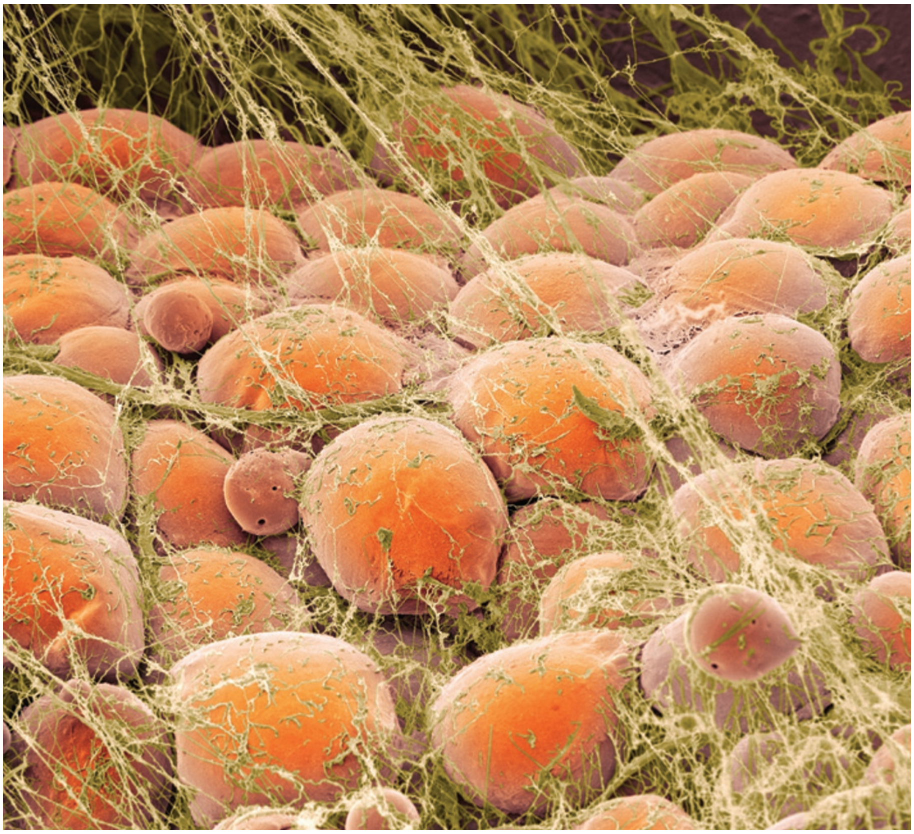
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Researchers are attempting to harness the ability of brown cells to burn fat.

CELL PHYSIOLOGY

The changing colour of fat

The different functions of white, brown and beige fat might yield new targets in the fight against obesity and metabolic disease.

BY BRIAN OWENS

When you think of fat in the human body, you might picture a homogenous, white substance, much like a block of lard. But researchers are learning that the role of fat in metabolism changes depending on where it is in the body, and even on the type of fat cell. Soon these differences could be harnessed to fight metabolic disorders such as diabetes and obesity.

The predominant form of fat in mammals, including in humans, is known as white fat. White fat cells are found throughout the body, primarily under the skin, as well as in larger deposits in the abdomen. They are highly specialized for energy storage, hoarding calories in the form of lipid droplets.

The white cells are complemented by brown fat cells, which specialize in converting chemical energy from glucose and lipids into heat, generally when an animal is exposed to the cold. This burning of carbohydrates and fat also helps counteract obesity and metabolic disorders.

But, says Patrick Seale, a developmental biologist at the University of Pennsylvania in Philadelphia, that does not mean the two types of fat are heroes or villains. "Often one portrays white adipocytes as the bad guy, and the brown adipocytes as the good fat cell," he says. "That's not really the case — white fat cells serve an important role in protecting against metabolic disease, but the key is to keep those cells healthy."

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Healthy white fat protects the body by providing a 'safe home' for lipids, which can be toxic to other tissues such as muscle or the liver. So these fat cells hold on to the lipids until the energy they are storing is needed, when they release them into the blood.

