Researchers uncover protective factor in diabetic eye disease

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Researchers at Joslin Diabetes Center have shown that a protein found in the eye can protect against and potentially treat diabetic eye disease. At high enough levels, Retinol Binding Protein 3 (or RBP3) prevents the development of diabetic retinopathy. If introduced early enough in the development of the disease, RBP3 was shown to reverse the effects of

the complication in rodent models of diabetes. These results are reported today in *Science Translational Medicine*.

"The level of RBP3 in the eye's vitreous and retina are higher in people who don't progress to diabetic eye disease than in those who do," says George King, Chief Scientific Officer at Joslin Diabetes Center and senior author on the paper. "Building on that observation, we saw that if you overexpress RBP3 by molecular methods [in animal models], you can prevent the onset of diabetic eye disease. And when we injected RBP3 itself into the vitreous of diabetic rats, we reversed some of the early changes of diabetic eye disease."

People with diabetes have a high risk of developing complications due to extended periods of elevated glucose levels. These complications could include nerve damage, kidney disease, and eye disease. But a rare subset of people who have had insulin-dependent diabetes for more than 50 years have avoided such complications. For 15 years, Joslin researchers have tracked these individuals as part of the Medalist Study. They noted that 35 percent of patients avoided retinopathy, even when they had elevated glucose levels.

Dr. King and his team deduced that these patients must have something endogenous—or created by their own body that are neutralizing the toxic effects of high glucose levels. This new study aimed to build on this observation, to determine which molecules could be responsible for the protection of the eye.

They took biosamples from the eyes of Medalists—both from living patients during surgery and from people who had donated their eyes postmortem. They then characterized the many proteins that were present, to determine if any proteins were elevated more in the protected eyes than in eyes of people who developed retinopathy.

They recognized that RBP3, a protein only made in the retina/eye, was elevated. To determine if this was indeed the protective factor they were looking for, they constructed experiments to compare normal versus increased expression of RBP3 in mouse models. Mice with increased RBP3 expression were protected from developing diabetic retinopathy.

Next, the researchers injected pure RBP3 into the vitreous of the eyes of mice in the early stages of retinopathy. The infusion of RBP3 reversed the damages done by early eye disease. They also discovered that diabetes seems to reduce the expression of RBP3 in eye in many subjects, which could explain why its protective effects are limited to only some patients.

"If we could find out what's causing the decrease of RBP3 in the retina in the first place, we could design some kind of treatment to maintain its production, allowing all diabetic patients to have an endogenous protection against eye disease," says Dr. King.

RBP3 is found in all eyes. Normally, it is used to regenerate a certain type of vitamin A in the eye that powers sight-giving rods and cones. But when the eye is exposed to high glucose levels, RBP3 changes its role.

"It appears to decrease the toxic effects of high glucose levels that exist in diabetes by reducing the entering of glucose into several important retinal cells by inhibiting the actions of a glucose transporter, GLUT-1." says Dr. King.

Understanding these mechanisms may allow researchers to develop a targeted treatment to fight early-stage retinopathy. Currently, severe retinopathy can be addressed by the Joslin-developed treatments of either laser photocoagulation or VEGF inhibitor injections.

"We are interested in how we can treat diabetic eye disease at its earliest

stages before it gets to the severe forms," says Dr. King.

One surprising finding from this study showed that RBP3, while it mainly resides in the eye, can also be detected to some degree in the bloodstream. Dr. King and team have planned follow-up studies to determine if RBP3 levels in the bloodstream correlate with severity of diabetic retinopathy. If they do, this circulating RBP3 could become a biomarker that doctors can use to screen for retinopathy during regular lab tests.

"That could be a very important screening tool for family or internal medicine doctors who are not experts at examining the eye," says Dr. King. "Right now, all people with diabetes have to be sent to ophthalmologists to really give us a sense of the status of their eyes with regard to diabetes. So, if this could be a general screen, we may be able to catch more cases of retinopathy earlier in the disease course."

Joslin and its Beetham Eye Institute have a strong history of developing treatments for retinopathy. This discovery brings them a step closer to prevention of the devastating complication.

"This has the potential to become equally as important as our previous discovery of VEGF as critical for diabetic proliferative disease or severe diabetic eye disease," King says.

More information: H. Yokomizo el al., "Retinol binding protein 3 is increased in the retina of patients with diabetes resistant to diabetic retinopathy," *Science Translational Medicine* (2019). stm.sciencemag.org/lookup/doi/ … scitranslmed.aau6627

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