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## Researchers Identify Signals that Cause Hair Follicles to Sprout

The delicate interplay of two chemical signals coaxes stem cells into becoming hair follicles, according to new research by scientists at the Howard Hughes Medical Institute at The Rockefeller University.

The research has implications for understanding hair growth and hair-follicle development, and it may also help explain how diverse structures, such as teeth and lungs, are formed or how some forms of skin cancer develop.

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— Elaine Fuchs

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In an article published in the March 20, 2003, issue of the journal *Nature*, researchers led by HHMI investigator Elaine Fuchs at The Rockefeller University discovered that two signaling molecules, Wnt and noggin, influence immature stem cells to begin the process of forming hair follicles.

According to Fuchs, studies in her laboratory and others revealed the possible involvement of Wnt and other proteins in the signal transduction pathways that trigger hair-follicle formation. In previous studies, Fuchs and her colleagues produced an abnormally furry mouse with high numbers of hair follicles by genetically altering the animals to produce a stabilized form of a protein called beta-catenin. They also knew that beta-catenin was affected by the Wnt protein. Among the other proteins they implicated in hair-follicle formation was "lymphoid enhancer-binding factor 1" (Lef1), which is part of a transcription complex that controls gene activity.

"One of the aspects that scientists have been trying to understand in development of hair follicles, tooth buds, mammary glands and lungs is how these various transduction pathways work together," said Fuchs.

The researchers also had evidence that a second mechanism, involving a signaling molecule called bone morphogenetic protein (BMP), is also required for creating epithelial buds—pockets in the skin that are the precursors of hair follicles.

Through experiments using mouse skin cell cultures and skin from embryonic mice with various genes knocked out, the researchers showed that Wnt stabilizes beta-catenin and increases its concentrations in the target stem cell. In concert, noggin inhibits BMP, leading to production of Lef1. In addition, beta-catenin activates Lef1, which in turn downregulates the gene for the protein E-cadherin. E-cadherin is important in cell adhesion. Reduced levels of E-cadherin trigger reduction of cell adhesion structures, called adherens junctions, a process important in initiating formation of the epithelial bud.

“Unlike the earlier experiments, in which we genetically altered the animals, in these experiments, we have altered the stem cells using external factors that the skin normally makes,” said Fuchs. “And in doing so, we have been able to elicit the initial responses that occur in the development of the hair follicles.

“The other important advance is that we now understand how Wnt and inhibition of the BMP signaling pathway work together by regulating this transcription factor complex. The discovery provides insights into how signals simultaneously operate together to activate a particular event, in this case, a transcription factor.”

The findings also hint at how different kinds of cells interact to produce epithelial buds, said Fuchs. “These signals are probably coming from different cells within the skin,” said Fuchs. “The Wnt pathway is likely coming from adjacent epithelial cells, and the noggin pathway from mesenchymal cells. But, they're working together on a single skin stem cell to produce an activated transcription factor.” Mesenchymal cells are unspecialized cells in embryonic skin from which the dermis will develop.

“How these signal transduction pathways are merging was not understood before, and we now have a much clearer picture of why they need to be there at the same place and time in the developing skin,” said Fuchs.

According to Fuchs, the findings also have implications for understanding how some forms of skin cancer arise. “Our studies suggest that too much or too little E-cadherin can be a bad thing,” she said. “Just the right amount of E-cadherin is needed to loosen the adhesion of the stem cells in the epithelium, to allow them to remodel and grow downward to form the hair follicle. What's interesting is researchers have found reduced levels of adherens junctions in squamous cell carcinomas of the skin. So, we think our findings may be relevant, because they suggest that if the E-cadherin levels are reduced too much, there can still be a downgrowth of the skin, but one that's deregulated. The early stages of hair follicle morphogenesis resemble, to some extent, what happens in the development of a tumor mass.”

The studies in Fuchs's laboratory seek to understand fundamental aspects of hair follicle formation, which could eventually suggest new ways to restore or inhibit hair growth. “These studies raise the possibility that drugs to activate these natural factors could promote hair follicle growth in wanted places, and inhibitory drugs could prevent hair growth in unwanted places,” she said.

Among the next steps in the research, said Fuchs, is to understand how the newly discovered machinery involved in epithelial bud formation links to the later steps that causes mature hair-producing follicles to sprout.