

Skin Bares Its Secrets

Skin is literally all around us, yet as a model system for studying human development and disease, it has kept a low profile. Now, two HHMI investigators, Elaine Fuchs at the University of Chicago and Greg Barsh at Stanford University School of Medicine, are helping skin's dynamic structure reveal its innermost self.

Even as a postdoctoral fellow in the late 1970s, Fuchs believed that the layers of interacting skin cells were far more than a nine-pound organ with a neglected pedigree. "There is a reservoir of stem cells in adult skin that drives the organ to nearly renew itself every two weeks. These cells can be maintained and propagated in a laboratory petri dish over generations," Fuchs explains. As such, skin cells offered a perfect opportunity for studying the three D's: development, differentiation and disease.

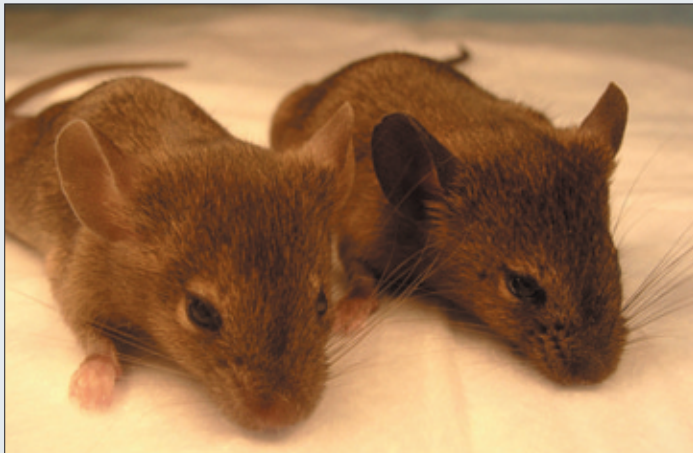
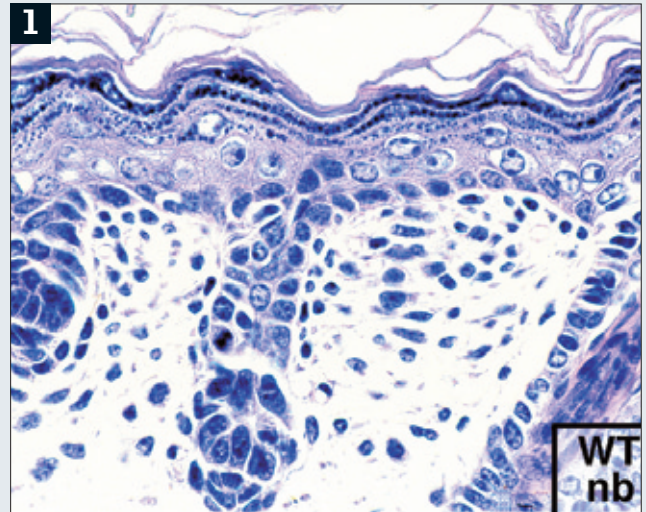
With the advent of mouse genetics in the late 1980s, Fuchs and her colleagues moved from cell cultures to a living mammalian model in which they could

track the consequences of genetic changes. The results have been dramatic. They've discovered some fundamental facts about skin and have revealed the genetic foundations of several human skin disorders. Most recently, they've learned how skin cells of the outer layer epidermis and hair follicle stick to each other to form sheets and why this process is

essential to the skin's function as a barrier. They also have determined the genetic basis of a tumor of the hair follicles called pilomatricomas, and they believe they're close to understanding the mechanisms by which precancerous lesions form in the skin.

The Fuchs team began its research by determining the genetic interplay that produces a part of the epithelial skin cell's internal scaffolding, or cytoskeleton, made of an extensive network of thin filaments called keratin filaments. Defects in the genes encoding keratin proteins cause blistering diseases in humans.

➤ Skin sections of a newborn mouse illustrate the multiple layers of the epidermis. Panel 1 shows a wild-type, or nonmutant, mouse. The top layer is the skin surface. The arm-like projections beneath are the hair follicles. Panel 2 shows a skin section of a mutant mouse lacking the protein alpha-catenin. Hair follicles do not form and the skin epidermis becomes overly thick, as in skin disorders involving excess cell division in the skin. In panel 3, also showing skin from a mouse lacking alpha-catenin, the epidermis has invaded the inner-layer dermis and formed a large mass of cells. This condition is similar to that seen in squamous cell carcinoma in situ, a precancerous lesion in the skin.



◀ The mouse on the right carries a mutation that causes dark skin. An increase in pigment cells in the epidermis leads to darkening of the ears, footpads (below right) and tail.



