Skin wounds in older mice are less likely to scar

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Researchers have discovered a rare example in which the mammalian body functions better in old age. A team at the University of Pennsylvania found that, in skin wounds in mice, being older increased

tissue regeneration and decreased scar formation. The same findings were confirmed in studies of human tissue. Their findings publish on September 25 in the journal *Cell Reports*.

Organisms repair wounds using two distinct processes: scarring or tissue regeneration. Wound healing results in scar formation. Tissue regeneration results in return of the original tissue architecture and absence of scar formation. Mammals generally repair injured tissue with wound healing. When the skin of young mice was exposed to trauma, a scar formed. The Penn team discovered that, when the skin of elderly mice was exposed to trauma, their skin wounds repaired without a scar. They were able to identify the molecular mechanism driving this age-defined change.

"Many dermatologists and plastic surgeons have observed that older people heal their surgical wounds with thinner scars, but why and how this occurs is not well understood," says senior author Thomas H Leung. "I saw this as an opportunity to study how aging normally affects scar thickness. If we could understand this mechanism, perhaps we can apply those principles to regenerate human skin."

To identify the mechanism, they turned to a well-established technique of parabiosis, where two different mice are surgically joined to share a common circulatory system. Once joined together, the mouse ear skin was then injured.

"We did this experiment many times and found that the elderly mouse healed its wounds like a young mouse; elderly skin no longer regenerated as well," explains Leung. "This suggested to us that the young mouse has a circulating factor in the blood that promotes scar formation and prevents tissue regeneration from occurring."

To identify the circulating factor, the team from Penn used genomic

studies to compare injured young and elderly mouse skin. They focused only on genes of circulating proteins and quickly homed in on stromal-derived-factor-1 (SDF1), which had previously been shown to play a role in tissue regeneration of the skin, lung, and liver.

To prove that SDF1 may be the causal factor, they engineered a mouse that lacked SDF1 only in the skin. When SDF1 function in the skin was eliminated, even young mice began to regenerate skin, behaving, in this sense, like older mice.

The team also learned that a different protein, EZH2, modifies the DNA at the SDF1 gene and prevents the gene from being activated. "As the mice aged, we found more EZH2 at the SDF1 gene," Leung explains. By using a drug to block EZH2 function in elderly mice, they saw that these mice regained SDF1 induction and lost their ability to regenerate their skin.

The same findings were seen in human skin. Just like in mice, skin injury in young people triggered SDF1 production and was diminished in elderly human skin. "This confirms that what we saw in the mouse is totally replicated in humans," Leung says. "We performed some additional experiments to show that EZH2 is also the reason why SDF1 induction is lost between young and old skin. In this case, mouse and human skin behaved in the same way."

Leung theorizes that scar formation in younger mice is evolutionarily preferable with speed dominating quality. Tissue regeneration is a slow process, requiring a month for skin injuries to regenerate compared with 3-5 days for scar formation. "As a young animal, one would want an injury to heal as quickly as possible to live to fight another day, so you will tolerate imperfect healing for a faster response," he says.

The researchers are currently planning a clinical trial with the drug,

plerixafor, an existing FDA-approved SDF1 inhibitor, to test its efficacy in preventing scar formation in humans. They are hoping this approach may be beneficial for many types of human tissue injuries, including the genetic disease epidermolysis bullosa, an extremely debilitating blistering disease, or in burn patients.

More information: *Cell Reports*, Nishiguchi et al.: "Aging Suppresses Skin-Derived Circulating SDF1 to Promote Full-Thickness Tissue Regeneration" www.cell.com/cell-reports/full … 2211-1247(18)31340-8 , DOI: 10.1016/j.celrep.2018.08.054

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