

Sugar saps FOXO1's healing power

Study finds that high glucose levels cause protein to thwart cell migration.

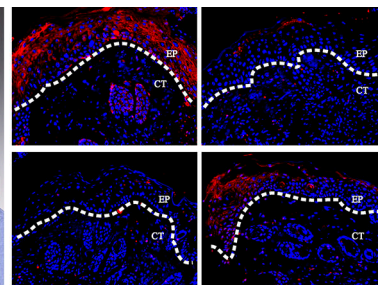
FOCAL POINT

Glucose's effect on the transcription factor FOXO1 isn't sweet. The protein usually fosters tissue repair, but Zhang et al. reveal that FOXO1 inhibits healing when sugar levels are high (1). This role reversal helps explain why wounds heal slowly in people with diabetes.

For diabetes patients, even a cut or scrape can result in severe complications. Because the skin doesn't close promptly, bacteria can get a foothold in the injured tissue, leading to chronic ulcers that in some cases require amputations (2). In a previous study, the researchers found that FOXO1 orchestrates an important early step in healing by promoting the skin cells known as keratinocytes to migrate into the injury, thus building an epithelial layer to cover the wound (3). FOXO1 spurs their movement by binding to the promoter of *TGFβ1*, which encodes a protein that triggers pro-healing responses. FOXO1 levels rise in wounds of diabetic mice (4). But nobody had determined whether the high sugar levels in these animals alter the transcription factor's function during healing.

Zhang et al. compared the healing capabilities of control mice and mice that lack FOXO1 in their keratinocytes. In animals with normal blood sugar, small skin wounds mended more slowly in the absence of FOXO1. But in mice that had diabetes, wounds healed faster if FOXO1 was missing. Seven days after diabetic animals were injured, for example, the wounds were mostly closed in the animals lacking FOXO1 but remained mostly open in the group that still produced FOXO1.

To determine whether sugar alters keratinocytes' behavior, the researchers grew the cells in culture dishes and then scratched them to simulate a wound. When the cultures contained little glucose, cells with normal amounts of FOXO1 filled in the gap faster than did FOXO1-deficient cells. But when the researchers boosted glucose



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Dana Graves (left), Chenying Zhang (right), and colleagues (not pictured) determined that high sugar levels impair tissue repair by changing the function of FOXO1. In skin from mice with normal glucose levels (top row), more keratinocytes (red) migrate into damaged tissue in control mice (left) than in mice lacking FOXO1 (right). But in diabetic mice (bottom row), more keratinocytes migrate into the wound in animals lacking FOXO1 (right) than in controls (left). In all four images, blue marks cell nuclei, and the dotted line delineates the boundary between the epidermis and the dermis.

levels in the cultures, the situation reversed. FOXO1-deficient cells were quicker to enter the scratch. Using a marker to pinpoint migrating keratinocytes, Zhang et al. demonstrated that glucose also affected the cells' movements in vivo.

Glucose changes FOXO1's relationship with TGF-β1, Zhang et al. found. At normal sugar levels, cultured keratinocytes synthesized 45% less TGF-β1 if they were missing FOXO1. But at high sugar concentrations, cells' FOXO1 status had no impact on their TGF-β1 production, suggesting that FOXO1 no longer regulates TGF-β1 under these conditions. High sugar levels prevented FOXO1 from binding to the *TGFβ1* promoter, the researchers found. Instead, FOXO1 turns on *SERPIN2* and *CCL20*, two genes that curb keratinocyte migration and block wound healing when expressed at high levels.

People with diabetes often produce too little insulin, and Zhang et al. showed that the hormone counteracts FOXO1. For example, high glucose levels boost production of FOXO1, but the researchers found that insulin reversed this effect. The hormone also turned down expression of *SERPIN2* and *CCL20*, and it sped up migration of keratinocytes cultured in high-sugar conditions.

Two other metabolic malfunctions common in diabetes can also impede wound healing through FOXO1, the researchers discovered. As blood sugar levels rise, glucose can glom onto proteins to form advanced glycation end products, or AGEs, and often alters the proteins' functions. The team found that one type of AGE prevented FOXO1 from attaching to *TGFβ1*'s promoter, thereby slowing keratinocyte movement. Levels of the inflammation-promoting molecule TNFα are often high in diabetics. Zhang et al. determined that like AGEs, TNFα blocked FOXO1's interaction with the *TGFβ1* promoter and inhibited keratinocyte migration.

"Whether FOXO1 is beneficial or harmful, whether it promotes healing or inhibits healing, depends on the environment of the cell," says senior author Dana Graves. Researchers still have questions to answer, such as how sugar prevents FOXO1 from binding to the *TGFβ1* promoter and whether FOXO1 affects other cell types involved in tissue repair. Previous studies showed that insulin stimulates wound healing in diabetics. Zhang et al.'s findings support further tests of this potential treatment and suggest that inhibiting FOXO1 could speed healing in patients with diabetes.

1. Zhang, C., et al. 2015. *J. Cell Biol.* <http://dx.doi.org/10.1083/jcb.201409032>.
2. Moulik, P.K., et al. 2003. *Diabetes Care.* 26:491–494.
3. Ponugoti, B., et al. 2013. *J. Cell Biol.* 203:327–343.
4. Siqueira, M.F., et al. 2010. *Diabetologia.* 53:378–388.

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