Decoding the Surprisingly Active Life Of Fat Cells

By Rob Stein
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For decades, scientists thought fat cells were passive blobs that did nothing more than store energy, bloat flabby hips and bellies, and perhaps wear down the body by forcing it to cart around a lot of extra weight.

But as the nation's obesity crisis has intensified scientific interest in fat, researchers have fundamentally altered that view: **Fat cells, they now realize, are extraordinarily dynamic, complex and influential entities that affect a staggering array of crucial bodily functions.**

The new insights into fat's commanding, self-sustaining powers, scientists say, have profound implications for understanding how flab forms, why it hangs on so stubbornly, how it causes disease, and therefore possibly how to help people shed pounds and avoid the devastating health problems wrought by fat cells.

"They were always thought to be poor, dumb sacks of lard," said Roger Unger, an obesity researcher at the University of Texas Southwestern Medical Center. "It turns out that they end up being very talented, very versatile, very important players."

Instead of sitting idly by, waiting for a famine or a foot race, fat cells continuously dispatch dozens of potent chemical signals to myriad tissues throughout the body, including the brain, liver, muscles, reproductive organs and immune system, orchestrating a host of activities.

"Knowing its whole communication network is going to help us answer many important questions, and possibly lead us in a direction to cure obesity and therefore the diseases caused by obesity," said Barbara Corkey, a Boston University scientist who serves as president of the North American Association for the Study of Obesity.

Like guardians of the nation's strategic oil reserve, fat coordinates how, when and where the body's energy supply is stored and how and when it is mobilized. Fat also emits signals that can unleash, or damp down, the immune system. Fat influences when blood clots and when blood vessels constrict. Fat even tells the body when it can reproduce, and when it must await more favorable conditions. And perhaps most insidiously, fat cells most likely beget new fat cells, perpetuating their existence and magnifying their effects.

"In the old days, people used to think fat tissue was a passive organ," said Rexford S. Ahima, an endocrinologist at the University of Pennsylvania. "Now it's obvious that it makes and secretes more hormones and proteins than probably any other. It's at the center of a very complex system. It coordinates how much we eat, how much energy we burn, how the immune system works, how we reproduce. The list goes on."

And scientists suspect they have just begun to unravel the intricate web of fat's reach, with perhaps dozens of other functions and signals awaiting discovery, including some that probably affect mood and behavior beyond just hunger and eating.

"Many people think your brain controls your fat," said Gokhan S. Hotamisligil, a professor of genetics and metabolism at the Harvard School of Public Health. "We promote the idea that your fat controls your brain."

The new understanding has led to the discovery of new chemical messengers that fat cells deploy, and drug companies are scrambling to find ways to manipulate those hormones to help people lose weight and avoid the health problems associated with obesity.

"Once you know the players you can try to cage them in," said Xavier Pi-Sunyer, chief of endocrinology at St. Luke's-Roosevelt Hospital in New York.

The new insights also may help alter societal views of obesity, further undermining the notion that obesity is a sign of moral defect and bolstering the case that it is a discreet and stubbornly self-perpetuating biological state.

"The rules of the game have changed. The way you look at an individual who is obese has to be radically changed as a result of this," said Rudolph L. Leibel, a molecular geneticist at Columbia University. "Before the naysayers could say this is all free will and has nothing to do with biology. I don't think anything could be farther from the truth."

The pivotal discovery came in 1994, when scientists identified a hormone produced by fat cells that they dubbed leptin. Among other things, leptin tells the brain how much fat is in the body. That raised the hope that it could be used as an anti-obesity drug, but that has yet to pan out. Still, the discovery revealed for the first time a direct communication link between the brain and fat cells.

That insight spawned a new wave of research that led to the identification of other fat signals and the new paradigm for the role of fat in the body. **Scientists now call fat an "endocrine organ," akin to the thyroid and adrenal glands that orchestrate many body functions.**

"But it's probably the biggest endocrine organ in the body," said Jeffrey M. Friedman of the Rockefeller University in New York, who led the team that discovered leptin. "Fat tissue plays such a vital role for the survival of any species that it should really come as no surprise that it would be involved in such dynamic regulation."

