Scientists target receptor to treat diabetic retinopathy

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This is a photo of Dr. Pamela Martin, biochemist at the Medical College of Georgia at Georgia Regents University. Credit: Phil Jones

Like a daily pill to lower cholesterol can reduce heart attack and stroke risk, an easy-to-use agent that reduces eye inflammation could help save the vision of diabetics, scientists say.

In fact, a receptor already targeted with high doses of niacin to decrease bad cholesterol levels and raise good ones, appears to also be an effective mark for these patients, said Dr. Pamela Martin, biochemist at

the Medical College of Georgia at Georgia Regents University.

Martin is Principal Investigator on a new $1.875 million grant from the National Eye Institute to further pursue this potential treatment for diabetic retinopathy, a leading cause of blindness in American adults.

She's talking about Gpr109a, a receptor first found on the surface of fat cells, where its targeted by niacin to improve cholesterol levels. More recently, Martin also found the receptor on the surface of cells of the retinal pigment epithelium, or RPE. The RPE is a tight group of cells at the back of the eye with many jobs, including protecting the eye from intruders like viruses, pulling desirables like oxygen and nutrients out of blood, and clearing waste.

RPE transporters do a lot of this heavy lifting and, while the role of Gpr109a isn't crystal clear, Martin has shown what happens when it's missing. When her research team deletes the receptor from the retina of non-diabetic mice, the rodents quickly develop the classic inflammation, retinal cell damage and cell death that occurs in patients with diabetic retinopathy. In fact, telltale inflammatory markers are 10 to 20 times higher in the eyes of these rodents, a good indicator of the receptor's role in regulating inflammation, Martin said.

MCG scientists also have early evidence that moderately activating the receptor in a diabetic retina inhibits inflammation. They suspect that, as it does on fat cells, it also helps regulate cholesterol in the retina and may even reduce the proliferation of abnormal blood vessels. This proliferation contributes to vision destruction in diabetes.

Martin's 2009 finding that Gpr109a was expressed on RPE cells still has scientists looking for the endogenous activator of the receptor on these cells. In the meantime, they have learned that niacin along with an alternate energy supply for the body called beta hydroxybutyrate can

activate the receptor in the eye. That's what piqued Martin's interest in investigating the therapeutic potential of the receptor in diabetic retinopathy.

Beta hydroxybutyrate is a ketone body, which scientists call rescue metabolites, because the body makes them when the usual fuel is scarce. One of the many results of diabetes is the body no longer being able to optimally use its primary energy source, glucose. "The glucose may be sitting there, but without insulin, the cell can't use it so the body is essentially tricked into thinking there is nothing available to function on and it will start producing these ketone bodies," Martin said.

While uncontrolled diabetes produces a lot of ketones, which is basically bad, ample evidence suggests that moderately increasing ketone productiion via a high-fat/low-carb diet can help manage neurodegenerative diseases such as Alzheimer's and Parkinson's, where inflammation also is a major player.

Martin and her colleagues started thinking that moderately stimulating Gpr109a with compounds like niacin or beta hydroxybutyrate just might help maintain a healthy retina in the face of diabetes. Early evidence indicates they are correct.

The new grant will enable the scientists to follow diabetic animal models over the long term, like ophthalmologists follow humans. "We want to see if we treat them for prolonged periods with Gpr109a-activating compounds like beta-hydroxybutyrate or niacin, whether or not we can suppress inflammation in diabetic eyes and, in the long term, prevent some of the damage and vision loss," Martin said.

They'll track changes in the expression of a number of cellular and molecular markers of inflammation and oxidative stress and regularly examine the eyes of diabetic mice, including dilating their eyes, to

monitor disease progression and treatment response.

Long-term follow-up also will enable the scientists to compare different doses of the compounds and modes of administration and ideally identify the most efficacious. One goal is a compound that can be taken by mouth, particularly since Martin suspects this will be a longterm therapy. Current diabetic retinopathy therapies focus on destroying the excessive, obstructive, and leaky blood vessels that emerge in response to inflammation with laser treatments or injections of anti-VEGF agents into the eye. She hopes her therapy will intervene much sooner, noting that even good control of blood sugar levels does not eliminate the risk of eye damage in diabetes.

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