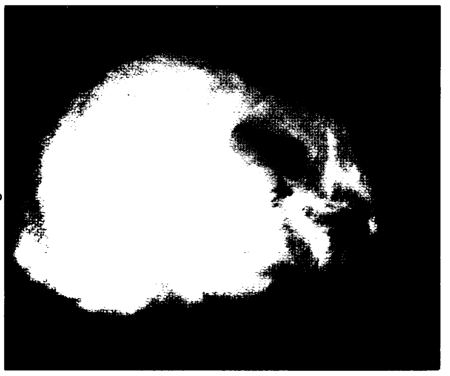
Gene Triggers New Hair in Adult Mice

In research that could one day suggest ways to combat baldness or curb excessive hair growth, scientists have created mice whose skin continues to sprout new hair follicles long after birth. However, proliferating cells within the follicles sometimes give rise to tumors as well.

In mammals, birth of hair follicles normally occurs only in a growing embryo. "During development, you're given a set number of hair follicles for the rest of your life," says Elaine Fuchs of the Howard Hughes Medical Institute at the University of Chicago.

In the mice genetically engineered by Fuchs and her colleagues, however, new follicles also start to emerge several weeks after birth and continue to do so throughout life. Supplementing the normal coat the mice were born with, the new hairs arise from skin cells in between the preexisting follicles or even spring forth from the original follicles.



Linda Degenstein and Chuck Wellek

Genetic engineering created this extra-furry mouse, which keeps adding hair follicles.

These unusually furry rodents highlight a previously unrecognized signaling pathway that can command adult skin cells to give rise to new hair follicles, says Fuchs. A key component of this pathway appears to be a protein called beta-catenin. Fuchs' group has been interested in beta-catenin because it interacts with Lef-1, a protein already implicated in the development of hair follicles. When beta-catenin attaches to Lef-1, the pair can travel to the nucleus of a cell and activate genes specific to hair cells.

In adult animals, any free beta-catenin in a cell is destroyed quickly. Fuchs and her colleagues, however, created mice whose skin cells had a gene encoding a form of beta-catenin that resists degradation. In some skin cells, but not all, this added beta-catenin ignited the development of new follicles. The scientists suspect that some still mysterious signal, perhaps released by existing follicles or other nearby cells, determines why only certain cells react to the extra beta-catenin.

The new hair growth in the mice was not fully normal, Fuchs' team reports in the Nov. 25 CELL. Hair follicles frequently weren't angled appropriately, so hairs emerging from them didn't break the skin but extended beneath it. There were so many of these misaligned follicles, notes Fuchs, that "the skin actually got thicker."

Two types of hair-follicle tumors also plagued the mice. Fuchs suggests that the tumors arise because the added beta-catenin gene is constantly stimulating cells to grow. She notes that similar cancers create bulges under the skin of some people and, though invariably benign, can be disfiguring.

While the new research offers the hope that physicians will learn to control the beta-catenin pathway with drugs or topical agents, and consequently learn to inhibit abnormal hair growth or cure baldness, investigators caution that such goals remain far off. "There's tremendous potential here, but there's an enormous amount of additional experiments that need to be done," says Fuchs.

Researchers, for example, need to test whether temporarily activating the beta-catenin pathway can generate new follicles without prompting tumors. Scientists note that the added beta-catenin gene functions during the mouse's embryogenesis and may cause permanent changes in skin cells that make them amenable to follicle formation in adulthood.

"Ideally, you would like to turn on beta-catenin just in an adult and see if you have the same effect: production of hair follicles," says George Cotsarelis of the University of Pennsylvania Medical Center in Philadelphia. —*J. Travis*

Gel swells during high-sugar spells

A soft gel that shrinks and swells in response to changing sugar concentrations could provide a new way to deliver insulin to people with diabetes.

Developed by a team of researchers in Japan, the gel absorbs water when it encounters a high concentration of glucose, a sugar found in the blood. As the gel expands, its pores open and allow insulin inside the gel to escape. Insulin is the hormone, normally secreted by the pancreas, that regulates blood sugar.

Unable to produce insulin, people with type I diabetes suffer from too much blood glucose. They must regularly take insulin by injection or from mechanical pumps that deliver a dose of the hormone at the press of a button.

An ideal device would control itself, administering insulin automatically according to prevailing conditions in the blood, says Sung Wan Kim of the University of Utah in Salt Lake City, who designs polymers for drug delivery. A gel such as the one made by the Japanese group could do just that, he says, if animal tests support the laboratory findings.

The Japanese team's gel consists of a liquid polymer that includes phenylboronic acid, a compound that binds to glucose. As glucose attaches to the acid, the resulting molecule acquires a negative charge, increasing the polymer's attraction to water. The gel "undergoes a remarkable change in the swelling," says Kazunori Kataoka of the University of Tokyo.

He and his colleagues load the gel with insulin by immersing it in a solution of the hormone for 24 hours. They can make the gel release insulin on demand in laboratory tests by raising and lowering the glucose concentration around the gel. Kataoka and his coworkers at the Science University of Tokyo and the Tokyo Women's Medical University reported their findings on Nov. 19 in the online version of the JOURNAL OF THE AMERICAN CHEMICAL SOCIETY.

A few polymers that release insulin automatically have been developed using natural proteins as the glucose-sensing agent, says Kataoka. Because of concerns about the stability of such proteins and the possibility of stimulating an immune attack, these gels have not been tested in humans, he says. "The most important feature of our system is that it consists of [a] totally synthetic polymer gel," which may present fewer problems with patient incompatibility.

The gel could be part of an implant placed in a diabetic person's abdominal cavity, Kataoka explains. The insulin-loaded gel would fill a pouch made from a thin membrane that would keep out unwanted proteins and cells but allow glucose and insulin to flow through. When glucose concentrations get too high, the gel would swell and release insulin through the membrane and into the blood.

The current version of the gel only works in alkaline solutions, Kataoka notes, while blood has a pH closer to neutral. He and his colleagues are now testing gels with a derivative of phenylboronic acid that should respond to actual physiological conditions. —*C. Wu*