Where white fat cells are located also matters. Subcutaneous white fat, scattered throughout the body in depots under the skin, is not associated with metabolic disorders, and may actually be preventative. It is only the abdominal white fat that, when it gets out of control, can cause health problems. And, adds Seale, people with too few fat cells, such as those with a condition called lipodystrophy, have many of the same sorts of problems as people with too much fat. "When they're functioning appropriately, white fat cells will limit metabolic disease," he says. "They're actually a protective cell type."

"When functioning appropriately, white fat cells will limit metabolic disease."

Problems arise when white fat cells store too much lipid. They begin expanding and proliferating rapidly in a process that resembles the growth of a solid tumour, says Philipp Scherer, a cell biologist at the University of Texas Southwestern in Dallas. The blood supply cannot keep up with this expansion, and the cells begin to suffer from lack of oxygen. This hypoxia attracts the protein HIF-1α, which in fat tissue stimulates the extracellular matrix surrounding the cells, leading to fibrosis. The huge, oxygen-starved fat cells do not have enough room to expand and get squeezed to death, releasing their lipid cargo.

As the cells start to die, macrophages swarm to the fat depots to try and clean up the mess by carrying away the lipid droplets. The problem is that the macrophages cannot clear up the lipids fast enough, and so they begin to spill over into other tissues, such as the liver and pancreas. "Those tissues form lipid droplets as well, but they aren't quite as good at it as fat tissue," says Scherer. This inappropriate accumulation of lipids in fat depots and in tissues that are not equipped to handle them results in continued low-grade inflammation and, ultimately, in metabolic disease, insulin resistance and type 2 diabetes.

Until a few years ago, it was generally thought that after infancy humans had only white fat, in contrast to hibernating animals and small rodents, in which brown fat is retained. "In babies it was considered some sort of strange vestige, a little like an appendix," says Jan Nedergaard, a physiologist at Stockholm University. "So it did not attract much attention outside a small circle."

That all changed in 2007, says Nedergaard, when he and his colleagues studied human

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adults and found brown fat deposits around the neck and collarbone — similar to where brown fat is found in mice[1]. "That changed the whole interest in brown fat," he says. "It became a tissue that could be of relevance to controlling body weight and other things."

NOT JUST BROWN AND WHITE

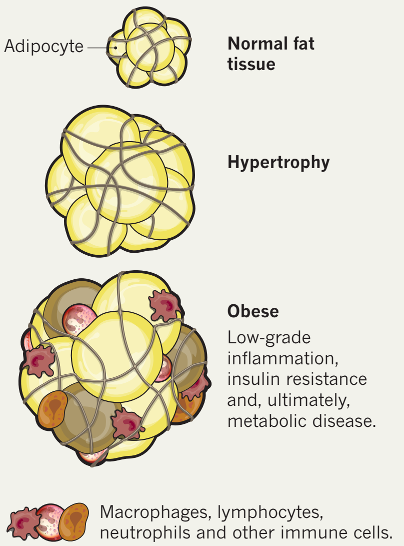
But brown fat is not the end of the story. Scientists had long known that when mice were exposed to cold, brown-fat-like cells would start to crop up in their white fat and begin producing heat by burning lipids, glucose and any other energy-storing molecules available to them. This is not a case of white cells suddenly transforming themselves into brown cells, says Bruce Spiegelman, a cell biologist at Harvard University in Cambridge, Massachusetts. Rather, the white fat depots are seeded with immature cells, which begin to change when exposed to the cold. But these cells are also not exactly brown fat, either. Although they seem to have similar functions, and express many of the same genes as brown fat, they are sufficiently distinct to be considered a new type of fat cell[2], says Spiegelman. Sticking with the colour theme, he calls them beige fat cells. And it is not just mice that have this third type of fat. In 2012, Spiegelman showed that most of the brown fat in humans is actually beige.

There is some disagreement, however, about the relative importance to metabolism of the two types of lipid-burning cell. Although Nedergaard agrees that humans have more beige than brown fat, he thinks that, taken all together, beige cells are less able to burn lipids and produce heat than brown cells. The beige fat cells "clearly have a lower capacity all in all," he says. "We think the main burning is in classical brown fat."

