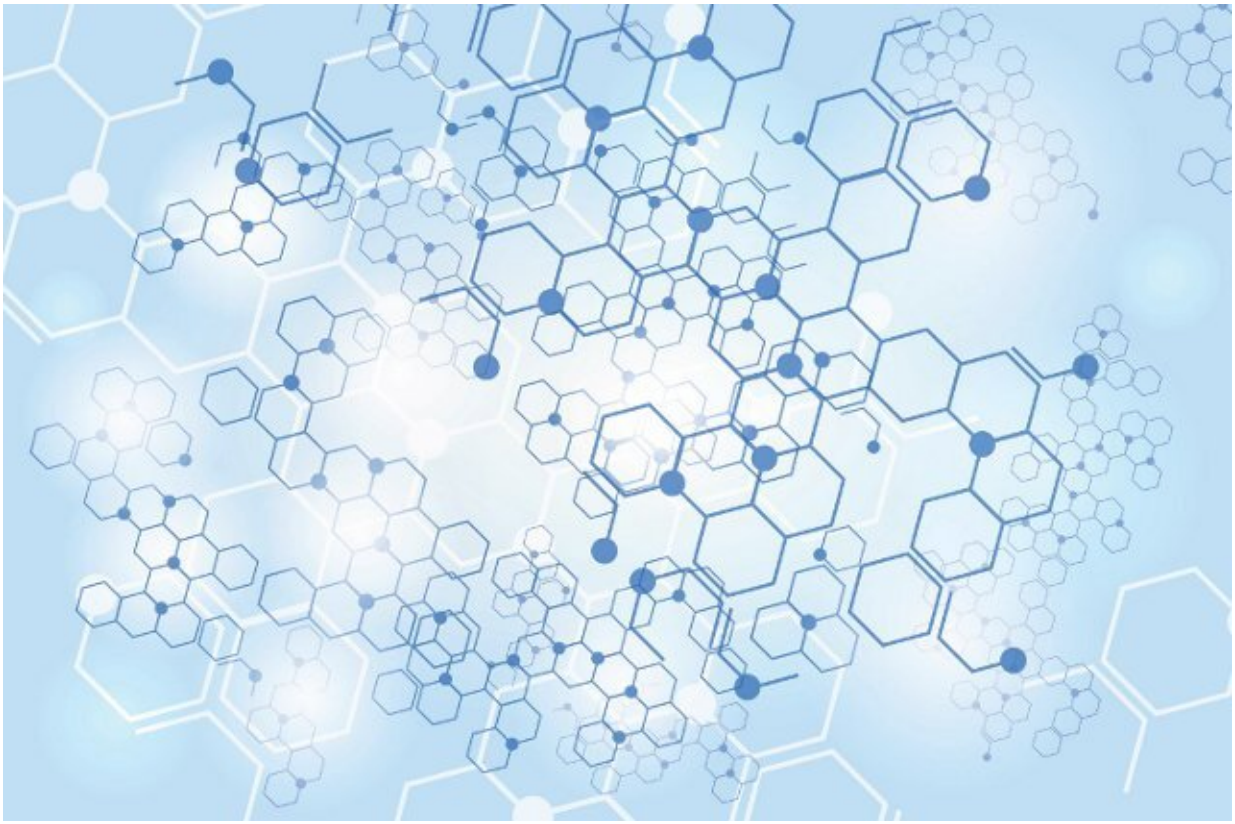

Because of changes in the gene ACSL4, mice “were protected from diet-induced obesity, fat-cell dysfunction, and the metabolic changes often seen as a consequence of obesity,” said Andrew Greenberg. Credit: Ingimage

Why does weight gain cause metabolic problems that can lead to heart disease and diabetes in some individuals, but not others? Researchers at

the Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts (HNRCA) have found one clue: a gene associated with obesity and development of type 2 diabetes, they discovered, is also connected to how cells regulate fat at the cellular level. The study about the research was published in the journal *Molecular Metabolism*.

The gene in question, ACSL4, codes for a protein that aids in the metabolism of specific fatty acids within cells, getting them ready to be used for energy storage and metabolism. ACSL4 is a member of the ACSL family of proteins that modifies fatty acids and essentially traps them within cells. ACSL4 is thought to play a role in fatty acid transport and storage, which is why it's important for maintaining proper cell metabolism and function.

In creating a new mouse model with reduced expression of ACSL4 in fat cells, the researchers discovered and detailed the protein's role in diet-induced obesity for the first time.

Tufts Now spoke recently with lead researcher Andrew Greenberg, director of the Obesity Metabolism Laboratory at the HNRCA, to learn more about the findings and how they might apply in humans.

Tufts Now: What did your study find?

Andrew Greenberg: We fed mice with reduced expression of ACSL4 specifically within fat cells a high-caloric diet and found that the mice gained less weight, had less inflammation from the high-caloric diet, and showed metabolic improvements. It was remarkable to see such an effect because ACSL4 represents only a small fraction of total ACSL expression in fat cells.

How did you measure metabolic improvements?

We measured metabolic rates, food intake, and general activity in these mice after three and seven weeks on a high-caloric diet. We also used a glucose-tolerance test to measure how quickly glucose can be cleared from the body, the same test used in humans to help diagnose diabetes.

What kind of metabolic improvements did you see?

Mice with reduced ACSL4 fed a high-caloric diet had increased metabolism of fatty acids within the targeted fat cells and an increase in whole body energy expenditure—metabolic rates. Remarkably, because of these changes they were protected from diet-induced obesity, fat-cell dysfunction, and the metabolic changes often seen as a consequence of obesity such as alterations in glucose metabolism.

Why is increased fat storage in cells harmful, and how does it lead to obesity and other metabolic diseases?

ACSL4 can regulate the incorporation of specific types of fatty acids into the cell membrane, which leads to an unbalanced membrane composition that is associated with diseases like obesity, diabetes, and heart disease.

With obesity, these specific types of fatty acids accumulate within fat cell membranes and are metabolized into molecules that detrimentally alter cellular metabolism. In our studies, even though we fed mice high-caloric diets, fat cell ACSL4 deficiency reduced levels of susceptible fatty acids and the generation of these toxic metabolites and maintained fat cells in a metabolically "healthy" state protecting against the development of diet-induced obesity.

How might this apply to people?

A class of anti-diabetic drugs, called thiazolidinediones, are known to directly inhibit ACSL4. Our findings suggest that reduction of ACSL4 gene expression may be one of the actions of these drugs. Although thiazolidinediones have some undesired side effects that have limited their clinical use, our studies may provide a more tailored therapeutic approach for research and drug development that may avoid some of the side effects previously observed. Learning more about how this gene works may also help us understand more about the underlying biology of weight gain and metabolic disorders.

More information: Elizabeth A. Killion et al. A role for long-chain acyl-CoA synthetase-4 (ACSL4) in diet-induced phospholipid remodeling and obesity-associated adipocyte dysfunction, *Molecular Metabolism* (2018). DOI: 10.1016/j.molmet.2018.01.012

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