



"The path to her group's hair growth discovery began with a search for factors that determine how embryonic skin cells are able to choose between becoming epidermis or a hair follicle," says HHMI investigator Elaine Fuchs.

Photo: Mark Segal

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MOVE OVER, ROGAINE?

Protein Spurs Hair Growth, Sheds Light on Tumor Formation

You could call it a hair-raising discovery. A research team led by [Elaine Fuchs](#), a Howard Hughes Medical Institute investigator at the University of Chicago, has for the first time induced new hair follicles to form in mature mammals. These surprising findings, achieved in mice, suggest that the protein β -catenin may be a long-sought signal that instructs embryonic skin cells to become hair follicles.

Fuchs' research, reported in the November 25, 1998, issue of the journal *Cell*, may be good news for the millions of men and women worldwide who have age-related hair loss or baldness. Scientists have long pursued cures for baldness, but with limited success, in part because there has been no way to coax the adult scalp to generate new hair follicles.

Fuchs' research team's findings offer more than a potential remedy for baldness, however. They give scientists a better understanding of how certain benign skin tumors form, and they may also suggest a way to create woollier sheep.

In mammalian embryos, skin begins as a single layer of epithelial cells that cover the surface of the embryo. Patterned developmental cues trigger some of these cells to form hair follicles, which appear as tiny pockets dotting the skin surface. As the follicles grow during development, they differentiate into distinct layers. At maturity—which occurs shortly after birth—the follicles consist of two sheaths surrounding the hair shaft, which is the portion of the hair that is visible to the eye.

Differentiating cells in an adult follicle produce the protein keratin, which forms intracellular fibers that harden within the dying cells that compose the budding hair shaft. As the follicle makes new hair cells, the shaft lengthens and pushes out through the skin surface, usually at a rate of about one centimeter a month. Hair growth is not constant, however, because follicles are "cycling" through stages of growth, rest and regression. When a follicle is in regression, its hair shaft falls out, to be replaced by a new

shaft when the follicle reenters the growth stage. Not all follicles cycle in synchrony. At any one time, 85 percent of a person's hair follicles produce hair while the others are in the resting or regressing stage.

Until now, researchers thought that hair follicles form only during embryonic development. This would mean that each individual is born with a fixed number of hair follicles. The average human head, for example, has about 100,000 hair follicles spread across the scalp. Each follicle in a developing embryo receives a reservoir of stem cells that are capable of differentiating to produce hairs. But that doesn't guarantee a lifetime of luxuriant hair growth. In some men and women, follicles shrink, or "miniaturize," with age, churning out shorter and fewer hairs. This can eventually lead to inactivation of the hair follicles and subsequent hair loss. In male and female pattern baldness, or androgenic alopecia, a combination of genetic and hormonal alterations can elicit this response.

Men with androgenic alopecia might begin to notice hair loss as early as their teens. The thinning tends to follow a characteristic pattern: the hairline recedes first from the forehead and temples and then from the crown of the head. Women are usually in their forties or older before any permanent hair loss begins, and the thinning is much more diffuse than in men. Scientists aren't sure exactly why some people's hair follicles miniaturize, but they suspect a genetic influence because androgenic alopecia runs in families.

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With no new follicles forming after birth, current treatments for various types of hair loss require the presence of active follicles—sometimes installed by surgical transplantation. That may change in light of Fuchs' new findings, however, which showed that, contrary to previous assumptions, it is possible to generate new follicles in adult skin and to

reactivate miniaturized ones. The key is to induce certain proteins, most notably β -catenin, to accumulate in the adult skin cells. The mice that Fuchs' team studied not only grew hair out of existing cycling follicles, but also formed entirely new follicles from scratch between the existing follicles. The result? Super-furry mice.

The story of these special mice began many years ago, when Fuchs and her team began searching for factors that determine how embryonic skin cells are able to choose between becoming epidermis or a hair follicle. "Hair is so structurally different from the epidermis that it seems extraordinary that you can generate both structures from one cell type," Fuchs says. "So we asked two questions: How does this happen, and what signals dictate this decision?"

For clues, Fuchs began looking at fibrous proteins called keratins. "We noticed that a potential regulatory sequence in a group of hair keratin genes was identical to a sequence that exists in lymphoid genes that are regulated by lymphoid enhancer factor (Lef-1)," Fuchs said. Lef-1 is what molecular biologists call a transcription factor, a protein that can combine with other proteins and then bind to specific sites on DNA, turning genes either on or off. They found that in adult mice, Lef-1 is expressed in the transiently dividing precursor cells of the follicle that go on to express the hair keratin genes. Surprisingly, Lef-1 was also expressed in embryonic skin. The pattern of Lef-1 had a certain "paint-by-numbers" quality, appearing on the surface of an embryo in a specific dot pattern that corresponded to where hair follicles are going to appear on the surface of the adult skin. "That began to lead us to wonder if Lef-1 might be important for the decision-making process that instructs embryonic skin to form a hair follicle," Fuchs says.

