MOLECULAR GENETICS

Obesity Gene Discovery May Help Solve Weighty Problem

Few medical problems have proved to be more intractable than obesity. The condition, which increases the risk of such potentially life-threatening conditions as diabetes and high blood pressure, is frustratingly hard to treat. And investigators trying to understand the molecular basis for some people's tendency to put on excess weight have had about as much success as dieters struggling with those last few stubborn pounds. Now, a discovery by a research team led by molecular geneticist Jeffrey Friedman at the Howard Hughes Medical Institute at Rockefeller University may help solve both the scientific and practical problems.

In the December 1 issue of *Nature*, Friedman and his colleagues report that they have identified and cloned the gene that, when mutated, causes a severe hereditary obesity in mice. What's more, the Rockefeller group has found that humans have a very similar gene, and while it's too early to tell whether mutations in the gene contribute to human obesity (which is known to have a large genetic component), researchers are hailing the work for its potential in understanding human metabolism—and disease.

"It's definitely a major breakthrough," says Joseph Goldstein of the University of Texas Southwestern Medical Center at Dallas. Although another gene that can cause obesity in mice was cloned previously, this one may be the first whose normal role is to regulate the size of the body's fat stores. As a result, says Goldstein, "it gives researchers a foot in the door for studying obesity that they haven't had before."

Indeed, Gerard Ailhaud, a specialist in fat cell development and metabolism at the University de Nice–Sophia Antipolis in France, compares identification of the new obesity gene with Goldstein's own discovery, with his longtime Dallas colleague Michael Brown, of the LDL receptor. "What we need in the obesity field is a clue, and just like the LDL receptor, this is a clue," Ailhaud says. And that is high praise, because the LDL work helped researchers crack the mysteries of how cells handle fats, leading, among other things, to a better understanding of the cause of high blood cholesterol concentrations and thus of heart attacks—not to mention a Nobel Prize for Goldstein and Brown. In addition, the discovery of the obesity gene, which appears to make a hormone, may open the way for drug therapies for obesity.

The mutation the Friedman group studied arose spontaneously in 1950 in the mouse colony at the Jackson Laboratory in Bar Harbor, Maine. It causes the animals bearing it to become grossly obese—they weigh up to three times as much as normal mice—and to develop a form of diabetes much like the type II (non–insulin dependent) diabetes that can afflict humans in later life. Work performed about two decades ago by the Jackson Lab's Douglas Coleman indicated the mutant mice were missing an obesity-regulating hormone. Hoping to confirm Coleman's hypothesis and learn more about the causes of obesity generally, Friedman and his colleagues set out 8 years ago to track down the gene at fault by using positional cloning.

Aided by a series of breeding experiments, they mapped the gene, dubbed *ob* for *obese*, to a 650-kilobase segment on mouse chromosome 6. The Rockefeller workers then screened normal mouse tissues to see whether any genes from that target area were expressed specifically in adipose tissue, where an obesity-regulating hormone might be produced. The search paid off. One gene, which encodes a protein containing 167 amino acids, was expressed in adipose tissue, but the researchers were unable to detect its activity in other tissues, Friedman says.

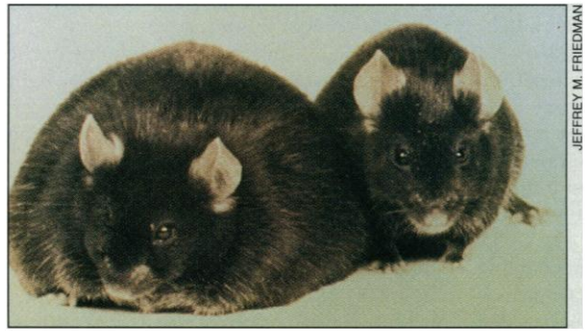
More definitive evidence that this gene is the site of the obesity-causing mutations came from the genetically obese mice. In one strain of those fat mice, the Friedman group found the gene to be completely inactive, indicating that the gene's protein product is required to keep the animals' weight under control. In another strain, the gene was expressed at much higher than normal levels, but because of a mutation its protein was probably inactive.

