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Researchers Identify a Key Regulator for Skin Stem Cells

By turning on a single gene, researchers can prevent skin stem cells from maturing into the three types of adult skin cells -- epidermal, sebaceous and hair cells. They say this finding could have important implications for scientists trying to grow stem cells in the lab, for both research and potential therapies.

As researchers seek ways to manipulate stem cells, which have the ability to differentiate into multiple types of tissues, one challenge they face is maintaining the stem cells in their immature state. The newly identified repressor switch could provide part of the answer.

Led by Howard Hughes Medical Institute investigator Elaine Fuchs, the researchers published discovery of this regulator, known as Tcf3, in an article in the October 6, 2006, issue of the journal *Cell*. Other co-authors on the paper include Hoang Nguyen and Michael Rendl in the Fuchs laboratory at The Rockefeller University.

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- Elaine Fuchs

Tcf3 is a transcription factor, a protein that controls the activity of a collection of genes in order to coordinate their action. In earlier studies, Fuchs and her colleagues had found that the gene for Tcf3 is activated in a region of the adult hair follicle called the bulge, where stem cells are expected to be. They also knew from studies in other laboratories that a relative of Tcf3, called Tcf4, appears to be important for the development of the intestine.

The researchers reasoned that if Tcf3 plays a role in maintaining adult follicle cells, it would also be present in embryonic skin, which consists mainly of stem cells. When they analyzed the epidermis of embryonic mice, they found

that the Tcf3 gene was, indeed, active in the embryonic skin stem cells.

The researchers next sought to pinpoint which genes Tcf3 controls. They genetically engineered a mouse in which they could switch the Tcf3 gene on at will in skin cells. They then used DNA microarrays to analyze which genes were affected when Tcf3 was activated. Microarrays, also known as “gene chips,” enable scientists to determine the activity of thousands of genes at once.

“When we compared the list of genes that Tcf3 repressed or induced, we found that it was very similar to the genes expressed when the skin is embryonic,” said Nguyen. “So, by turning on Tcf3, we were essentially reverting the postnatal skin cells to be more similar to embryonic skin cells. The genetic program induced by Tcf3 is also very similar to that seen in bulge cells, where adult stem cells are thought to reside,” she said.

In particular, the researchers found that Tcf3 repressed members of a gene family called *PPAR*, which themselves produce key transcription factors that promote skin stem cells to differentiate into epidermal and sebaceous gland cells.

The biggest surprise, said Fuchs, came when the researchers analyzed how switching on Tcf3 affected the differentiation of embryonic skin stem cells. They found that activating the gene in mice blocked differentiation of all three types of mature skin cells -- epidermal, sebaceous, and hair follicle. “We've known for some time that Tcf3 can operate with a co-factor called β -catenin and initiate skin stem cells to make hair follicles. But we hadn't realized that Tcf3 could act on its own to keep skin stem cells in an undifferentiated state,” Fuchs explained. β -Catenin is stabilized in response to Wnt signaling, which Fuchs' team earlier showed plays a key role in the ability of stem cells to make hair.

Fuchs said that Wnt signaling has been shown to play a role in many different types of stem cells in the body. The discovery that one of β -catenin's partners, Tcf3, can repress genes in the absence of a Wnt signal may be important in understanding how these transcription factors work in stem cells. In further studies, Fuchs and her colleagues plan to study in more detail how Tcf proteins govern stem cell biology.