Gene may open new avenue for fighting fat

Researchers have found a gene that turns up the furnace in the metabolism of mice. Understanding what controls the gene, they speculate, may lead to new ways to help obese people burn calories.

The scientists isolated the gene, *PGC-1*, from brown fat, a specialized heat-producing tissue present in many mammals. Brown fat is abundant in newborn mammals, and some animals, such as mice, retain their brown fat into adulthood.

The newly discovered gene activates adaptive thermogenesis—the process by which an animal burns stored fat to dissipate excess calories or stay warm. Heat production by brown fat warms newborn humans and helps hibernating mammals wake up (SN: 1/15/77, p. 42; 12/24/88, p. 424). This process is different from the body's more obvious generation of heat by shivering.

When cold, the body switches on adaptive thermogenesis in brown fat and in skeletal muscle cells, but what controls the mechanism is poorly known, notes Bruce M. Spiegelman of the Dana-Farber Cancer Institute and Harvard Medical School in Boston. He and his colleagues from Dana-Farber, Harvard, and the University of Chicago report their finding in the March 20 CELL.

"We've discovered a molecule that has all the properties to suggest that it's a key regulator of thermogenesis," he says.

The researchers identified *PGC-1* by sorting through genes that are active in brown fat. They were seeking a gene that codes for a protein that binds to PPAR-gamma, a protein involved in fat metabolism (SN: 12/9/95, p. 390).

Since adaptive thermogenesis helps animals tolerate cold, the researchers hypothesized that whatever genes regulate the heat-generating process would become active when an animal was kept cold. When the researchers held mice at refrigerator temperatures for 3 hours, *PGC-1* activity in the animals' brown fat tissues increased 30- to 50-fold. After 12 hours in the cold, *PGC-1* activity in skeletal muscles increased also.

To test how *PGC-1* influences adaptive thermogenesis, the researchers inserted a turned-on copy of the gene into white fat cells, which store excess calories. *PGC-1* in white fat cells normally remains inactive. Because thermogenesis takes place in a cell's mitochondria, the researchers could gauge the effect of the added *PGC-1* by looking for changes in those organelles. Mitochondria dissipate food calories as heat or convert them into the energy-storage molecule ATP.

Compared to unaltered white fat cells, those containing the activated *PGC-1* showed increased mitochondrial production of several key enzymes. The number of mitochondria also rose.

Spiegelman's team basically turned white fat into brown fat, says molecular biologist Ronald M. Evans of the Howard Hughes Medical Institute at the Salk Institute for Biological Studies in La Jolla. Brown fat is rich in mitochondria.

Adaptive thermogenesis can also kick in when an animal overeats. "It's already been established that when animals are deficient in thermogenesis, they get fat," Spiegelman says. "When people talk about having a fast or slow metabolism, this is actually what they mean." Manipulating the component of metabolism that dissipates energy might be a way to combat obesity, he says.

"If you could understand the regulation of this gene, you might be able to trigger its expression and therefore increase thermogenesis even in white fat," says Evans. "This is really the discovery of a new road toward our understanding of fat cell biology."

Jean Himms-Hagen of the University of Ottawa says that recent work on thermogenesis is exciting because it might lead to ways of increasing the amount of brown fat in adult people. "Having a lot of brown fat would not make you fat. It would increase your capacity to oxidize fat—it's an alternative to exercising." —*M.N. Jensen*

Giant seabed slides may have climate link

British researchers surveying the Mediterranean seafloor have discovered a vast blanket of sand and silt laid down by an underwater landslide larger than any witnessed in historical time. The deposit formed at the peak of the last ice age, 22,000 years ago, a finding that supports the idea that submarine slides and climate influence each other.

The legacy of this ancient landslide lies between France and Algeria at a depth of 2,800 meters, report R. Guy Rothwell and his colleagues at the Southampton Oceanography Centre in the March 26 NATURE. The researchers found the layer of deposited sediments, which measures 8 to 10 m thick, by probing the seabed with sound waves and drilling into selected sites. The volume of sediments is enough to bury the island of Manhattan beneath a pile of debris nearly the height of Mount Everest.

Marine geologists label such formations turbidites. These formations develop only during certain submarine landslides, when the mostly solid sliding mass breaks apart, mixes with water, and turns into a turbulent current. Flowing downhill, this roiling slurry can move fast enough to scour the seafloor, a process that adds more sediment to the flow.

Rothwell and his colleagues carbon-dated the turbidite to a time near the end of the ice age, when so much water was locked up in glaciers that global sea levels lay 120 m lower than they do today.

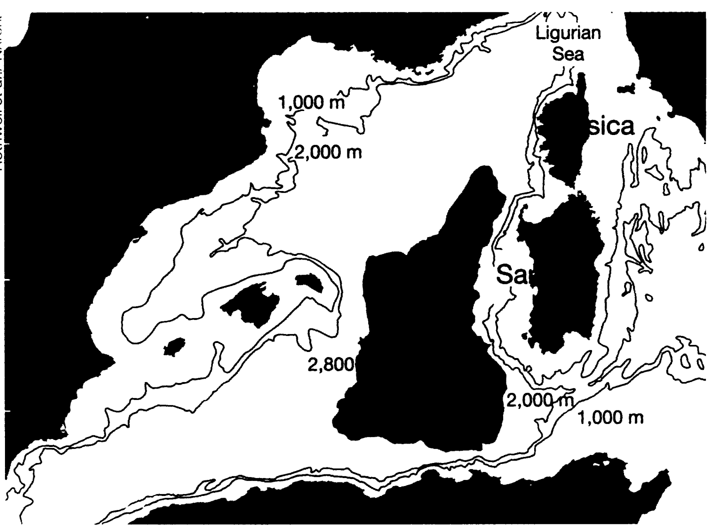
Researchers have found many other examples of gigantic turbidites, but they lack such precise information about the timing of those slides, says David J. W. Piper, a marine geologist at the Bedford Institute of Oceanography in Dartmouth, Nova Scotia.

The timing is crucial because some scientists have suggested that the lowering of sea levels during the last ice age helped trigger oceanic landslides. According to this theory, the drop in ocean heights reduced pressure on the seabed and destabilized buried deposits of methane hydrates—icelike molecules that contain solid water and methane gas. As the hydrates broke down, the seafloor weakened and gave way as landslides.

If so, such landslides could have released the greenhouse gas methane into the atmosphere, where it would have warmed the climate, argue Piper and Euan G. Nisbet of the University of London's Royal Holloway College in Egham, England, in an accompanying commentary. In fact, they say, the warming triggered by one large slide could have destabilized methane hydrates in other locations.

"With regard to climate, these could be very important events," says Rothwell.

Researchers have looked for signs of such massive methane releases but have thus far found no direct evidence of them in ancient ice deposits. —*R. Monastersky*



Rothwell *et al.*/NATURE

Dark blue area shows debris from a submarine landslide.