Studies uncover new approaches to combat hair loss in men and women

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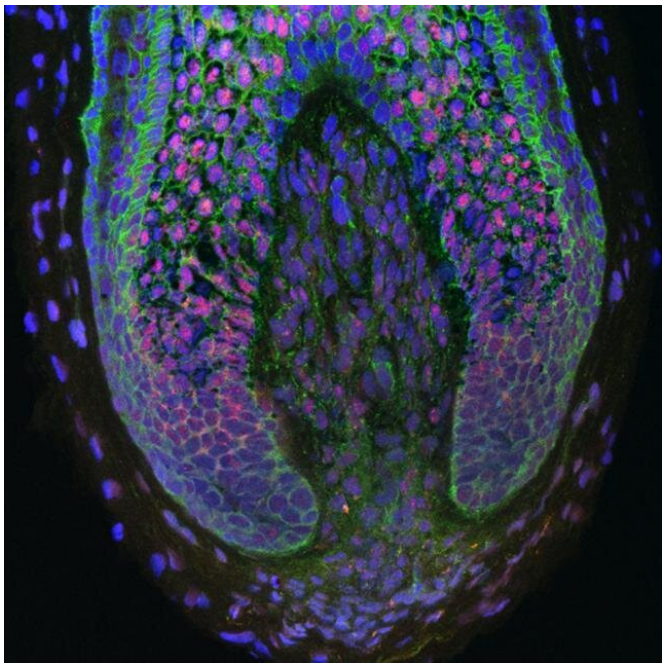

Cross section of a hair follicle. Credit: Angela Christiano / Columbia University Irving Medical Center.

Two recent studies highlight novel ways to combat pattern hair loss in men and women using small molecules such as JAK inhibitors that reawaken dormant hair follicles, as well as stem cell therapies aimed at growing new follicles.

In the first study, researchers led by Angela Christiano, Ph.D., the Richard & Mildred Rhodebeck Professor of Dermatology at Columbia University Vagelos College of Physicians and Surgeons, discovered previously unknown cells that keep mouse hair follicles in a resting state and show that inhibiting the activity of these cells can reawaken dormant follicles.

In a second study, Christiano's team created a way to grow human hair in a dish, which could open up hair restoration surgery to more people, including women, and improve the way pharmaceutical companies search for new hair-growth drugs.

Study Discovers Cells That Put Hair Follicles to Sleep

In male and female pattern baldness, many hair follicles still exist but are dormant. The search for new drugs that reawaken follicles and induce hair growth has been limited by the field's focus on finding drugs that work along the same pathways as finasteride and minoxidil, the only two drugs currently available for men with male pattern baldness.

Christiano and her colleagues previously discovered a new pathway, called JAK-STAT, that is active inside the stem cells of resting hair follicles and keeps them in a dormant state. They previously demonstrated that JAK inhibitors applied to mouse skin are a potent way to reawaken resting hair follicles in mice.

In their latest study, the researchers wanted to get a detailed picture of the natural processes that keep follicles dormant, so they looked for factors that controlled the JAK pathway activity in the hair follicle.

New Cells Called Trichophages

The search revealed a previously unknown immune-related cell type that produces a substance known as Oncostatin M that keeps the follicles in a state of dormancy. "Rare subsets of immune cells were previously difficult to identify in whole skin, but this work was facilitated by our ability to sequence individual cells and pinpoint the ones making Oncostatin M," says Etienne Wang, Ph.D., first author of the study. These cells are most similar to macrophages, which are scavenger cells of the immune system, and the team found them in close association with resting hair follicles.

The researchers named these cells trichophages, after the Greek word tricho for hair.

Targeting the trichophages can also turn on the hair cycle. By using small molecule inhibitors and antibodies to block Csf1R, a receptor on the trichophages, the researchers could block the flow of Oncostatin M and restart the hair cycle.

Reawakening Dormant Hair Follicles with New Drugs

"Our previous studies implicated JAK-STAT signaling as one potential new therapeutic pathway for hair loss disorders by targeting hair follicle stem cells with JAK inhibitors," Christiano says. (A biotech company recently reported results of a small phase 2 trial of a topical JAK-STAT inhibitor based on these studies.) "Here, we show that blocking the source of the JAK activating signal outside the hair follicle is another way to target this mechanism."

