New findings offer hope for diabetic wound healing

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University of Notre Dame researchers have discovered a compound that accelerates diabetic wound healing, which may open the door to new treatment strategies. Non-healing chronic wounds are a major complication of diabetes, which result in more than 70,000 lower-limb amputations in the United States alone each year. The reasons why diabetic wounds are resistant to healing are not fully understood, and there are limited therapeutic agents that could accelerate or facilitate their repair.

A team of researchers from Notre Dame's Department of Chemistry and Biochemistry, led by Mayland Chang, previously identified two enzymes called matrix metalloproteinases (MMPs), MMP-8 and MMP-9, in the wounds of diabetic mice. They proposed that the former might play a role in the body's response to wound healing and the latter was the pathological consequence of the disease with detrimental effects. The researchers used the MMP-9 inhibitor referred to as ND-322, which accelerated wound healing in diabetic mice.

In a new study that appears in the journal *Proceedings of the National Academy of Sciences* (*PNAS*), the researchers report the discovery of a better MMP-9 inhibitor referred to as ND-336.

"ND-336 is a six-fold more potent inhibitor than ND-322 and has 50-fold selectivity towards inhibition of MMP-9 than MMP-8," Chang said. "In contrast, ND-322 has three-fold selectivity towards inhibition of MMP-9 compared to MMP-8. The current paper compared the efficacy of ND-336 versus ND-322. We found that wounds treated with ND-336 healed significantly faster than those treated with ND-322 because of the better selectivity of ND-336 than ND-322 for inhibition of MMP-9 over MMP-8. In the current paper we applied the enzyme MMP-8 to wounds of diabetic mice and found accelerated wound healing. We also combined the MMP-9 inhibitor ND-336 and the enzyme MMP-8 and found further acceleration of diabetic wound healing."

The researchers found that a combination of a selective inhibitor of MMP-9 (a small molecule) and applied MMP-8 (an enzyme) enhanced healing even more, in a strategy that holds considerable promise in healing of diabetic wounds.

"The compound ND-336 has potential as a therapeutic to accelerate or facilitate wound healing in diabetic patients," Chang said. "Likewise, the enzyme MMP-8 could be used to accelerate/facilitate diabetic wound repair. The combination of a small molecule (ND-336) and the enzyme MMP-8 has the potential to accelerate further diabetic wound repair."

The researchers are currently recruiting diabetic patients to ascertain the levels of MMP-8 and MMP-9 in their wounds. This study is in collaboration with the Center for Wound Healing at Elkhart General Hospital.

More information: Acceleration of diabetic wound healing using a novel protease–anti-protease combination therapy, *PNAS*, www.pnas.org/cgi/doi/10.1073/pnas.1517847112

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