Brown fat can metabolize white fat through thermogenesis // It’s potentially the ideal weapon to fight obesity // And to provide therapy for metabolic diseases // Now the main question is how does it work?

The Fitter Fat
ike many innovations in medicine, this discovery began as a problem. In the early 1990s, radiologists began using positron emission tomography, a type of body-scanning technology, to hunt for cancerous tumors. They would inject a dose of radioactive glucose into the bloodstream. Tumors consume glucose, so the PET scan would track the uptake of glucose in different parts of the body and might point the way to a previously unnoticed cancer.

Because glucose is a type of fuel, the radiologists knew that energy-burning organs such as the brain and the heart would suck up some of it. What they didn’t expect was that the glucose would also wind up being drawn to a region around the neck and shoulders, often in a symmetrical pattern. Tumors are generally not symmetrical in shape, so the radiologists were pretty sure what they were looking at was not cancer.

But what was it? In 2002, radiologists began routinely combining the PET technology with CT scans, which gave them a clearer view. They were stunned to realize that they were looking at brown adipose tissue, more commonly known as brown fat. For those specialists searching for malignancies, the brown fat was a nuisance, because its presence could obscure a tumor. But for researchers who study certain circumstances—for example, when a person is sitting in a cold room—it triggers a chemical reaction within the mitochondria that results in heat production. Like any fire, this process requires fuel, and brown fat maintains its heat partly by burning regular body fat, commonly known as white fat.

For decades, although researchers knew it existed in babies and animals, no one believed adult humans harbored brown fat, and its discovery in some adults—it’s still unclear how much of the human population possesses it—has opened the way for the medical research and pharmaceutical communities to pursue a compelling new kind of weight-loss treatment.

The stakes are potentially enormous. About one-third of all adults in the United States are obese and another third are overweight, according to the Centers for Disease Control and Prevention. The CDC forecasts that as many as one in three adult Americans could have diabetes by 2050, in some measure as a result of the projected rise in obesity rates. The direct annual medical cost associated with obesity exceeds 147 billion in the United States alone.

metabolism and obesity, the discovery of brown fat in adults was a watershed moment.

Brown fat is not actually fat, but rather a tissue that possesses a unique uncoupling protein, known as UCP1, embedded in its mitochondria. When the protein becomes activated under

No one knows yet how significant a discovery of brown fat in humans might be. A sweeping new round of studies—some funded by drug companies—is aimed at finding ways to enhance the stores of brown fat in people who are overweight and to activate the tissue to do its work. Many researchers believe that in terms of the struggle to turn the dial back on obesity, brown fat might be the most important thing to come along for some time.
Brown fat has been the subject of fascination and controversy within the medical community for centuries. In 1551, Swiss naturalist Konrad Gessner characterized the tissue, which he observed in marmots, as “neither fat, nor flesh—but something in between.” Modern researchers began to grasp its potential significance in the 1960s, when a UCLA physiologist, measuring the vital signs of a marmot awakening from hibernation, noted that the animal’s temperature was higher than expected, and the scientist linked that fact to the marmot’s stores of brown adipose tissue.

Barbara Cannon, then a graduate student in Sweden and now a professor at the Wenner-Gren Institute at Stockholm University, was an early researcher who took up the question of brown fat function. Cannon and her colleagues were particularly
interested in the physiology of newborn babies, who are now known to possess substantial quantities of brown fat. “Infants go from a 98.6-degree womb, naked and wet, to a room that’s more than 20 degrees cooler—and yet they don’t shiver,” Cannon observes. Cannon and others theorized that the tissue that was keeping infants warm was the same substance that stoked the marmot’s furnace during its long sleep.

In the 1970s, a British obesity researcher named Michael Stock fed rats a fat-laden diet without increasing their activity level. Stock was startled to discover that, while the rats gained weight, they didn’t become as obese as he had expected. That led to an obvious conclusion: “If you eat a lot,” Cannon says, “and you don’t gain as much weight as you should, you must be burning it somehow.”

But how? Metabolism is a chemical process that converts food into energy that the body uses to accomplish such tasks as digestion and muscle contraction. When people take in more calories than they need to do the work at hand, those calories get stored as fat. When Stock’s rats were overfed, however, the rats generated more brown fat, and their metabolic rates increased accordingly to burn off the unneeded fuel—a phenomenon known as diet-induced thermogenesis. But Stock and his colleagues were unable to confirm that adult humans also possessed brown fat. As a result, Stock’s work was considered controversial, and pharmaceutical companies weren’t inclined to underwrite research.