Nedergaard is also not convinced that brown and beige fat have different roles in the body, and so is doubtful that beige fat is of any particular interest for treating human disease. But Spiegelman believes that a study he published earlier this year should put those doubts to rest. Spiegelman's team selectively disabled the beige fat in mice by targeting the protein PRDM16, which is found only in these cells, leaving the white and brown fat intact. The animals ended up with severe metabolic dysfunction — obesity, insulin resistance and damaging fat accumulation in the liver, known as hepatic steatosis[3]. The loss of the beige fat destroys the protective abilities of subcutaneous white fat. "Nobody can look at the data and say the animals aren't screwed up when they lose their beige fat," says Spiegelman. "I think we have to consider the discussion closed in terms of whether beige fat is important in normal physiology."

TISSUE TURNS BAD

Cells overloaded with lipids rapidly outgrow oxygen supply, leading to cell death and inflammation.



FUELLING INTEREST

Whether the target is brown or beige, fat tissue is attracting attention as a possible way to fight obesity and metabolic disease. Researchers are hoping to stimulate the growth of more of the helpful fat cells. "If you have enough of them, and they're efficiently activated, they can alter the energy balance of the body," Seale says.

The most natural way to do that is through cold exposure. "If you said you wanted to build your beige fat, I'd say go lightly dressed in a Canadian winter for a week or two and you'll have plenty of beige and brown fat," says Spiegelman. However, although some researchers have suggested that turning down the thermostat might be a good way to fight obesity[4], any effect will last only as long as the drop in temperature, and exposure to the cold is not really a practical therapy. It would be better, says Seale, if researchers could find a way to stimulate the biochemical pathway that activates the cold response.

One receptor involved in this pathway is known — the β3 adrenergic receptor. In mice, administering a compound that activates it (an agonist) prevents obesity and lowers the incidence of diabetes[5]. Unfortunately, says Seale, no equivalent agonist has been found in humans and the search has largely been abandoned by pharmaceutical companies.

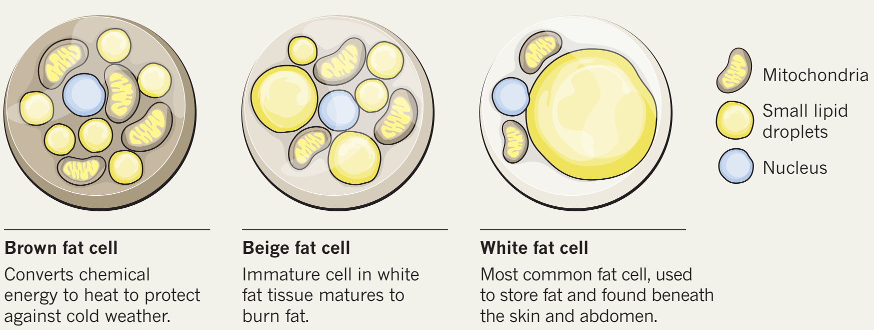
There are other ways to stimulate the activity of brown and beige fat, however. Physical activity seems to do it, says Spiegelman. Irisin, a hormone produced by skeletal muscle in response to exercise, can induce the formation of more beige fat[6]. The hormone FGF21 is another promising candidate. Obese humans treated with a synthetic version of FGF21 showed improvements in their cholesterol counts and body weight[7]. "It's only a matter of time before some of these things become targets for chemicals that can activate the pathways," says Seale.

In the meantime, there is still much to be learned about the characteristics of the different types of fat cells themselves, including the question of whether there are any additional categories waiting to be discovered. One possibility, says Seale, is that white subcutaneous and white abdominal fat — which have very different effects on metabolism — might actually be distinct. "If you take the cells out and isolate them, they have different gene-expression profiles and they really just look like different cell types," he says. "Fat cells might behave very differently and respond differently to different diets and disease states."

Spiegelman agrees. He likens the present understanding of fat cells to changing concepts of white blood cells. "It became B cells and T cells, and monocytes, and macrophages. And macrophages became dendritic cells, and T cells became regulatory T cells and killer T cells," he says. "It's entirely possible that within the category of white we have two or three different categories, and within the category of beige maybe we'll have two or three different categories." ■

SHADES OF A CELL

Three distinct types of fat cell have been identified to date, are there more to follow?



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