Researchers identify new stem cell

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(PhysOrg.com) -- Scientists have discovered a new type of stem cell in the skin that acts surprisingly like certain stem cells found in embryos: both can generate fat, bone, cartilage, and even nerve cells. These newly-described dermal stem cells may one day prove useful for treating neurological disorders and persistent wounds, such as diabetic ulcers, says Freda Miller, an HHMI international research scholar.

Miller and her colleagues first saw the cells several years ago in both rodents and people, but only now confirmed that the cells are stem cells. Like other stem cells, these cell scan self-renew and, under the right conditions, they can grow into the cell types that constitute the skin's dermal layer, which lies under the surface epidermal layer. "We showed that these cells are, in fact, the real thing," says Miller, a professor at the University of Toronto and a senior scientist in the department of developmental biology at the Hospital for Sick Children in Toronto. The dermal stem cells also appear to help form the basis for hair growth.The new work was published December 4, 2009, in the journal *Cell Stem Cell*.

Though this research focuses on the skin, Miller has spent her career searching for cures for neurological diseases such as Parkinson's. About a decade ago, she decided to find an easily accessible cell that could be coaxed into making nerves. Brain stem cells, some of which can grow into nerves, lie deep in the middle of the organ and are too difficult to reach if the scientists eventually wanted to cultivate the cells from individual patients. "I thought, 'This is blue sky stuff, but you never know.'" She searched the literature and found that amphibians can

regenerate nerves in their skin. She also found published "hints" that mammalian nerve cells could do the same.

Her team looked in the dermal layer of the skin in both mice and people. Hair follicles and sweat glands are rooted in the dermis, a thick layer of cells that also help support and nourish blood vessels and touch-perceiving nerves. In 2001, Miller's team hit paydirt when they discovered cells that respond to the same growth factors that make brain stem cells differentiate. She named them skin-derived precursors (SKPs, or 'skips').

Miller soon discovered that the cells act like neural crest cells from embryos—stem cells that generate the entire peripheral nervous system and part of the head—in that they could turn into nerves, fat, bone, and cartilage."That gave us the idea that these were some kind of embryonic-like precursor cell that migrated into the skin of the embryo," Miller said. "But instead of disappearing as the embryo develops, the cells survive into adulthood."

Even though the SKPs acted like stem cells in Petri dishes, Miller didn't know if they behaved the same way in the body. "We were obviously very excited about these cells," she said. "The problem was, cells can do all kinds of weird things in culture dishes that look right but really aren't. We thought, 'Maybe we're being deceived.'"So lab member Jeffrey Biernaskie put the cells through their paces, performing a series of experiments to test whether the SKPs indeed acted like stem cells in the body.

Earlier work in the lab had shown that the SKPs produce a transcription factor called SOX2, which is produced in many types of stem cells. The team used genetically engineered mice with SOX2 genes tagged with green fluorescent protein, which allowed them to track where SOX2 was expressed in the animals. They found that about 1% of skin cells from

adult mice contained the SOX2-making cells, and they were concentrated in the bulb at the base of hair follicles.When the team cultured these cells, they began behaving like SKPs.

Next, the scientists decided to see if the cells would not just settle at the base of hair follicles but grow new hair. They took the fluorescent cells, mixed them with epidermal cells—which make up the majority of cells in a hair follicle—and transplanted the mixture under the skin of hairless mice. These mice began growing hair, and analysis showed the green cells migrated to their "home base" in the bulb of the new hair follicles. The team also transplanted rat SKP cells under the skin of mice. The cells behaved exactly like dermal stem cells - they spread out through the dermis and differentiated into various dermal cell types, including fat cells and dermal fibroblasts, which form the structural framework of the dermal layer. Intriguingly, the mice that carried transplanted rat SKPs also grew longer, thicker,rat-like hair, instead of short, thin mouse hair. "These cells are instructive, they tell the epidermal cells - which form the bulk of the hair follicle - to make bigger, rat-like hair follicles," Miller said. "There are a lot of jokes in my lab about bald men running around with rat hair on their heads."

Finally, the team gave mice small puncture wounds and then transplanted their fluorescent SKPs next to the wound. Within a month, many transplanted cells appeared in the scar, showing they had contributed to wound healing. The SKPs were also found in new hair follicles in the healed skin.

The cells behavior both in wound healing and hair growth led the team to conclude that the SKPs are, in fact, dermal stem cells. Miller said the finding complements work by HHMI investigator Elaine Fuchs, who found epidermal stem cells, which help renew the top layer of skin. Combining the evidence from the two labs suggests a possible path to baldness treatments, Miller said—the dermal stem cells at the base of the

hair follicle seem to be signaling the epidermal cells that form the shaft of the follicle to grow hair. But much about the signaling mechanism remains unknown.

Miller wants to investigate less cosmetic applications, such as treating nerve and brain diseases. Experiments she published between 2005 and 2007 showed that SKPs can grow into nerves and help repair spinal cord damage in rats. Her lab is continuing to pursue that research. She is also searching for signals that could trigger the dermal stem cells to rev up their innate wound-healing ability. If such a signal can be found and mimicked, Miller can envision one day treating chronic wounds - such as diabetic ulcers - with a topical cream. Such a treatment is years or decades away, she said, but now researchers know which cell types to focus on. Another possibility: improving skin grafts, which today consist of only epidermal, not dermal, cells. While skin grafts can dramatically help burn victims, those grafts don't function like normal skin.

"Stem cell researchers like to talk about building organs in a dish," said Miller. "You can imagine, if you have all the right players - dermal stem cells and epidermal stem cells - working together, you could do that with skin in a very real way."

Source: Howard Hughes Medical Institute