Bone Marrow Cells Aid Wound Healing

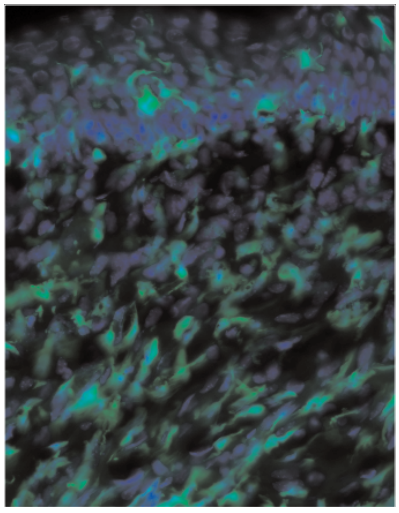
Research published in the 3 September 2004 issue of *Stem Cells*, demonstrates that bone marrow contributes to the development of new skin in wounds.

When a wound occurs, the body mounts an inflammatory response to fight infection by directing white blood cells to the area. The inflammation abates within a few days to a week—provided that there is no continued infection. "Scientists have long assumed that once the inflammatory response concludes, the white blood cells mostly either then die or go into circulation in the bloodstream. We did not know, until now, that the bone marrow-derived cells go on to become a significant part of the new skin," said Dr. Frank Isik, professor of surgery at the University of Washington.

Isik and colleagues removed bone marrow from mice whose cells had been engineered to express GFP and transplanted them into the same strain of normal mice used to engineer the GFP-expressing mice. The fluorescence of the bone marrow of the transplanted cells allowed them to track its whereabouts. They observed that the highest concentration of bone marrow cells was in the skin.

There are normally a few white blood cells in the skin that can lead to contact dermatitis from an inflammatory reaction to a substance that touches the skin. The white blood cells involved in contact dermatitis express CD45, whereas the cells identified in the transplanted mice did not. Even after six weeks, the bone marrow-derived cells clustered within the healing area of a wound. The researchers found that the GFP-expressing cells produced collagen type III, which is one of the two most abundant collagens in skin.

"What we have here is a new cell population that was not previously recognized," Isik said, "The bone marrow cells help form the matrix of the skin." Follow-up studies are underway to determine the role of the bone marrow-derived cells within the skin. One question is whether diseases such as diabetes, which leads to poor wound healing, affect the function of bone marrow cells in the skin and wounds.



An epithelialized (closed or healed) skin wound in the transplanted mice. The bone marrow-derived, GFP-expressing cells both repopulate the dermis and interdigitate to contribute to the new epithelium. Image courtesy Frank Isik, The University of Washington.

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Move over Rogaine...

A study has shown that stem cells isolated from the skin of a mouse can proliferate in culture, and can then be used in grafts to produce new skin, hair and oil glands. The study appears in the 3 September 2004 issue of the journal *Cell*. "This is the first work that indicates a single skin stem cell can generate both epidermis and hair, even after propagation," says lead investigator, Elaine Fuchs.

The next step is to see if these methods can be adapted to isolate human hair stem cells that might be used to develop treatments for baldness, she says. In the new study, the researchers were able to isolate stem cells from normal mice and graft them onto the backs of hairless mice, so as to generate new hair and oil glands.

Previous studies suggested that a structure called the bulge, which is located within each hair follicle, might contain stem cells that provide the source of both new skin and hair follicles. "However, two major questions remained," said Fuchs. "One was whether there was a single type of multipotent stem cell within the bulge, or a bag of different kinds of stem cells—some of which could repopulate the epidermis and others that could produce hair follicles.

"The second major question was whether these cells were capable of undergoing self-renewal. And of particular interest to clinicians was whether they could undergo division in culture and still have the capability to perform either epidermal repair or hair-follicle generation."

The authors characterized the cells by taking advantage of the cell-surface markers that they had previously identified from molecular profiling experiments. What they found were two distinct populations of stem cells. One type, called "basal" cells, is active during early development. In contrast the "suprabasal" cells appear only after the first hair generation cycle.

However, both populations were capable of self-renewal, said Fuchs. They also found that both types of cells—even after being cultured—produced hair follicles when grafted onto the skin of a strain of hairless mice.