Most drug development has focused on treatments for male pattern hair loss, and the majority of clinical trials are conducted exclusively in men.

"These new pathways may lead to new treatments for both men and women suffering from hair loss, since they appear to be acting independently of male hormone pathways," Christiano says. "Especially if treatments are used topically, that could avoid the related side effects seen with finasteride and minoxidil."

Growing New Hair Follicles in a Dish

In a second study, aimed at using stem cells for hair growth, the Columbia researchers have created a way to grow human hair in a dish, which could open up hair restoration surgery to more people, including women, and improve the way pharmaceutical companies search for new hair growth drugs.

It is the first time that human hair follicles have been entirely generated in a dish, without the need for implantation into skin.

For years it's been possible to grow mouse or rat hairs in the lab by culturing cells taken from the base of existing follicles.

"Cells from rats and mice grow beautiful hairs," Christiano says. "But for reasons we don't totally understand, human cells are resistant."

To break the resistance of human hair cells, Christiano has been trying to create conditions that mimic the 3-D environment human hair cells normally inhabit. The lab first tried creating little spheres of cells inside hanging drops of liquid. But when the spheres were implanted in mice, the results were unpredictable: The cells from some people created new hair while others didn't.

3-D Printing Creates Patterned Hair Follicles

In the new study, Christiano's team exploited the unique capability of 3-D printers to create a more natural microenvironment for hair follicle growth.

The researchers used 3-D printing to create plastic molds with long, thin extensions only half a millimeter wide. "Previous fabrication techniques have been unable to create such thin projections, so this work was greatly facilitated by innovations in 3-D printing technology," says Erbil Abaci, Ph.D., first author of this study.

After human skin was engineered to grow around the mold, hair follicle cells from human volunteers were placed into the deep wells and topped by cells that produce keratin. The cells were fed a cocktail of growth factors spiked with ingredients, including JAK inhibitors, that the lab has found stimulates hair growth.

After three weeks, human hair follicles appeared and started creating hair.

Hair Farms Could Expand Availability of Hair Restoration

Though the method needs to be optimized, engineered human hair follicles created in this way could generate an unlimited source of new hair follicles for patients undergoing robotic hair restoration surgery.

Hair restoration surgery requires the transfer of approximately 2,000 hair follicles from the back of the head to the front and top. It is usually reserved for male patients whose hair loss has stabilized and who have enough hair to donate.

"What we've shown is that we can basically create a hair farm: a grid of hairs that are patterned correctly and engineered so they can be transplanted back into that same patient's scalp," Christiano says.

"That expands the availability of hair restoration to all patients—including the 30 million women in the United States who experience hair thinning and young men whose hairlines are still receding. Hair restoration surgery would no longer be limited by the number of donor hairs."

The engineered follicles also could be used by the pharmaceutical industry to screen for new hair growth drugs. Currently, high throughput screening for new hair drugs has been hampered by the inability to grow human hair follicles in a lab dish. No drugs have been found by screening; the only two approved for the treatment of pattern hair loss—finasteride and minoxidil—were initially investigated as treatments for other conditions.

The team hopes that cultured hair farms will open up the ability to perform high throughput drug screens to identify new pathways that influence hair growth.

The first study, titled "A Subset of TREM2+ Dermal Macrophages Secretes Oncostatin M to Maintain Hair Follicle Stem Cell Quiescence and Inhibit Hair Growth," was published in *Cell Stem Cell*.

The second study, titled "Tissue engineering of human hair follicles using a biomimetic developmental approach," was published in *Nature Communications*.

More information: Etienne C.E. Wang et al. A Subset of TREM2+ Dermal Macrophages Secretes Oncostatin M to Maintain Hair Follicle Stem Cell Quiescence and Inhibit Hair Growth, *Cell Stem Cell* (2019). DOI: 10.1016/j.stem.2019.01.011

Hasan Erbil Abaci et al. Tissue engineering of human hair follicles using a biomimetic developmental approach, *Nature Communications* (2018). DOI: 10.1038/s41467-018-07579-y

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