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Fundamental discovery reveals how fat is stored in cells

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In discovering the genes responsible for storing fat in cells, scientists at the Albert Einstein College of Medicine of Yeshiva University have answered one of biology's most fundamental questions. Their findings, which appear in the December 17 to 21 "Early Edition" online issue of the *Proceedings of the National Academy of Sciences*, could lead to new strategies for treating obesity and the diseases associated with it.

Scientists had previously identified the genes responsible for synthesizing fat within cells. But the genes governing the next step--packaging the fat inside a layer of phospholipids and proteins to form lipid droplets—have long been sought, and for good reason.

"Storing fat in lipid droplets appears crucially important for enabling cells to use fat as an energy source," says Dr. David Silver, assistant professor of biochemistry at Einstein and senior author of the article. "From yeast to humans, partitioning fat into droplets is a universal feature among animals. And in humans, of course, acquiring excessive amounts of these fat droplets in our fat tissue leads to obesity."

Dr. Silver and his colleagues identified two genes that are crucial for packaging fat into lipid droplets. They called the genes FIT1 and FIT2 (for Fat-Inducing Transcripts 1 and 2). Both genes code for proteins that are more than 200 amino acids in length, and the two genes are 50 percent similar to each other. The amino acid sequences of the FIT proteins do not resemble any other known proteins found in any species, indicating that the FIT genes comprise a novel gene family.

The researchers conducted several different experiments to confirm the roles of FIT1 and FIT2 in fat storage. In one experiment, they overexpressed both FIT1 and FIT2 genes (i.e., inserted extra copies of them) in human cells. While the rate of fat synthesis stayed the same in both “overexpressed” and control cells, the number of lipid droplets in the “overexpressed” cells increased dramatically, between four- and six-fold.

Using a different tactic to evaluate FIT function, the researchers next “knocked down” FIT2 in mouse fat cells (FIT1 is not expressed in these cells). Their reasoning: If FIT2 is indeed essential for lipid droplet formation, then suppressing FIT2 expression should abolish lipid-droplet accumulation. Examination of these fat cells for lipid droplets revealed that cells with suppressed FIT2 expression had a drastic reduction in lipid droplets.

Finally, the researchers carried out a similar FIT2 “knock down” experiment in a whole animal—the zebrafish. Zebrafish eggs were injected with a segment of DNA designed to interfere with FIT2 expression. Then, to induce lipid droplet formation in zebrafish larvae (where it is localized mainly in the liver and intestine), free-swimming six-day-old larvae were fed a high-fat diet for six hours. Although the larvae had exhibited normal feeding behavior, examination of their livers and intestines revealed a near-absence of lipid droplets.

“These lines of evidence supported our conclusion that FIT genes are necessary for the accumulation of lipid droplets in cells,” says Dr. Silver. “Now that we’ve identified the genes and the proteins they code for, it should be possible to develop drugs that can regulate their expression or activity. Such drugs could prove extremely valuable, not only for treating the main result of excess lipid droplet accumulation—obesity--but for alleviating the serious disorders that arise from obesity including type 2 diabetes and heart disease.”

Source: Albert Einstein College of Medicine