The overproduction of the defective protein supports Coleman's original proposal that the obesity-regulating factor is a hormone. Ordinarily, hormones are controlled by feedback loops that shut down further production once they've accomplished their job. But an inactive hormone can escape that feedback inhibition. "Because [the gene] makes a defective protein, the level goes up, trying to compensate," Friedman says. A structural feature of the normal protein also suggests that it is a hormone: It contains a "signal sequence," a hallmark of proteins that are secreted from cells as hormones are. It's not yet clear where and how such a hormone might act, although the brain structure called the hypothalamus is a likely site. Previous work has shown the hypothalamus to be important for controlling food intake and energy expenditure, two major factors regulating fat deposition.

But whatever the *ob* gene product does, its action is apparently not limited to mice. The Friedman team finds that the protein encoded by the comparable human gene is 84% identical to the mouse protein. The resemblance raises the possibility that mutations in the *ob* gene also contribute to human obesity, which is thought to be about 60% determined by genetic factors, and the Friedman group has begun experiments aimed at finding out if that is the case.

The possibility that the obesity gene does encode a hormone is adding to researchers' excitement about the discovery. "This would just be extraordinarily fortunate, because there may be a relatively immediate application for [obesity] therapies," says Arlen Price of the University of Pennsylvania School of Medicine, whose work focuses on the genetics of human obesity. He is referring to the possibility that human obesity might be treated by administering the human protein, much as diabetes is treated with insulin injections. The protein might be useful for therapy, Price suggests, even if human obesity is not caused by mutations in the *ob* gene. Friedman cautions, however, that before any of this can come about, researchers will first have to show that the protein really does function as a hormone that regulates the amount of fat stored by the body.

And on a more fundamental level, researchers are excited because the *ob* gene may provide the key to deciphering the biochemical machinery the body uses to regulate fat reserves. It's probable that this machinery includes several components, because mutations in at least six different genes have been found to cause obesity in mice. One gene, known as *db* (for *diabetes*), has not yet been cloned, but Coleman's work suggests that it may encode the receptor through which the *ob* gene product exerts its effects. Another is the *agouti* gene, cloned about 2 years ago by Richard Woychik and his colleagues at



JEFFREY M. FRIEDMAN

Genetic overload. Researchers are identifying the genes that can cause gross obesity in mice such as the one on the left.

Oak Ridge National Laboratory in Tennessee. *Agouti* seems to influence the fat-regulating machinery of mice only when mutated; normally it is active only in mouse skin, where it regulates coat color. But the human equivalent, which was just cloned by Woychik's group working with a group led by William Wilkison of Glaxo Research Institute in Research Triangle Park, North Carolina, is normally active in adipose tissue and may yet turn out to have a role in human weight regulation.

Obesity researchers clearly have a lot more work to do to figure out just what *ob* and the other obesity genes do and what their impact might be on human obesity. But now that they are starting to get their hands on the actual genes and thus the proteins, Goldstein predicts rapid progress. "That's the beauty of modern molecular biology," he says. "Once you have the protein, the work can be done very quickly." And that, of course, could have weighty implications for obesity research.

–Jean Marx

OPTICS

Coaxing Light From Single Atoms

In the last few years, physicists have turned the atom from an abstract concept to a tangible entity they can isolate in traps, see with special microscopes, and pick up with optical "tweezers." They have even put single atoms to work as the moving part in nanoscale switches. Now a group of physicists at the Massachusetts Institute of Technology has taken atomic-scale technology a step further: They have built a laser that wrings its light from individual atoms.

This single-atom laser, described in last week's *Physical Review Letters*, is based on excited barium atoms trickling one by one through a tiny mirrored cavity, where the atoms release bursts of light that "resonate" in the cavity and build up into a laser beam. This microlaser isn't likely to find a use in surgery or metal-working, but it may eventually lead to advances in precise optical communication, say the researchers, led by physicists Michael Feld and Kyungwon An. In addition, says MIT physicist Daniel Kleppner (not a member of the group), "Life gets kind of interesting when you have just one atom at a time in a laser cavity." Over the last 20 years physicists have written hundreds of theoretical papers predicting how individual atoms would behave in these optical echo chambers. Now, by studying the light of the single-atom laser, says Feld, they can start testing these predictions against the real thing.

