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Seeing the Pattern in Hair Follicle Development

Studying the unruly fur that swaddles certain mutant mice in the laboratory of Howard Hughes Medical Institute researcher Jeremy Nathans has provided the scientist and his colleagues with a glimpse of how hair follicles communicate their position and orientation to neighboring follicles. This communication - which goes awry in the mutant mice - normally helps hair follicles organize and align themselves into a well ordered pattern.

Nathans says his group's findings suggest how hair, feathers and scales organize themselves during development, and they might also aid in understanding how the nervous system wires up during development.

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— Jeremy Nathans

Nathans and his colleagues at the Johns Hopkins School of Medicine studied mice that carry a knockout mutation in the gene called *Frizzled6*. In contrast to the well-organized hair follicles of normal mice, the fur of *Frizzled6* knockout mice shows a complex disruption of hair follicle patterns. The researchers report that global and local signaling mechanisms contribute to the overall patterning of hair follicles in the skin of mice. Their studies are being published during the week of December 11, 2006, in the online Early Edition of the *Proceedings of the National Academy of Sciences (PNAS)*.

They say the global-orienting system, which depends on *Frizzled6*, acts early in development to establish the general orientation of hairs. However, this general orientation is refined by a local orientation system that kicks into gear later in development. In the *PNAS* article, Nathans and co-authors Yanshu Wang and Tudor Badea, both at Hopkins, also described their development of a computer algorithm that models the essential features of the hair-follicle patterning process.

In previous studies, Nathans and his colleagues had discovered that *Frizzled6* was expressed in the skin and hair follicles, and that mutation in the gene disrupts hair patterning. The hairs in these mutant mice are in every respect normal, except that they are organized into amazing patterns of whorls and waves and tufts, said Nathans. What's peculiar is that some of these patterns are identical from animal to animal — such as the direction of whorls on the foot — whereas other patterns are unique to the individual, like fingerprints. These phenomena made us very curious to see what the developmental origin of the hair-patterning defects is, he said.

Frizzled6 is a member of a family of genes that control cell orientation during development. Aside from regulating hair orientation, *Frizzled* genes also control closure of the neural tube during development and the growth and guidance of axons during wiring of the nervous system.

The researchers used microscopy techniques to study follicle orientation in both normal and mutant mice, including newborn mice during development and mature animals. Those observations suggested that the hair follicles in normal mice were initially more organized than those of the mutant mice, which tended to be random. But as development proceeded, the hair follicles in the normal mice organized themselves, while those of the mutant mice tended to form an array of patterns. The findings implied the existence of two distinct orienting systems, said the researchers. One system acts early in development and globally, and a second acts later and locally, they said.

For example, when we looked at the hairs on the head, they don't start out parallel; they are a little bit off, said Nathans. But over time, they line up. And in a normal animal, the global system has already created an initial arrangement that is almost perfect, but in the mutant animal you start out random, so there are huge changes as the system organizes, he said.

The researchers also studied the spatial scale over which the local orientation system functions. They created mice, in which normal hairs were intermingled with mutant hairs. And, they created small wounds in the skin of the mice to study how follicle orientation was affected. Those studies showed that the follicles are, indeed, mobile in their orientation, and that they transmit signals that can alter that orientation. The observations indicated that the normal follicles seem to influence orientation of the mutant follicles, but not vice versa, said Nathans.

Finding that kind of mobility was quite remarkable, because until now most people working on skin biology described hair follicles in the dermis as basically like telephone poles stuck in cement, he said.

Nathans and his colleagues also developed an algorithm, a mathematical model that describes the interaction of the global and local hair-follicle orientation systems. The model was based on the conceptual similarity between the hair-follicle orientation system the researchers identified and how the atoms in a ferromagnet influence one another to align to form a magnet. The researchers tested their model and found that it mimicked how local interactions influence follicle orientation.

It's a case where we don't know the mechanism, but this model shows how a global signal produces only a rough alignment of follicles that is refined by application of a local rule, said Nathans. We could start out with random orientation and run the model and see these little patterns coalesce. And those patterns would expand and compete with one another, with the better patterns gobbling up the neighboring ones that aren't quite as good. That is exactly what we see in the skin.

While the mathematical model does not provide direct insight into the molecular mechanism underlying follicle orientation, said Nathans, it will guide the search for the regulatory molecules involved. Insights from such studies could be applied to similar systems, including feathers, scales, the sound-detecting cilia of the inner ear, and the distinctive loops and whorls found in fingerprints, said Nathans.

In the nervous system, *Frizzled3*, a gene closely related to *Frizzled6*, is essential for growth and guidance of certain neurons, as they extend long projections called axons to their target destination in the central nervous system. Thus, said Nathans, the findings with *Frizzled6* could offer insights into nervous system development. The problem of hair orientation is not all that different from axonal development, because they are both basically guidance problems — essentially a sort of global positioning system for the body, he said. Also, he said, *Frizzled3* and *Frizzled6* work together to close the neural tube during embryonic development, suggesting another guidance role for the genes.