Importantly, said Fuchs, the stem cells they isolated showed a gene expression profile consistent with their "stemness." Such characteristics, she said, represent the beginning of a broader effort to compare the genes activated in many stem cell types, to

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understand the factors that control their proliferation and differentiation.

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Cold Virus Causes Polio in Mice

Duke virologists have discovered that a common cold virus closely related to poliovirus can cause polio in mice. The researchers injected Coxsackievirus A21 into mice that were engineered to express its receptor. However, instead of developing a cold, the mice unexpectedly displayed paralytic symptoms characteristic of polio. The researchers determined that administering the virus directly into muscle instead of the nasal cavity was critical for development of polio. The study appears in the 6 September 2004 issue of the *Proceedings of the National Academy of Sciences*.

The findings challenge traditional definition of a poliovirus, said Matthias Gromeier, senior author of the study. "In principle, Coxsackieviruses could cause polio in humans," said Gromeier. "We are in the process of eradicating polio worldwide, but if we eliminate the poliovirus and cease polio vaccinations, our immune systems wouldn't produce antibodies against polio, and Coxsackievirus could theoretically fill the niche of eradicated polio," he said.

It was thought that Coxsackievirus and poliovirus cause distinct illnesses because they bind to different receptors. Poliomyelitis has long been associated with poliovirus, a virus that binds to the CD155 receptor. However, the mice were genetically engineered to express only the Coxsackie A21 receptor, called ICAM-1, and not the poliovirus receptor. Still, when the mice were injected with Coxsackievirus, it initiated infection through the ICAM-1 receptor, and caused symptoms of polio.

The virus was injected into the calf muscle, an unusual route of entry. Following the injection, the mice began to display symptoms of polio, including an abnormal gait, dropfoot, and lower hind limb paresis. The workers found that the virus traveled from the calf muscle to the central nervous system along motor neuron axons, which extend from the central nervous system to muscles throughout the body. Axons physically attach to muscles in a region called the neuromuscular junction, which was likely the cold virus' portal into the nervous system.

Such a subtle change in entry mode significantly changed the virus' behavior, and therein lies one of the greatest dangers associated with viruses, said Gromeier. Viruses are extremely adaptable and they can alter themselves dramatically based upon their environment. Coxsackievirus A21 is one of a large group of cold viruses that are genetically very similar to polioviruses. Gromeier's team is now collaborating with the Centers for Disease Control to test numerous Coxsackievirus samples from patients around the world. Their goal is to determine which genetic features of the Coxsackievirus induce polio and under what conditions.

The Proceedings of the National Academy of Sciences, online, doi: 10.1073/0403998101

New Mechanism Found for Herceptin Action

For many patients with advanced breast cancer, the drug Herceptin (trastuzumab) has offered new hope when traditional cancer drugs failed to work, shrinking tumors and sending some patients into remission. Now researchers have uncovered why some HER-2 positive patients don't respond as well to the drug and also offers a potential solution that could allow more HER-2 positive patients to benefit from the treatment.

The study, which appears in the August 2004 issue of the journal, *Cancer Cell*, demonstrates that the presence of a protein called PTEN in HER-2-positive patients' tumor cells is a powerful predictor of the response to Herceptin. In normal cells, PTEN helps control cell division, but in about half of breast tumors PTEN levels are very low or the protein is completely missing. Those PTEN-missing tumors did not respond to Herceptin treatment. "Previously, it was known that Herceptin binds to the HER-2 protein and causes it to degrade," says Dihua Yu, the study's principal investigator. "But this process takes days. What we found is that very quickly, within ten minutes of administration, Herceptin activates PTEN, a powerful tumor suppressor gene."

The scientists studied the tumors of 47 metastatic HER-2 positive breast cancer patients who had received Herceptin and chemotherapy as well as 37 patients who received chemotherapy alone. PTEN levels varied widely among both groups, but only 11 percent of patients who had a very low level of PTEN responded to Herceptin, versus 66 percent of those with high levels of PTEN. There was no correlation between PTEN level and response to chemotherapy agents.

PTEN inhibits tumor growth by blocking the effect of PI3K. The workers found that administration of a drug that hits PI3K in cultured breast cancer cells sensitizes them to Herceptin. Yu noted that there are several PI3K inhibitors being tested in clinical trials, and if they prove safe, they could potentially be combined with Herceptin to boost its effectiveness in breast cancers with low levels of PTEN.

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