Researcher identifies cell mechanism leading to diabetic blindness

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Scientists have long known that high blood sugar levels from diabetes damage blood vessels in the eye, but they didn't know why or how. Now a Michigan State University scientist has discovered the process that causes retinal cells to die, which could lead to new treatments that halt the damage.

Diabetic retinopathy is a common side effect of diabetes and the leading cause of blindness in young adults in the United States. It's estimated that between 40 percent and 45 percent of people diagnosed with diabetes have some degree of diabetic retinopathy.

Research by Susanne Mohr, MSU associate professor of physiology, found the siah-1 protein is produced by the body when blood sugar levels are high. She then discovered that the siah-1 protein serves as a type of chauffeur for another protein, glyceraldehyde-3-phosphate dehydrogenase (GAPDH), shuttling the GAPDH into the nucleus of Müller cells, special cells that have contact with the blood vessels in the eye. When GAPDH accumulates in their nuclei, the Müller cells die, which leads to the vascular damage associated with diabetic retinopathy.

The research is published in the Jan. 29 issue of the Journal of Biological Chemistry.

"Our earlier research showed that high glucose levels cause GAPDH to accumulate in the nuclei of Müller cells in the retina," Mohr explained. "But we weren't sure how the GAPDH was getting in there. It doesn't

contain any of the necessary signaling motifs. I read about the siah-1 protein and cell death in white blood cells in a *Nature* paper, so we decided to investigate them. We had no idea if the siah-1 protein was even in the retina."

Mohr's research also found that lowering levels of siah-1 proteins stopped GAPDH from moving into the nuclei of Müller cells, which stopped them from dying.

"This is very exciting," Mohr said. "We know that we can't regulate production of GAPDH because it's necessary for producing energy throughout the body. But since siah-1 is produced only when glucose levels are high, regulating it doesn't cause any problems. If we can figure out how to stop siah-1 production, it may lead to new treatments for diabetic retinopathy."

Mohr explained that stopping GAPDH from moving into Müller cell nuclei is important to halting the progress of diabetic retinopathy. Even after glucose levels are lowered and stabilized in diabetics, GAPDH continues to accumulate in Müller cell nuclei. So the retinal damage keeps worsening, just more slowly.

"If we can keep GAPDH out of the nuclei, we may be able to completely stop diabetic retinopathy," Mohr said. "Our next step is to figure out if both the GAPHD and the siah-1 proteins have to be together in a complex to cause cell death."

Provided by Michigan State University