Elevated arginase levels contribute to vascular eye disease such as diabetic retinopathy

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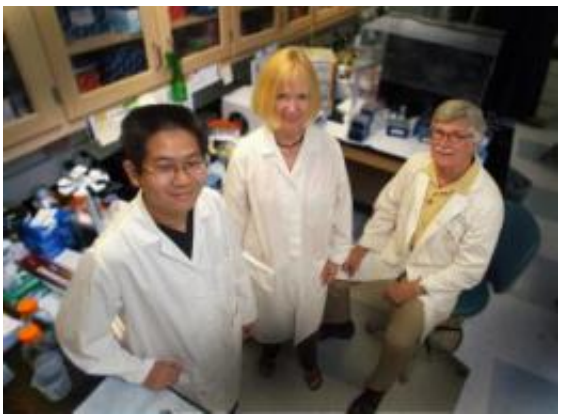

Drs. Wenbo Zhang (from left), Ruth Caldwell and R. William Caldwell have shown that elevated levels of the enzyme arginase contribute to vascular eye damage in diseases such as diabetic retinopathy. Credit: Medical College of Georgia

Elevated levels of the enzyme arginase contribute to vascular eye damage and Medical College of Georgia researchers say therapies to normalize its levels could halt progression of potentially blinding diseases such as diabetic retinopathy.

Their work, published in the August issue of *The* American Journal of Pathology, is the first to make the connection between eye disease and arginase, an enzyme known to be a player in cardiovascular disease,

according to researchers at MCG and Charlie Norwood Veterans Affairs Medical Center.

"The goal is to find a new strategy for preventing progression of diabetic retinopathy," says Dr. Ruth Caldwell, a cell biologist at the MCG School of Medicine and VA Medical Center, and the study's corresponding author.

Because they could measure arginase levels in the blood, it also could become a biomarker for a disease process that can work silently in the eye for months or even years, she says.

More broadly, understanding just how arginase regulates inflammation should lead to new therapies for many acute and chronic inflammatory diseases in the eyes and other organs, says Dr. Wenbo Zhang, postdoctoral fellow in Dr. Caldwell' lab and the paper's first author.

The researchers suspect an elevated arginase level is a red flag of early vascular damage in the eyes as well as the heart, kidneys and other organs. "We don't think this is going to be specific to the retina," Dr. Caldwell says, noting that inflammation often precedes full blown vascular disease.

"We know that people with diabetes have a greater incidence of heart attack and we know that vision is a sense that suffers greatly in diabetes," says Dr. R. William Caldwell, study co-author who chairs the Department of Pharmacology and Toxicology in the MCG School of Medicine. "We are finding arginase is a common player."

To create an animal model of the inflammation that occurs early in vascular eye disease, they used bacterial proteins to produce a severe and rapid inflammation of the eye called uveitis, which can also cause blindness but is easier to detect and treat than diabetic retinopathy.

"Inflammation of the blood vessel walls in the retina is some of the earliest eye damage that occurs in diabetes. This is like hitting the same system with a sledge hammer," Dr. Ruth Caldwell says. Short term, inflammation causes redness and irritation as it lays the groundwork for an unhealthy remodeling of blood vessel walls that restricts blood flow.

Inside the diabetic eye, high glucose levels trigger inflammation and, in an apparent effort to fight it, arginase actually ends up contributing to inflammation and vascular disease as well. The crux of the problem seems to be too much competition for L-arginine, an amino acid arginase requires to take any action - good or bad, says Dr. William Caldwell.

The retina, located at the back of the eye, is essentially an extension of the brain that receives light and transforms it to a neural impulse that travels back to the brain via the optic nerve. It can withstand assaults, such as elevated glucose levels that occur in diabetes, for years before vascular cells become damaged and die. That destruction spurs development of new blood vessels to deliver oxygen to oxygen-starved tissue but instead the proliferation blocks vision and they leak, increasing retinal damage.

Early in the diabetic process, high levels of glucose trigger high levels of inducible nitric oxide synthase, which makes nitric oxide. Under conditions of acute inflammation, nitric oxide helps control injury by killing off invaders. But during diabetes, it increases oxidative stress, causing further tissue damage. As part of the fight, arginase increases to provide substrates for tissue repair and to dampen the actions of inducible nitric oxide synthase. The complicating news is that nitric oxide synthase in endothelial cells, which makes the nitric oxide that enables blood vessels to relax, also is competing with arginase for the L-arginine.

The net effect can be too little nitric oxide inside blood vessel walls to help them relax and keep white blood cells and platelets from sticking to them.

"It's taking L-arginine away from the nitric oxide synthase so it can accelerate wound healing but the lack of substrate for nitric oxide synthase leads to vascular constriction and occlusion which causes further tissue damage, " Dr. Ruth Caldwell says. The researchers, who also are studying this process in a model of diabetic retinopathy, want to fully delineate the complex scenario. They already know high levels of the signaling molecule reactive oxygen species is another factor. As with arginase, some reactive oxygen species formation is a good thing but too much causes blood vessel damage.

"Our studies demonstrate that if we inhibit arginase, we also reduce the reactive oxygen species level and vice versa," Dr. Zhang says. "It appears that arginase and nitric oxide synthase influence each other in a positive feedback loop."

Rather than drugs that generally suppress arginase, the researchers want to find new drugs that can restore healthy levels of arginase. "You need arginase. If you don't have it, you are in big trouble," says Dr. William Caldwell. "We want to delineate the events that cause elevation and limit the elevation to prevent the resulting pathology."

The only U.S. Food and Drug Administration approved therapy to intervene in diabetic retinopathy is to use lasers to burn holes in the retina, which reduces the oxygen needs of the tissue by destroying some of it.

In related studies, Dr. William Caldwell, in conjunction with Dr. Maritza Romero, MCG assistant research scientist, has shown that in diabetes blood vessels throughout the body suffer from too much competition for

L-arginine and that another amino acid, L-citrulline, as well as statin drugs used to treat cholesterol can prevent unhealthy elevation of arginase.

Source: Medical College of Georgia