Brown fat might have remained a footnote in medical history if not for the observant eyes of Cannon and her husband, Jan Nedergaard, who is also a professor at Stockholm University and a long-time researcher in the same field. While combing the PubMed database for mentions of brown fat, Nedergaard and Cannon eventually caught wind of articles published in nuclear medicine journals exploring the question of how to deal with the presence of brown fat while searching for tumors. In 2007, with a third colleague, Nedergaard and Cannon published a survey of the radiologists’ findings in the American Journal of Physiology—Endocrinology and Metabolism, citing this new evidence that brown fat existed in adult humans. That article in turn triggered a wave of new studies. Two articles in The New England Journal of Medicine reported that the tissue appeared in glucose-uptake scans done on test subjects who wore only light clothing as they spent time in cold rooms.

In studying the tissue, researchers had already been able to map out the molecular pathways involved in the creation of white fat and brown fat. In 2007, Bruce Spiegelman, a cell biologist at the Dana-Farber Cancer Institute in Boston, found a gene called PRDM-16 that seemed to turn on all of the other genes involved in the differentiation and function of brown fat; among those genes was the one that produced the uncoupling protein, UCP1, that was known to trigger heat generation when brown fat was activated. “It began to be accepted that brown fat was one of the body’s natural ways of warming itself and protecting against obesity,” says Lee Kaplan, director of the Obesity, Metabolism & Nutrition Institute at Massachusetts General Hospital. “So the next question was, how does it work?”

Researchers have made headway on that question during the past couple of years. André Carpentier, an endocrinologist at the University of Sherbrooke in Quebec, headed a study in which scientists put six healthy men, aged 23 to 42, into water-cooled suits. The men were chilled, though not so much that they would begin shivering, because that burns calories on its own. Then Carpentier and colleagues from Laval University in Quebec City studied the subjects using a type of PET scan that shows the metabolism of fat. They discovered that after the subjects’ brown fat burned the fat deposits within its own cells, it began to pull in fatty acids and glucose from elsewhere in the body to keep generating heat. The subjects’ metabolic rates increased by 80% during the period of cold exposure, and the more brown fat a man had, the more cold he could tolerate before he began shivering. In other words, according to the study, reported in the February 2012 issue of The Journal of Clinical Investigation, cold is capable of “turning on” brown fat.

Many researchers believe that in terms of the struggle to turn the dial back on obesity, brown fat might be the most important thing to come along for some time. A second study published earlier this year also stirred excitement. A second type of brown fat—one that is intermingled among white fat cells rather than appearing in isolated clusters—has long intrigued physiologists. This
type is alternately called beige fat, brite (brown-in-white) fat or recruitable fat. Researchers at the Dana-Farber Cancer Institute reported in an article in *Nature* that mice could generate this type of brown fat by exercising. When mice exert themselves, the study found, their muscle cells discharge a newly discovered hormone that the researchers named irisin, which in turn converts white fat cells into brown. The researchers said they found irisin in humans as well, and they hypothesized that people are similarly able to produce brown fat during exercise.

These latest discoveries have led to grand notions about what brown fat might accomplish. “Irisin could be therapeutic for human metabolic disease”—such as diabetes—“and other disorders that are improved with exercise,” the study’s authors assert. Another study in *Nature Medicine* examined what happened when mice were given a dose of either triglyceride (a type of fat in the bloodstream) or glucose. It turned out that brown fat combusted half the triglyceride and three-quarters of the glucose. That result, says Cannon, suggests that a pharmaceutical product that increased brown fat might help lower the blood glucose and lipid levels of patients with type 2 diabetes. Cannon also points out that if brown fat could be activated, even in small quantities, it could be an ideal agent for weight loss. Suppose someone consumes 3,500 calories a day but burns only 3,200; if his metabolism could be fired up to burn an extra 500 calories on the same diet, he would begin to trim away pounds. “As we jokingly say, this is a hot area,” Cannon says.

The pace of research into brown fat’s special properties promises to pick up speed during coming years, as small biotechnology companies join pharmaceutical giants in the pursuit of a therapeutic drug that can be used to combat obesity and diabetes.

One of the more aggressive players has been Ember Therapeutics. Researchers give mice injections of irisin, a hormone that appears to turn white fat deposits into brown fat. And initial indications are that the animals show increased amounts of brown fat. Ember’s scientists are also intrigued by BMP7, a protein used to augment healing in spinal injuries that also appears to facilitate the growth of brown fat tissue. Yet another target is FoxC2, a molecule that may cause brown fat to convert energy into heat at room temperatures.

