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Team shows why wound healing is impaired in diabetics

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One of the most troubling complications of diabetes is its effect on wound healing. Roughly 15 percent of diabetics will suffer from a non-healing wound in their lifetime. In some cases, these open ulcers on the skin lead to amputations.

For years, researchers have investigated the reasons for problems with wound healing in diabetics. And while many factors contribute, the specific molecular events responsible have remained unclear, and therapies to treat these stubborn wounds are few.

Now, scientists at the University of Pennsylvania School of Dental Medicine have identified a critical molecule that helps explain why diabetics suffer from this problem and pinpoints a target for therapies that could help boost healing.

The research was led by Dana T. Graves, professor in Penn Dental Medicine's Department of Periodontics and vice dean for scholarship and research. Collaborators from the School included lead author Fanxing Xu, Badr Othman, Jason Lim, Angelika Batres, Bhaskar Ponugoti, Chenying Zhang, Leah Yi, Jian Liu, Chen Tian, Alhassan Hameedaldeen, Sarah Alsadun and Rohinton Tarapore. Their paper appears in the journal *Diabetes*.

In a study published in 2013, Graves and colleagues found that a molecule called Foxo1 played an unexpected role in wound healing (Foxo1 refers to the protein and FOXO1 refers to the gene.) While

earlier findings had suggested its presence might be detrimental to healing, their team showed that it in fact promoted healing by "doing two things that are beneficial: protecting cells against oxidative stress and inducing TGF-β1, a molecule critical to the healing process," Graves said.

Yet the team members wondered if the same factor be responsible for the poor healing seen in people with diabetes.

To find out, they compared mice with diabetes to normal mice, creating small wounds on their tongues under anesthesia. As expected, the diabetic mice healed more slowly than normal mice.

But, when the researchers performed the same experiment in diabetic mice that had been bred to lack Foxo1 in their keratinocytes, the primary cells comprising the outer layer, wound healing was significantly improved. Surprisingly, the effect of deleting the FOXO1 gene in keratinocytes was opposite in diabetic compared to normal mice.

To drill down more precisely on how reducing Foxo1 improved healing, the researchers examined various aspects of healing, focusing on the movement of keratinocytes to fill in the hole left by the injury and the proliferation of cells to close the gap, in this case, in the layer of cells on the tongue's surface known as the mucosal epithelium.

"A critical aspect of wound healing is to cover the wound to limit its exposure to the environment and prevent it from being colonized by a microbial biofilm," Graves said.

Looking at mice with diabetes, the team observed that both cell movement and, to a lesser extent, cell proliferation were suppressed in diabetic mice, unless the keratinocytes of the mice lacked Foxo1, in which case the negative impact of diabetes was largely reversed.

The same response was seen in cells in culture: Cells grown in a high-sugar media had an impaired ability to move and proliferate compared to cells grown in standard solution. This impairment was reduced when Foxo1 was silenced.

Additional experiments indicated that the signaling molecules CCL20 and IL-36γ, both of which are regulated by Foxo1, play a role in how diabetes impairs cell movement, and thus wound healing.

The researchers demonstrated that FOXO1 stimulates production of the protein TGF-β1 to improve healing in normal mice, as they had seen in their 2013 study, but fails to induce TGF-β1 in diabetic wounds. Instead, in diabetic conditions FOXO1 stimulates an increase CCL20 and IL-36γ production, which interferes with keratinocyte migration. Thus, FOXO1 switches from being a positive factor for healing to a negative factor based upon whether the animal is normal or diabetic.

"In terms of a wound-healing response, it looks like Foxo1 might be one of the central regulators that are affected by the diabetic condition," Graves said. "This may make it a good drug target, which could possibly be administered locally to minimize systemic effects in diabetic wounds."

To follow up on these findings, the researchers are exploring how Foxo1 behaves in other animal models, seeing if a human drug might be a possibility.

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