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Hormone that controls maturation of fat cells discovered

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Scientists at the Stanford University School of Medicine have discovered a hormone that controls the first step in the maturation of fat cells. Its actions help explain how high-fat diets, stress and certain steroid medications cause obesity.

The new findings will be published Oct. 25 in *Science Signaling*.

Around the body, fat depots contain many mature fat cells and small numbers of stem cells. These stem cells can differentiate into more fat cells, but until now, no one has known how the process was triggered.

The new research shows that mature fat cells make a hormone called Adamts1 that toggles the switch controlling whether nearby stem cells differentiate and prepare to store fat. High-fat diets and glucocorticoid medications change Adamts1 production, telling nearby stem cells to begin maturing, the research found.

"Intuitively, people understand that when you eat more, you get fatter," said Brian Feldman, MD, PhD, assistant professor of pediatrics and the study's senior author. "You're ingesting food, and some signal has to tell your body to make more fat. We didn't know what was gating or triggering that process in vivo. This new research goes a long way to fill in the in-between steps."

The paper's lead author is postdoctoral scholar Janica Wong, PhD.

In recent decades, scientists around the world have debunked the idea that fat cells are passive bags of calories. In addition to their storage function, mature fat cells are now known to send and receive many hormonal signals that help regulate metabolism.

Experiment with fat cells

To identify the role of Adamts1 and understand how it works, Feldman's team conducted a series of experiments using fat cells and their precursors in a dish, followed by studies in mice and humans. They started their search by looking for genes that change activity in response to glucocorticoid medications. These medications, which include prednisone and dexamethasone, have the serious, negative side effects of promoting obesity and diabetes. The scientists wanted to understand how. Among their findings:

- Experiments using fat tissue from mice showed that mature fat cells normally make and secrete Adamts1. Its levels drop when mice are given glucocorticoids.
- Mice that are genetically engineered to make more Adamts1 than normal have smaller-than-normal fat depots, and fewer mature fat cells.
- When purified Adamts1 is added to fat stem cells in a dish, it can block glucocorticoid-induced differentiation, suggesting that it normally acts as an extracellular signal.
- Once it reaches the fat stem cell, Adamts1 transmits its message through a set of intracellular signals that overlap with the cells' glucocorticoid response pathway. A cell-signaling molecule called pleiotrophin plays an important role in the pathway; blocking the molecule's signal blocks the stem cell's entire response to Adamts1.
- Finally, after gathering this evidence that Adamts1 is a hormone, and that it plays a big role in controlling whether fat stem cells

> differentiate, the researchers fed high-fat diets to mice and humans and examined how this affected the Adamts1 signal. As expected, mice became fatter after eating a high-fat diet, with new fat cells maturing mostly in the animals' visceral fat tissue, the fat located around internal organs. The mice had decreased Adamts1 in this type of fat tissue. In subcutaneous fat tissue, the fat under the skin, the opposite response was seen: there was more Adamts1 production and less fat cell maturation.

These findings are consistent with earlier research showing that more visceral, but not more subcutaneous, fat cells mature when someone eats a high-fat diet, and suggest that Adamts1 is a major regulator of this difference between the two types of fat. In humans who gained weight while eating a high-fat diet, the research team saw that the Adamts1 responses were consistent with what was seen in mice.

The effect of stress hormones

The results suggest how both high-fat diets and synthetic and natural stress hormones are tied to greater obesity. In essence, stress hormones send a message via Adamts1 to make more fat cells mature. "We think it is a signal that there may be hard times ahead, a trigger to store as much available energy as you can," Feldman said.

And the same set of signals works when people eat a high-fat diet but are not stressed or taking glucocorticoid medications, he added. "We've basically seen that the glucocorticoid signal is embedded in the high-fat feeding pathway. Connecting those dots together was really exciting."

The study's results do not exclude the possibility that other, undiscovered hormones also influence fat cells' decision to mature; however, Adamts1 is probably one of the most important, Feldman said. "There may be a group of regulators, but the potency of Adamts1 suggests it's a dominant

signal, a major player," he said.

The scientists still have many questions left to answer about Adamts1, including whether it might somehow be used as a target for anti-obesity drugs.

"That won't be a simple answer," Feldman said. "If you block fat formation, extra calories have to go somewhere in the body, and sending them somewhere else outside fat cells could be more detrimental to metabolism. We know from other researchers' work that liver and muscle are both bad places to store fat, for example. We do think there are going to be opportunities for new treatments based on our discoveries, but not by simply blocking fat formation alone."

The results could also help scientists understand how fat formation in childhood influences lifelong obesity risk, Feldman said. "We know that fat is a critical endocrine organ, formed almost exclusively during childhood," he said. "The rate of fat formation in childhood has lifelong implications, and understanding how that's controlled and regulated is very important."

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