

Study reveals an ancient gene for lean

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Researchers have revealed an antiobesity gene that has apparently been keeping critters lean during times of plenty since ancient times. The gene, first discovered by another team in flies, also keeps worms and mice trim, according to the new report in the September issue of *Cell Metabolism*, a publication of Cell Press. If the gene works similarly in humans, the findings could lead to a new weapon against our burgeoning waistlines, according to the researchers.

Animals without a working copy of the gene, known as Adipose (Adp), become obese and resistant to insulin, while those with increased Adp activity in fat tissue become slimmer, the researchers found. Moreover, the gene's "dose" seems to determine how slender an animal turns out to be.

"Maybe if you could affect this gene, even just a little bit, you might have a beneficial effect on fat," said Jonathan Graff of the University of Texas Southwestern Medical Center, noting that people often become overweight very gradually—adding just one or two pounds a year. "After 30 years, that's a lot."

While worms and flies are routinely studied as models of human health and disease, that trend has been less true in fat biology, Graff said. That's because unlike mammals, worms and flies store their fat in multifunctional cells rather than in dedicated fat cells known as adipocytes. However, those differences didn't preclude the possibility that the animals might use similar genes to accomplish their fat storage goals, he added.

In the new study, Graff's team found that worms lacking Adp activity became fat, although they appeared to be otherwise healthy and fertile. The researchers scoured the genetic database in search of related genes and found one with "tremendous" similarity in flies.

Indeed, another scientist, Winifred Doane, had found a naturally occurring strain of plump flies in Nigeria almost 50 years ago that carried a mutation

in their Adp gene. The flies lived in a climate marked by cycles of famine, where they may have benefited from being highly efficient at fat storage, Doane had suggested.

To explore Adp's function even further, Graff and his colleagues produced a strain of mutant flies like those that Doane had found years earlier. They found that the mutant flies were indeed fat and also had trouble getting around. Flies with only one copy of the Adp mutation fell somewhere in between the fat and normal flies, evidence that the gene's effects are "dose dependent," they reported.

Treatments that increased Adp in the insects' fat tissue led them to lose weight, evidence that the gene operates within fat cells themselves. In mice that expressed the gene in fat-storing tissues, the same patterns emerged.

"We made mice that expressed Adp in fat-storing tissues, and lo and behold, what happened!" Graff said. "They were skinny—weighed less with markedly less fat—and their fat cells were smaller." Smaller fat cells usually translate into better metabolic function, he said, including better blood sugar control.

"It's a striking conservation of genes that restrain fat," he said. While fat storage is an important mechanism for getting through lean times, "too much fat in times of plenty has deleterious consequences."

The search for molecules underlying weight gain and poor blood sugar control "has taken on additional urgency due to the recent dramatic increase in obesity and diabetes," Graff said. But in a modern world where many people have essentially unlimited access to food, it's a wonder that even more people aren't overweight, he added. If this gene plays a similar role in humans, "it may be that some people's Adp works very well."

Source: Cell Press

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