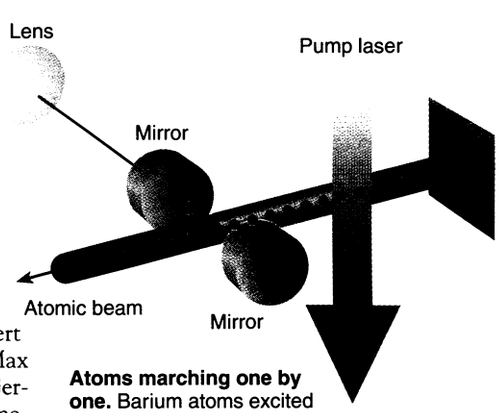
Conventional lasers rely on vast numbers of atoms "pumped" into unstable energetic states by an external light source so that they all will emit light in concert. The light emitted by each atom as it drops into a ground state bounces back and forth within the laser cavity and triggers other atoms to emit light of exactly the same frequency and phase, eventually leading to a sort of chain reaction. But researchers realized years ago that even if the cavity holds just one atom at a time, the light emitted by each atom can resonate for long enough to stimulate atoms entering the cavity a split-second later to emit light of the same frequency.

Even so, says An, extracting a measurable laser beam from single atoms was a demanding assignment. He and his colleagues needed superefficient mirrors that could trap light 10,000 times better than do the mirrors used in an ordinary laser. They also had to build the tiny mirrored cavity to exactly the right size so that the specific frequencies of light emitted by the atoms would resonate within it. To get the most from the atoms, the cavity size had to equal an exact multiple of half the light's wavelength—with only a millionth of a wavelength of error.

This sort of precision is easier to achieve for longer wavelength radiation, Kleppner notes. Ten years ago, Herbert Walther and his colleagues at the Max Planck Institute for Quantum Optics in Germany did manage to build a single-atom maser—a laserlike device that generated coherent microwaves from single atoms. But building a cavity that would work for visible light took the MIT group years of failed attempts, says An. To keep the spacing from getting jostled out of place by every passing footstep, they eventually rigged a sensitive feedback system that generates an electrical voltage in response to small tremors. The voltage in turn drives piezoelectric actuators that readjust the mirrors to the right position.

Through this tiny mirrored box, just a millimeter across, the MIT workers send a procession of barium atoms that have been boosted into an excited state by a conventional laser. As the individual atoms pass though the cavity, each one in turn couples to the electromagnetic field already resonating there from previous visitors, Feld says: "You have a stream of atoms that enter and leave the cavity and each time contribute more energy to the electromagnetic field." Eventually, he says, the intensity of the field reaches an equilibrium. At that point light leaking out of the cavity through one of the mirrors generates a faint beam of laser light that the researchers have been able to detect.

Part of the laser's appeal to quantum physicists is the effect that starts the lasing process when the first atom enters the cavity. It might seem that there's nothing in the dark, empty cavity to trigger light emission from the first atom. On the scale of the atom, however, this "quantum vacuum" bubbles with little fluctuations of energy at every possible wavelength. Because the resonator is exactly the right size to amplify wavelengths that match those emitted by the atom, the first atom to enter the cavity "feels" these vacuum fluctuations, and they are enough to stimulate emission. "I've always thought that was fascinating," says Kleppner. "The atom and the empty vacuum become coupled together."



SOURCE: KYUNGWON AN/MIT ILLUSTRATION: C. FABER SMITH

Atoms marching one by one. Barium atoms excited by a pump laser release their light in a mirrored cavity, where it builds up into a laser beam.

Only when they are on their own can atoms display such quantum effects so vividly, say Feld and An; when atoms gather in crowds, these effects tend to be swamped by random behavior. As a result, the MIT researchers hope to put their single-atom laser to work in probing the workings of the uncertainty principle, which dictates that if you know too much about one property of a quantum system, such as an atom, you lose knowledge about another. In one demonstration, Feld and his colleagues will rig their laser to produce light in what they call a "pure number state," in which they will know the exact number of photons of light in the cavity. The cost, according to quantum theory, is all knowledge of the photons' phase. "No one has ever achieved this before," says Feld.

Eventually, the ability to reduce one form of uncertainty in the laser signal at the cost of increasing another could help researchers push back the limits of optical communication, says Feld. But for now, he and his coworkers want to focus on basic science. "The physics is rich," he says, and that will be enough to keep them busy.

–Faye Flam