Study identifies molecule critical to healing wounds

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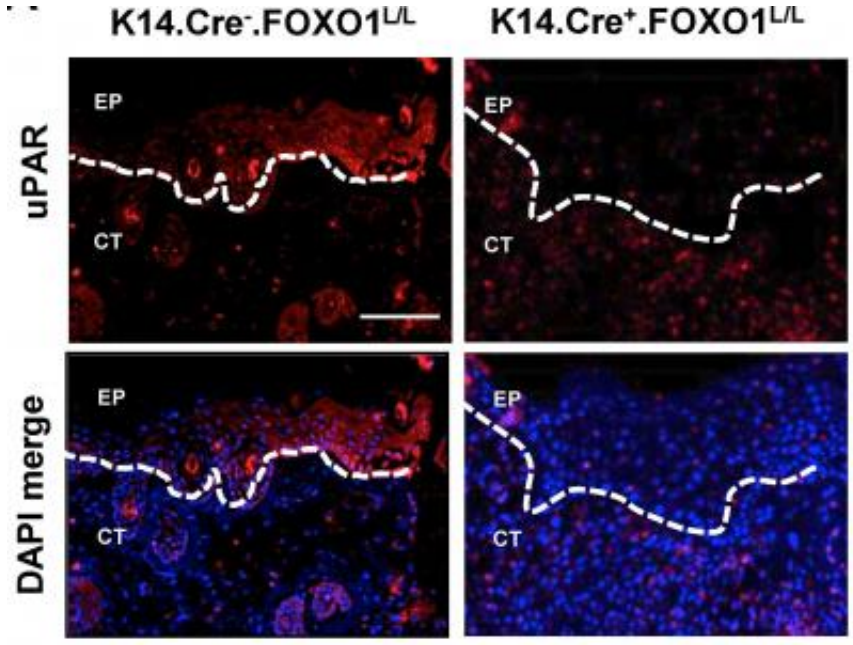

When cells lack the protein FOX01, (shown in the right column), they are much less likely to migrate-- a critical activity in wound healing. Migrating cells are stained red. Credit: University of Pennsylvania

Skin provides a first line of defense against viruses, bacteria and parasites that might otherwise make people ill. When an injury breaks that barrier, a systematic chain of molecular signaling launches to close the wound and re-establish the skin's layer of protection.

A study led by researchers from the University of Pennsylvania's School

of Dental Medicine and published in the *Journal of Cell Biology* now offers a clearer explanation of the role of one of the players in the wound-healing process, a molecule called FOX01. Contrary to what had been expected, FOX01 is critical to wound healing, providing researchers with a possible new target for drugs that could help speed that process for people with impaired wound healing.

Senior author Dana Graves is a professor in Penn Dental Medicine's Department of Periodontics and is vice dean for scholarship and research. He collaborated on the study with Penn's Bhaskar Ponugoti, Fanxing Xu, Chenying Zhang, Chen Tian and Sandra Pacio.

A critical element of wound healing involves the movement of keratinocytes, the primary cells comprising the epidermis, or the outer layer of skin. Previous research had found that FOX01 was expressed at higher levels in wounds, but scientists did not understand what role the molecule was playing. In other scenarios, such as in cancer cells, FOX01 promotes cell death and interferes with the cell reproduction, two actions that would seem to be detrimental to healing.

To investigate the role of FOX01 in wound healing, Graves and colleagues bred mice that lacked the protein in their keratinocytes and then observed the wound healing process in these mice compared to mice with normal FOX01.

"We thought that deleting FOX01 would speed up the wound-healing process," Graves said, "but in fact it had the opposite effect."

The mice that lacked FOX01 showed significant delays in healing. Whereas all wounds on control mice were healed after one week, all of the experimental mice still had open wounds.

Digging deeper into this counterintuitive finding, the researchers

examined the effect of reducing FOX01 levels on other genes known to play a role in cell migration. They found that many of these genes were significantly reduced, notably TGF-β1, a critical growth factor in wound repair. When the team added TGF-β1 to cells lacking FOX01, the cells behaved normally and produced the proper suite of molecules needed for healing, indicating that FOX01 acts upstream of TGF-β1 in the signaling pathway triggered during the healing process.

Further experimenting revealed that mice lacking FOX01 had evidence of increased oxidative stress, which is detrimental to wound healing.

"The wound healing environment is a stressful environment for the cell," Graves said. "It appears that upregulation of FOX01 helps protect the cell against oxidative stress."

The fact that FOX01 behaves in this unexpected way could have to do with the specialized microenvironment of a cell in a wound, Graves noted. While FOX01 does indeed promote cell death when it is highly activated, it does the opposite when moderately activated. Which activity it promotes depends on the environment in which it is acting.

Taken together, the study's findings demonstrate that FOX01 plays an integral role in two key processes in wound healing: activation of TGF-β1 and protecting the cell against oxidative damage. Its involvement in these aspects of healing make it a potential target for pharmaceuticals that could help speed healing.

"If you had a small molecule that increased FOX01 expression, you might be able to upregulate TGF-β1 as well as protect against the oxidative stress associated with wound healing," Graves said.

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