Around this time, Rudolf Grosschedl and colleagues at the University of California, San Francisco, found that when they knocked out the gene that codes for Lef-1 in mice, the animals had far fewer hair follicles than normal. And not long after that discovery, many laboratories simultaneously reported that Lef-1 has a partner in its function as a transcription factor: β -catenin. "That work led us to wonder if β -catenin may not also be playing a central role in the development of the hair follicle," says Fuchs.

β -catenin is an interesting protein that has two very different functions in the body, Fuchs points out. Its most studied role is to bind neighboring cells together to facilitate communication between them, a process known as cell-cell adhesion. Any excess β -catenin made during this process is quickly marked for degradation.

Several years ago, researchers also discovered that β -catenin was a key player in what is known as the "Wnt signaling pathway," a major biochemical route that determines the developmental fate of cells. For embryonic skin cells, that fate is to become either an epidermal cell or a hair follicle cell. The Wnt pathway may help decide that fate through its ability to transiently inhibit the breakdown of β -catenin. When the Wnt pathway is active, normal β -catenin degradation stops. As a result, leftover

β -catenin can accumulate within cells. If those cells contain Lef-1, β -catenin will not interact with it to create an active transcription factor.

To test the theory that β -catenin has a role in hair follicle development, Uri Gat, an HHMI associate in Fuchs' lab, created a strain of mice that carries an extra copy of the *β -catenin* gene. This wasn't an ordinary *β -catenin* gene; instead, it coded for a stabilized variant of the protein, known as the constitutive form, which resists normal degradation. In essence, this alteration in β -catenin mimics the effect of permanently turning on a Wnt signal in the skin.

"By expressing this constitutive form of β -catenin, the [mature skin] cells acted as if they were embryonic skin cells, or stem cells," says Fuchs. "They started to produce hair follicles in many places over the skin surface where normally we wouldn't see those follicles."

The new hair follicles began to appear on the mice within a month after birth, filling in the spaces between existing follicles. Hair did not form, however, on the footpads or on other naturally hairless areas. Apparently, only transgenic skin already primed for hair growth could be induced to create new follicles.

As hoped, Fuchs' super-furry mice did shed new light on why some embryonic skin cells become epidermis and others develop into hair follicles. The key appears to be the cell's ability to receive a Wnt signal. "We effectively made the adult skin cells act as if they were receiving a Wnt signal and showed that they behaved like embryonic skin cells or so-called stem cells," Fuchs says. "We therefore postulate that a distinguishing quality of a skin stem cell may be its ability to receive and respond to a Wnt signal."

Unlike embryonic cells, however, the skin of the transgenic mice produced an endless supply of β -catenin. This overabundance created some unwanted side effects. The mice had thicker-than-normal skin, which developed into ridges around their ears, eyelids, and nose, and benign tumors began to form in the new follicles. Their hind paws also were three times larger than normal. "This is an example of how too much of a good thing can lead to a bad thing," says Fuchs.

For scientists interested in tumor development, however, some of the side effects had a silver lining. Two types of benign tumors, trichofolliculomas and pilomatricomas, showed up in the mice. Both are rare in mice, but pilomatricomas in particular are relatively common in humans. These noncancerous lesions appear as small, sometimes bluish bumps on the skin. "Little was known about their origins before we began the studies," says Fuchs. "But now we know that the tumors are definitely coming from the hair matrix, the transiently dividing precursor cells that express Lef-1 and that differentiate to form the hair shaft. Our research also suggests that defects in the Wnt pathway are involved in the formation of these types of tumors in humans." Fuchs and her colleagues are now investigating this theory.

Fuchs notes that more research is needed before scientists will even know whether manipulating β -catenin and the Wnt pathway in skin might be a feasible treatment for certain types of hair loss. Scientists need to find a factor that can stabilize the natural β -catenin within skin cells just long enough for new follicles to form—but not so long that the skin thickens and develops tumors. At the same time, researchers must find ways to induce the expression of Lef-1 so that it can bind the stabilized β -catenin in order to create new hair.

If there are to be practical benefits of this research, the first is likely to be woollier sheep rather than hairier middle-aged men, Fuchs says. It should be possible, she says, to genetically engineer sheep in a way that allows controlled activation of transgenic β -catenin. The research may also propose a way to stop unwanted hair growth by inhibiting β -catenin and the Wnt pathway.□

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