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Cell type responsible for scarring, skin-cancer growth identified

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A skin cell responsible for scarring, and a molecule that inhibits the cell's activity, have been identified by researchers at the Stanford University School of Medicine.

The molecule slowed wound healing in mice but alleviated scarring, the researchers said.

The researchers also found that the cell may play a role in the growth of melanoma and in skin damage caused by radiation. A drug that acts in the same way as the inhibitory molecule is already approved for use in humans as a treatment for type-2 diabetes, so it could potentially move quickly into clinical trials for the treatment of scarring and melanoma.

"The biomedical burden of scarring is enormous," said Michael Longaker, MD, co-director of Stanford"s Institute for Stem Cell Biology and Regenerative Medicine. "About 80 million incisions a year in this country heal with a scar, and that's just on the skin alone. Internal scarring is responsible for many medical conditions, including liver cirrhosis, pulmonary fibrosis, intestinal adhesions and even the damage left behind after a heart attack."

A paper describing the researchers' findings will be published April 17 in *Science*. Longaker, a professor of surgery, and institute director Irving Weissman, a professor of pathology and of developmental biology, are the senior authors. Postdoctoral scholar Yuval Rinkevich, PhD, and graduate student Graham Walmsley share lead authorship.

Scars are comprised mainly of collagen, a fibrous protein secreted by a type of cell found in the skin called a fibroblast. Collagen is one of the main components of the extracellular matrix—a three-dimensional web that supports and stabilizes the cells in the skin.

An early observation

Twenty-five years ago, Longaker observed that prior to the third trimester of pregnancy, human fetuses heal without scarring after surgery. Furthermore, many animals heal without scarring.

"We are the only species that heal with a pathological scar, called a keloid, which can overgrow the site of the original wound," said Longaker. "Humans are a tight-skinned species, and scarring is a late evolutionary event that probably arose in response to a need, as hunter-gatherers, to heal quickly to avoid infection or detection by predators. We've evolved for speedy repair."

In late 2013, a study led by researchers at King's College London showed that fibroblasts in the skin of mice arise as two distinct lineages. One, in the lower layer of the skin, mediates the initial steps of repair in response to wounding.

Longaker, Rinkevich and Walmsley wondered whether this fibroblast type, which expresses a protein called engrailed, could be responsible for the collagen deposition that leads to scarring. They generated genetically engineered mice in which the cells, called EPF cells for "engrailed-positive fibroblasts," were labeled with green fluorescent protein to allow tracking of the cells' location during the animals' development. The cells were also engineered to carry a "kill switch" that could be activated by the presence of diphtheria toxin, which would allow the researchers to assess how wounds healed in the absence of EPF cells.

The researchers found that the proportion of EPF cells, compared to the overall number of fibroblasts in the skin on the backs of the animals, increased dramatically from less than 1 percent in 10-day-old embryos to about 75 percent in mice that were 1 month old.

Role of cell type in scarring

The researchers also found evidence pointing to a major role for EPF cells in scarring. After diphtheria toxin was applied to wounds on the backs of mice, the wounds healed with less scarring.

"The EPF cells are clearly responsible for the vast majority of scarring," said Longaker. Complete healing in the diphtheria-toxin-treated wounds required an additional six days compared to controls, but much of the repaired skin looked and appeared to function normally. In contrast, scarred skin is frequently less flexible and weaker than uninjured skin.

When the researchers analyzed the EPF cells more closely, they found that they express a protein called CD26 on their surface. CD26 activity has been implicated in the metabolism of many hormones, including insulin, and the human version of the protein is a target for inhibitors such as sitagliptin (distributed by Merck under the trade name Januvia) and vildagliptin (distributed by Novartis) that are marketed for treating low blood sugar levels in people with type-2 diabetes.

The researchers found that a small molecule that blocks the activity of CD26 also reduced the amount of scarring in a manner similar to that seen when EPF cells were eliminated. In particular, scars that formed on wounds treated with the CD26-inhibitor covered an area of only about 5 percent of the original wound. In contrast, untreated skin formed scars that covered over 30 percent of the original wound area.

Radiation damage, melanoma and EPF cells

In addition to examining the role played by EPF cells in scarring, the researchers investigated skin damage caused by radiation, as well as the growth of melanoma cancer cells. Radiation therapy for cancer frequently causes damage to the skin it must pass through to reach the inside of the body. Eliminating the EPF cells in the mice also eliminated much of the fibrosis caused by radiation exposure, the researchers found. Furthermore, melanoma cancer cells transplanted onto the backs of the laboratory mice grew more slowly when EPF cells were eliminated.

"I've been obsessed with scarring for 25 years," said Longaker. "Now we're bringing together the fields of wound healing and tumor development in remarkable new ways. It's incredibly exciting."

More information: "Identification and isolation of a dermal lineage with intrinsic fibrogenic potential," *Science*. www.sciencemag.org/lookup/doi/ … 1126/science.aaa2151

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