Study identifies how diabetes slows healing in the eye

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Investigators from Cedars-Sinai have provided new understanding of how diabetes delays wound healing in the eye, identifying for the first time two related disease-associated changes to the cornea.

The findings, published today in the peer-reviewed journal *Diabetologia*, also identified three therapeutic pathways that reversed these changes and partially restored wound-healing function to the cornea—a discovery that could ultimately inform new treatments for diabetes.

"We have found that diabetes induces more cellular changes than we were aware of previously," said Alexander Ljubimov, Ph.D., director of the Eye Program at Cedars-Sinai's Board of Governors Regenerative Medicine Institute and senior author of the paper. "The discovery does not affect gene sequence but entails specific DNA modifications altering gene expression—what are known as epigenetic alterations."

More than 37 million people in the United States—11% of the population—have diabetes, a systemic disorder that can result in kidney disease, heart disease, amputation, stroke and nerve damage. Most diabetes drugs are designed to increase glucose tolerance or supply depleted insulin, but do not address molecular and cellular changes or their associated complications.

The new research also identifies for the first time an important role of Wnt-5a, a secreted signaling protein investigators found responsible for corneal wound healing and the function of stem cells—cells capable of differentiating into many cell types.

"Current treatments only address symptoms, so there is an urgent need to understand the molecular mechanisms of diabetes-related wound-healing problems," said Ruchi Shah, Ph.D., a scientist in Ljubimov's lab and the study's first author. "Understanding of this novel epigenetically regulated wound-healing mechanism could lead to therapeutic treatments that could help patients avoid further long-term ocular health issues."

Though much focus of diabetic eye disease is on the retina, up to 70% of diabetes patients suffer from problems of the cornea, the transparent,

protective exterior surface of the eye. In advanced diabetes, corneal stem cells become dysfunctional, and the cornea heals more slowly and less completely following an injury or procedures such as cataract surgery and laser treatment for diabetic retinopathy.

To identify the epigenetic changes discovered in this study—changes not hard-wired into the genome from birth, but introduced later—Ljubimov and his team compared cells from the corneas from six diabetic patients with those of five healthy donors. They found that in diabetic corneas, the protein product of the WNT5A gene was repressed. Additionally, in diabetic samples, they found an increase in the microRNA that inhibits WNT5A.

The team of scientists then induced wounds to corneal cells in culture and corneal organ cultures, and tested three interventions designed to normalize Wnt-5a protein expression. They added the Wnt-5a protein directly; they introduced a DNA methylation inhibitor, originally approved to treat cancer; and they targeted microRNA levels with a novel gene therapy approach using a nanoscale compound. The team developed the compound, which uses synthetic molecules to block the microRNA, as a substitute for a viral gene therapy they found to be toxic to stem cells.

All three therapeutic methods, in the diabetic samples, stimulated stem cell marker production and improved tissue regeneration, accelerating wound healing.

"Novel therapies to reverse epigenetic effects could improve corneal function, and may also prove significant in other diabetic complications," said Clive Svendsen, Ph.D., director of the Board of Governors Regenerative Medicine Institute and study co-author. "This work certainly helps move the field forward."

Investigators will continue to analyze their data to better understand the mechanisms of *WNT5A* and other genes related to wound healing. They are also studying a combination therapy to target both microRNA and DNA methylation in hopes that it will more thoroughly normalize wound healing by increasing Wnt-5a protein.

"Our goal is to develop topical, sustained-release drugs for corneal wound healing," said Ljubimov. "Drugs that are FDA [Food and Drug Administration] approved and could be easily applied may be one of the most promising approaches for effective future therapies."

More information: Ruchi Shah et al, Reversal of dual epigenetic repression of non-canonical Wnt-5a normalises diabetic corneal epithelial wound healing and stem cells, *Diabetologia* (2023). DOI: 10.1007/s00125-023-05960-1

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