GREG BARSH (3)

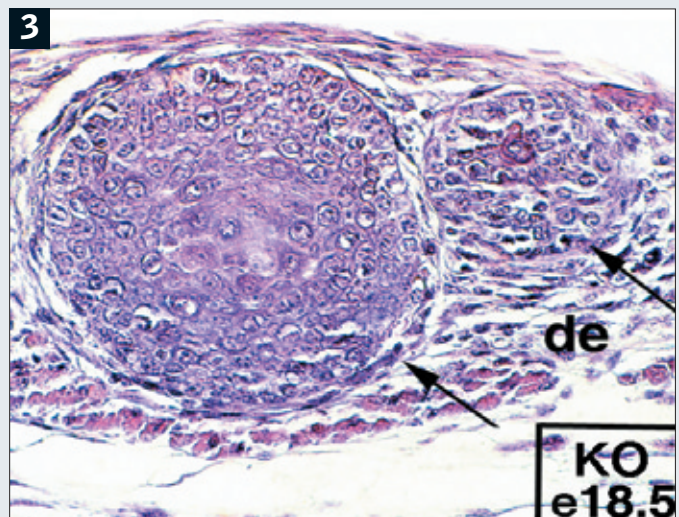
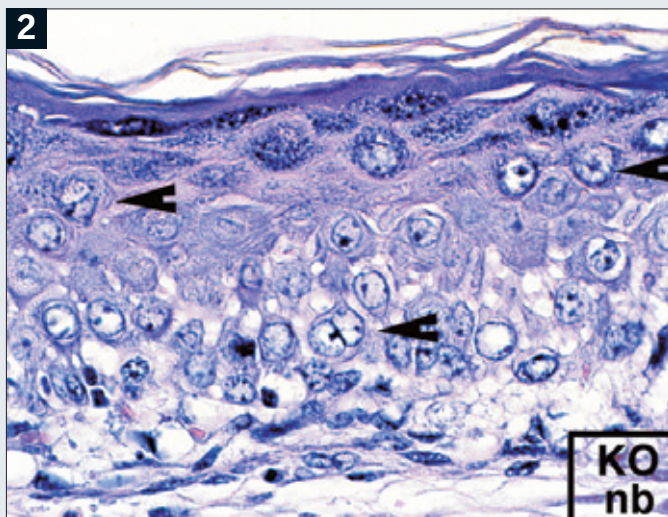
They also studied a second cytoskeletal network of filaments composed of a different protein, called actin: The actin cytoskeleton aids in cellular movement. It is actin that enables epithelial skin cells to begin their ascent to the skin surface, swarm to close a wound or assemble into a hair follicle.

Fuchs and her colleagues have been studying how skin cells use their filament networks and cell-to-cell adhesion to orchestrate cellular movements and maintain structural integrity. In research reported in the January 21, 2000, issue of *Cell*, Fuchs and her colleagues showed how actin fila-

absolute necessity when an organ is taking shape, but a dangerous quality when cells stall on their way to becoming specialized and instead start down the pathway to cancer development. “The studies help us to begin to understand how cells coordinate cell-to-cell adhesion with proliferation during development or wound healing and how this process goes awry in skin cancer,” says Fuchs.

Greg Barsh studies the genetics of skin and hair color. Although variations in these traits provide one of the most obvious signs of human diversity, Barsh’s interest is based on the variations’ ability to offer a sensitive

thought much about these color spots before,” says Barsh. “Some occurred on the pads of the feet, others between the pads. Some were superficial. Some were deep.” What intrigued him in particular were the genetic controls that governed the travels of the pigment cells from the neural tube (during development) to the epidermis and from there to the hair follicles, and the failures in this system that caused the pigment blotches. “No one had studied this developmental pathway before,” he says with some amazement. Because mice and humans are only 80 million years apart on the evolutionary



VALERI VASIOUKHIN AND ELAINE FUCHS (3)

ments attach to some cell-surface proteins to bring cells together while keratin filaments work with other cell-surface proteins to clamp the cells into place. Genetic mutations in the cell-surface proteins that normally “clamp and hold” give rise to skin blistering defects similar to the consequences of genetic mutations in the keratin genes. In contrast, genetic mutations in the cell-surface proteins that associate with the actin cytoskeleton give rise to disorders in which cells multiply excessively, including cancer.

As an HHMI postdoctoral fellow in Fuchs’ lab, Valeri Vasioukhin, now at the Fred Hutchinson Cancer Center in Seattle, found that a protein called alpha-catenin helps skin cells touch and stick to each other. The protein also plays a role in proliferation, an

measure of gene expression for pathways involved in the same three D’s Fuchs is studying: development, differentiation and disease.

For more than 10 years, he has analyzed mutations that affect pigment type-switching, which is the ability of melanin-producing cells in the hair follicle to switch from black/brown to red/yellow. Along the way, Barsh and his colleagues discovered a connection between hair pigment and regulation of body weight. A hormone that causes red hair in mice, Agouti protein, is very similar to a neuropeptide that causes overeating and obesity.

Two years ago, however, Barsh saw spots. That is, he noted that some mutant mice had pigment accumulations in varying patterns on the skin. “No one had really

scale, discovering a pathway in one is likely to reveal a similar process in the other.

To that end, Barsh and his colleagues have zeroed in on 12 specific genetic mutations and are cataloging which dark patches are the result of a cell surplus and which are caused by excessive pigment in an otherwise normal number of cells. Either way, “I would be very surprised if the pathways used to make dark skin patches are not used in other parts of the body,” he says. As in the link between pigment type-switching and obesity, what hair and skin reveal, genes conceal—at least, until now. “That is one of the interesting possibilities. The mutations may turn out to have nothing to do with skin disease and may be more relevant for entirely different systems.” —JEFF MILLER