Discovery points toward anti-inflammation treatment for blinding disease

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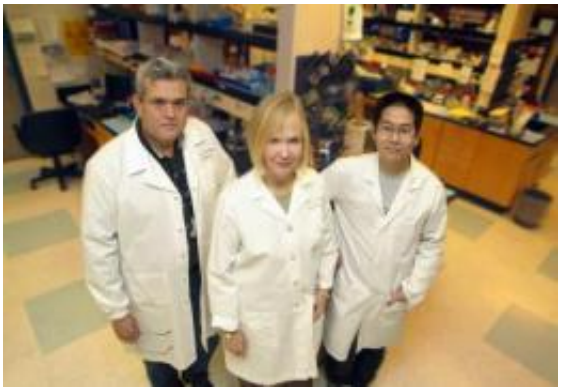

Drs. Modesto Rojas (from left), Ruth Caldwell and Wenbo Zhang's research indicates that an antibody already under study to treat rheumatoid arthritis may help treat diabetic retinopathy as well. Credit: Medical College of Georgia

The discovery of an inflammatory mediator key to the blinding effects of diabetic retinopathy is pointing toward a potential new treatment, Medical College of Georgia researchers said.

Interleukin-6, known to contribute to the debilitating joint inflammation of rheumatoid arthritis, also helps ignite inflammation of the retina, a first step in a disease that is the leading cause of blindness is working-age adults, MCG researchers reported online in *Investigative Ophthalmology & Visual Science*.

The finding has the scientists looking at whether an interleukin-6

antibody, which is showing success in treating rheumatoid arthritis, can halt inflammation in mice with diabetic retinopathy. "We expect that this neutralizing antibody can be used to treat diabetic retinopathy in the future," said Dr. Wenbo Zhang, assistant research scientist in MCG's Vascular Biology Center. Drs. Zhang and Modesto Rojas, senior postdoctoral fellow, are co-first authors on the paper.

Angiotensin II, a powerful constrictor of blood vessels, is typically associated with the kidneys where it plays a vital role in regulating blood pressure. The scientists suspect angiotensin II helps promotes wound healing and regulation of pressure within small blood vessels in the eye.

However in diabetes, angiotensin II levels increase in the eye - probably in response to high glucose levels - and help promote inflammation, spurring remodeling of blood vessels and tissue destruction, Dr. Rojas said. "Vascular inflammation is one of the first steps to inducing the changes in the retina."

MCG scientists have shown interleukin-6 is a needed accomplice whose previously undetectable levels in the eye also increase, said Dr. Ruth Caldwell, cell biologist a the Vascular Biology Center and the Charlie Norwood Veterans Affairs Medical Center and the study's corresponding author.

With the help of interleukin-6, angiotensin II induces white blood cells to stick to the endothelial cells lining blood vessels of the retina, which slows blood flow. The white blood cells also start producing inflammatory and vascular growth factors that cause blood vessel walls to leak and thicken, further constricting blood flow. Retinal cells start dying from the reduced blood and oxygen supplies that result. In response, the body prompts growth of new blood vessels, presumably to help but instead causing more vision impairment.

If the trigger, high glucose, was temporary, these natural responses might help clear damaged cells and protect the eye. "Inflammation is a compensatory mechanism that gets activated as a survival mechanism," Dr. Rojas said. "If it continues, the effect is bad."

"We have known for along time if patients keep their blood sugar under perfect control, they don't have these problems, but that's hard," Dr. Caldwell adds. "That is why it's such a difficult disease."

To examine interleukin-6's role in the destruction, the researchers injected angiotensin II into the vitreous portion of the eyes of mice missing the gene for the inflammatory factor as well as normal mice. The extra angiotensin did little to the retinal vessels of mice lacking interleukin-6 but vessels in the normal mouse retina mimicked the inflammatory reaction found in diabetic retinopathy. When they reintroduced interleukin-6 to the genetically altered mice, the damage mimicked that of the normal mice. "So when we knock out interleukin-6, we can block the effects of angiotensin II," Dr. Caldwell said.

The scientists want to see whether the interleukin-6 antibody can be used to prevent damage by giving it shortly after the onset of diabetes in rodents and as a treatment by using it later in the disease process.

Provided by Medical College of Georgia