How to Heal Skin Without the Scars

Posted on July 15th, 2021 by Dr. Francis Collins

Credit: ZEISS Microscopy and Getty Images

Most of us can point to a few unwanted scars on our bodies. Every scar tells a story, but people are spending billions of dollars each year trying to hide or get rid of them [1]. What if there was a way to get the wounds on our skin to heal without scarring in the first place?

In a recent paper in the journal *Science*, a team of NIH-supported researchers has taken an important step in this direction. Working with mice, the researchers deciphered some of the key chemical and physical signals that cause certain skin cells to form tough, fibrous scars while healing a wound [2]. They also discovered how to reprogram them with a topical treatment and respond to injuries more like fetal skin cells, which can patch up wounds in full, regrowing hair, glands, and accessory structures of the skin, and all without leaving a mark.

Of course, mice are not humans. Follow-up research is underway to replicate these findings in larger mammals with skin that's tighter and more akin to ours. But if the preclinical data hold up, the researchers say they can test in future human clinical trials the anti-scarring drug used in the latest study, which has been commercially available for two decades to treat blood vessel disorders in the eye.

The work comes from Michael Longaker, Shamik Mascharak, and colleagues, Stanford Medicine, Palo Alto, CA. But, to be more precise, the work began with a research project that Longaker was given back in 1987, while a post doc in the lab of Michael Harrison, University of California, San Francisco.

Harrison, a surgeon then performing groundbreaking prenatal surgery, noticed that babies born after undergoing surgery in the womb healed from their surgeries without any scarring. He asked his postdoc to find out why, and Longaker has been trying to answer that question and understand scar formation ever since.

Longaker and his Stanford colleague Geoffrey Gurtner suspected that the difference between healing inside and outside the womb had something to do with tension. Inside the womb, the skin of the unborn is bathed in fluid and develops in a soft, tension-free state. Outside the womb, human skin is exposed to continuous environmental stresses and must continuously remodel and grow to remain viable, which creates a high level of skin tension.

Following up on Longaker and Gurtner's suspicion, Mascharak found in a series of mouse experiments that a particular class of fibroblast, a type of cell in skin and other connective tissues, activates a gene called *Engrailed-1* during scar formation [3]. To see if mechanical stress played a role in this process, Mascharak and team grew mouse fibroblast cells on either a soft, stress-free gel or on a stiff plastic dish that produced mechanical strain. Importantly, they also tried growing the fibroblasts on the same strain-inducing plastic, but in the presence of a chemical that blocked the mechanical-strain signal.

Their studies showed that fibroblasts grown on the tension-free gel didn't activate the scar-associated genetic program, unlike fibroblasts growing on the stress-inducing plastic. With the chemical that blocked the cells' ability to sense the mechanical strain, *Engrailed-1* didn't get switched on either.

They also showed the opposite. When tension was applied to healing surgical incisions in mice, it led to an increase in the number of those fibroblast cells expressing *Engrailed-1* and thicker scars.

The researchers went on to make another critical finding. The mechanical stress of a fresh injury turns on a genetic program that leads to scar formation, and that program gets switched on through another protein called Yes-associated protein (YAP). When they blocked this protein with an existing eye drug called verteporfin, skin healed more slowly but without any hint of a scar.

It's worth noting that scars aren't just a cosmetic issue. Scars differ from unwounded skin in many ways. They lack hair follicles, glands that produce oil and sweat, and nerves for sensing pain or pressure. Because the fibers that make up scar tissue run parallel to each other instead of being more intricately interwoven, scars also lack the flexibility and strength of healthy skin.

These new findings therefore suggest it may one day be possible to allow wounds to heal without compromising the integrity of the skin. The findings also may have implications for many other medical afflictions that involve scarring, such as liver and lung fibrosis, burns, scleroderma, and scarring of heart tissue after a heart attack. That's also quite a testament to sticking with a good postdoc project, wherever it may lead. One day, it may even improve public health!

References:

[1] Human skin wounds: A major and snowballing threat to public health and the economy. Sen CK, Gordillo GM, Roy S, Kirsner R, Lambert L, Hunt TK, Gottrup F, Gurtner GC, Longaker MT. Wound Repair Regen. 2009 Nov-Dec;17(6):763-771.

[2] Preventing Engrailed-1 activation in fibroblasts yields wound regeneration without scarring.
Mascharak S, desJardins-Park HE, Davitt MF, Griffin M, Borrelli MR, Moore AL, Chen K, Duoto B, Chinta M, Foster DS, Shen AH, Januszyk M, Kwon SH, Wernig G, Wan DC, Lorenz HP, Gurtner GC, Longaker MT. Science. 2021 Apr 23;372(6540):eaba2374.

[3] Skin fibrosis. Identification and isolation of a dermal lineage with intrinsic fibrogenic potential. Rinkevich Y, Walmsley GG, Hu MS, Maan ZN, Newman AM, Drukker M, Januszyk M, Krampitz GW, Gurtner GC, Lorenz HP, Weissman IL, Longaker MT. Science. 2015 Apr 17;348(6232):aaa2151.

Links:

Skin Health (National Institute of Arthritis and Musculoskeletal and Skin Diseases/NIH)

Scleroderma (NIAMS)

Michael Longaker (Stanford Medicine, Palo Alto, CA)

Geoffrey Gurtner (Stanford Medicine)

NIH Support: National Institute of General Medical Sciences; National Institute of Dental and Craniofacial Research