Eli Lilly, meanwhile, has been investigating a hormone called FGF21 which, already known to reduce blood glucose levels, also contains the potential to activate brown fat. “Treatment of obese mice with FGF21 can activate brown fat; this appears to be a major component of the mechanism by which FGF21 causes weight loss in animals,” says David Moller, vice president, endocrine and cardiovascular research and clinical investigation for the drug company.

Still another contender, three-year-old Energesis Pharmaceuticals, is focusing on cells found in skeletal muscle that become what appears to be brown fat. The Boston-based company seeks to identify molecules that cause these so-called brown fat stem cells to differentiate into brown fat, and capture them in a drug. A second route is to take a small biopsy from a patient, isolate the brown fat cells in the sample, manipulate those cells so that they proliferate, and then re-inject them. Testing on animals is imminent and expected to last about 18 months.

The Burning Question //
Who will be the first to tap the potential of this unusual and mysterious tissue?
still, it seems as if every promising development involving brown fat generates as many questions as it answers. “We now know brown fat exists in adults,” says Eric Ravussin, a clinical investigator in the field of obesity at Louisiana State University’s Pennington Biomedical Research Center. “We know it’s mostly inactive, unless it’s wintertime or the person is otherwise exposed to cold. And we know it may play a role in energy expenditure, but we don’t yet know the extent to which that happens.” Ravussin is currently conducting two simultaneous research efforts, both focused on brown fat and exposure to cold. That’s because some of the largest stores of brown fat found in healthy adults, he says, were in Finnish lumberjacks cutting wood north of the Arctic Circle. Ravussin hypothesizes that their work in frigid environments not only activates brown fat but also increases their stores of the tissue.

One of the most pressing mysteries so far is why some people have more brown fat than others. Scientists are unsure whether there is a gender difference, but they have clear evidence that age is a factor: Virtually everyone in their 20s has some brown fat, but few people in their 60s and older possess any. Most vexingly, though, people who are obese may be less likely to have the tissue, and what they do have appears less prone to being activated. In one study in the Netherlands, only three of 15 obese subjects showed an activation of brown fat on PET scans after being cooled nearly to the point of shivering. The most likely explanation is that fat insulates the body, minimizing the biological mandate to keep warm, says Carpentier.

That’s one of the questions he is now hoping to make headway with. He’s currently repeating the experiment in which he chills people to try to stimulate their brown fat—only this time his subjects are adults with type 2 diabetes, who have seven times less activation of brown fat, Carpentier said.

And there are practical concerns. Sven Enerbäck, a researcher at Göteborg University in Sweden who has been studying brown fat for more than two decades, worries that the more activated brown fat a person has, the more likely he or she is to feel hungry, he says. “There’s never going to be a treatment to which that happens.” Ravussin is currently exploring new potential treatments with Ember Therapeutics, which has received $34 million in venture capital funding so far. The holy grail is a protocol that doesn’t require prolonged exercise or exposure to cold.

The ideal weapon in the struggle against obesity, says Enerbäck, would be an element of human physiology that has evolved for the sole task of naturally dissipating excess stores of energy. Enerbäck described this as “the dream organ,” and brown fat appears to fit that description perfectly. D. Aled Rees, a researcher at the Centre for Endocrine and Diabetes Sciences at Wales’ Cardiff University, and his colleagues hypothesized that brown fat might even be useful in preventing obesity from occurring in the first place.

Pharmaceutical companies are exploring the possibilities. Clinical trials of irisin could begin within two years, with the aim of discovering ways to increase the number of brite cells. And if research advances as scientists hope, the promise of the brown- and beige-fat research is undeniable: Eventually, perhaps, there will be a way to help the body shed weight in an utterly natural way—no gimmicky diet required.

DOSSIER

1. “Brown Adipose Tissue Oxidative Metabolism Contributes to Energy Expenditure During Acute Cold Exposure in Humans,” by Véronique Ouellet et al., The Journal of Clinical Investigation, Feb. 1, 2012. Previously, brown fat was thought to generate heat only in rodents exposed to cold; this small but groundbreaking study shows that in fact humans get the same warmth-giving, calorie-burning response from their cells in chilly climes.

2. “Brown Adipocytes Are a Distinct Type of Thermogenic Fat Cell in Mouse and Human,” by Jun Wu et al., Cell, July 20, 2012. This study establishes that the hormone irisin stimulates beige cells’ thermogenesis, raising hopes for a treatment for obesity and diabetes.

3. “Michael J. Stock: An Appreciation,” by Paul Trayhurn, International Journal of Obesity, September 2001. This paean to a pioneer in brown fat research is eye-opening for a number of reasons, not least the fighting within the field on the subject. Trayhurn notes that Stock’s inroads in the laboratory were “attacked with ferocity”—fascinating, given the enthusiasm for the topic among researchers today.