Scientists have long known, for example, that fat cells play a role in synthesizing sex hormones such as estrogen, which enables the cells to regulate the reproductive process. That explains, for example, why ballerinas, female professional athletes and other women who are very thin often stop menstruating.

"If a female doesn't have enough energy stored, the pregnancy can be in jeopardy and so reproduction is shut down. The body is waiting for more favorable conditions," Friedman said.

But far beyond simply monitoring energy reserves, fat cells are the hub of a complex communication system that regulates many metabolic functions, continuously telling the brain how much energy the body has left, signaling muscles when they can burn fat, instructing the liver and other organs when to replenish fat stores, and controlling the flow of energy in and out of cells.

One of the most important newly recognized players in that finely tuned system is a protein called adiponectin, which affects the liver and muscles.

"This hormone lowers blood glucose by blocking its production in the liver and by increasing the burning by muscle to make energy," said Harvey Lodish, a professor of biology at the Massachusetts Institute of Technology. "It activates part of the same signaling pathway in muscles [that is] activated by exercise."

Adiponectin levels fall as fat levels rise. Because the hormone affects how sensitive cells are to insulin, scientists believe it helps explain how obesity increases the risk for diabetes.

"It's been pretty well established now that levels of this protein are a good measurement of insulin sensitivity," said Philipp Scherer, a cell biologist at the Albert Einstein College of Medicine in New York who identified the substance.

Drugs that affect adiponectin, therefore, may help prevent or treat diabetes. The drugmaker Serono Inc., has started studying adiponectin, both as a possible preventative for diabetes and as a weight-loss drug.

Soon after adiponectin's importance was recognized, scientists discovered another fat cell hormone called resistin, which also appears to play a crucial role in insulin sensitivity and energy storage.

"It's clearly important, but its exact mechanisms are still something we're trying to understand," said Mitchell A. Lazar, an endocrinologist at the University of Pennsylvania School of Medicine who discovered the hormone. "So far we haven't found net changes in energy storage -- weight is not affected in a significant way by either too much or too little resistin."

At the same time, scientists have come to the surprising conclusion that fat has the power to mimic the effects of the body's immune system, in particular by provoking an inflammatory response.

"There's a growing realization about the convergence of the medical problems associated with obesity and chronic inflammation, which wasn't appreciated for a long time but is coming to the fore scientifically," Lazar said. "Where does the inflammation come from? Surprise: It's the fat cells themselves."

But not from the fat cells alone. Scientists recently discovered that fat tissue is comprised of far more than just fat cells -- it is a complex amalgamation that includes key immune system cells called macrophages. Macrophages and fat cells produce powerful substances called tumor necrosis factor-alpha and interleukin-6, which help regulate the immune system.

Fat probably evolved a close connection to immune function because the body needs energy when it is fending off threats, scientists say.

"It's like if you are sending troops into battle," Hotamisligil said. "You have to send not just rifles but bullets."

But a surplus of fat cells and macrophages probably triggers unnecessary inflammation, which most likely explains at least part of why obesity increases the risk for so many diseases, including cancer, heart disease and diabetes.

"As fat mass increases, this is associated with a systematic stress response and inflammatory response, and that exhibits itself in a variety of diseases," Hotamisligil said.

Fat cells also send out signals that cause blood vessels to constrict, raising blood pressure, and make blood clots form, which may explain how obesity increases the risk for heart attack and stroke. At the same time, fat cells emit signals that promote blood vessel and cell growth, which could help explain why obesity increases the risk of cancer.

The more scientists learn about fat, the more intimidating it becomes. Because fat is so vital to survival, nature has created a complex system of overlapping feedback loops that make it very difficult to override the body's imperative to store energy.

"What we're trying to do is do like the physicists do: Build a theory of everything about fat tissue," Leibel said. "We'd really like to understand not only what the signals are but how they are integrated. There's so much that we simply do not yet understand about this."