# Receptor that helps protect brain cells has important role in support cells for the retina

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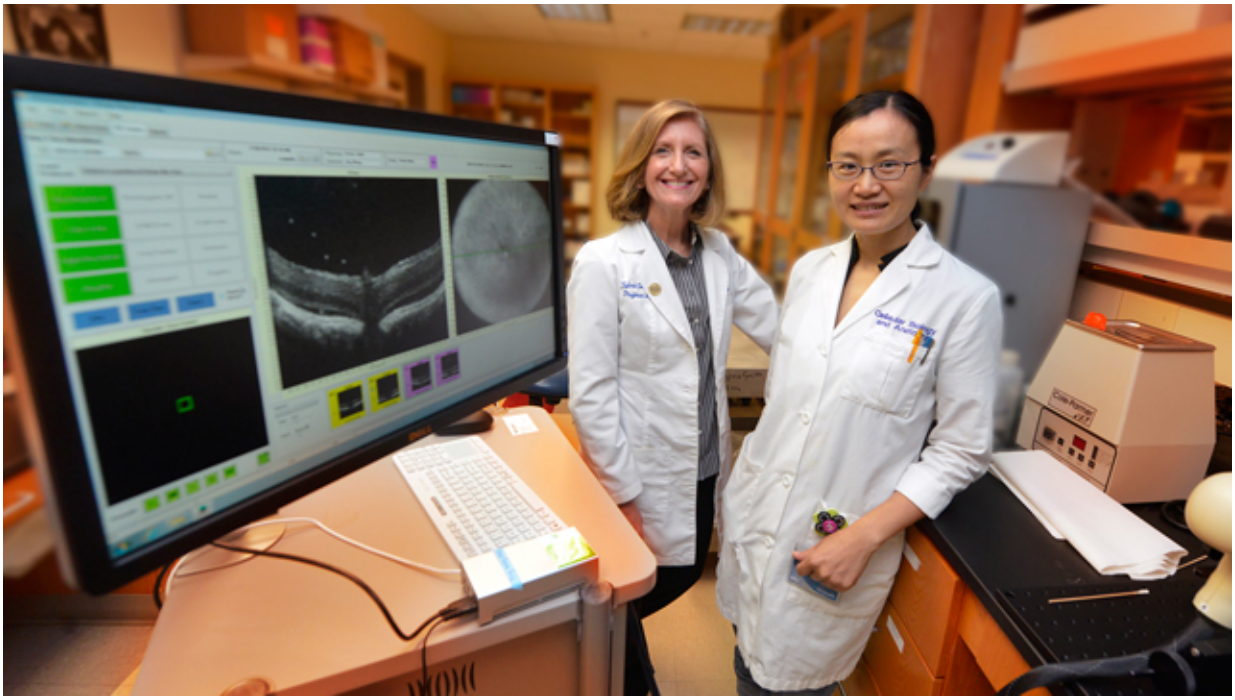

Dr. Sylvia Smith, retinal cell biologist and Chairwoman of the Department of Cellular Biology and Anatomy at the Medical College of Georgia at Georgia Regents University and Jing Wang, Research Scientist and the study's first author. Credit: Phil Jones

A receptor that is already a target for treating neurodegenerative disease also appears to play a key role in supporting the retina, scientists report.

Without sigma 1 receptor, the Müller cells that support the retina can't seem to control their own levels of destructive oxidative stress, and consequently can't properly support the millions of specialized neurons that enable us to transform light into images, scientists report in the journal *Free Radical Biology and Medicine*.

Without support, well-organized layers of retinal cells begin to disintegrate and vision is lost to diseases such as retinitis pigmentosa, diabetic retinopathy and glaucoma, said Dr. Sylvia Smith, retinal cell biologist and Chairwoman of the Department of Cellular Biology and Anatomy at the Medical College of Georgia at Georgia Regents University.

The surprising finding makes the sigma 1 receptor a logical treatment target for these typically progressive and blinding retinal diseases, said Smith, the study's corresponding author. It has implications as well for other major diseases, such as cardiovascular disease and cancer as well as neurodegenerative disease, where oxidative stress plays a role.

What most surprised the scientists was that simply removing sigma 1 receptor from Müller cells significantly increased levels of reactive oxygen species, or ROS, indicating the receptor's direct role in the oxidative stress response, Smith said. They expected it would take them giving an oxidative stressor to increase ROS levels.

So they looked further at the sigma 1 receptor knockouts compared with normal mice, and found significantly decreased expression in the knockouts of several, well-known antioxidant genes and their proteins. Further examination showed a change in the usual stress response.

These genes that make natural antioxidants contain antioxidant response element, or ARE which, in the face of oxidative stress, gets activated by NRF2, a transcription factor that usually stays in the fluid part of the

cell, or cytoplasm. NRF2 is considered one of the most important regulators of the expression of antioxidant molecules. Normally the protein KEAP1 keeps it essentially inactive in the cytoplasm until needed, then it moves to the cell nucleus where it can help mount a defense. "When you have oxidative stress, you want this," Smith said of the stress response, which works the same throughout the body.

Deleting the sigma receptor in the Müller cells altered the desired response: NRF2 expression decreased while KEAP1 expression increased. The unhealthy bottom line was that ROS levels increased as well.

The study is believed to provide the first evidence of the direct impact of the sigma 1 receptor on the levels of NRF2 and KEAP1, the researchers write.

"We think we are beginning to understand the mechanism by which sigma 1 receptor may work and it may work because of its action on releasing antioxidant genes," Smith said.

While the ubiquitous receptor was known to help protect neurons in the brain and eye, its impact on Müller cell function was previously unknown. The significant impact the MCG scientists have now found helps explain the dramatic change they documented after using pentazocine, a narcotic already used for pain relief, in animal models of both retinitis pigmentosa and diabetic retinopathy. Pentazocine, which binds to and activates the sigma 1 receptor, seems to preserve functional vision in these disease models by enabling many of the well-stratified layers of photoreceptor cells to survive.

Next steps include clarifying whether it's actually preservation or regeneration of the essential cell layers and how long the effect lasts. "We do see some retention of function, that is clear and that I am very

excited about," Smith said.

Müller cells are major support cells for the retina, helping stabilize its complex, multi-layer structure, both horizontally and vertically; eliminating debris; and supporting the function and metabolism of its neurons and blood vessels. Typically bustling Müller cells can become even more activated when there is an insult to the eye, such as increased oxidative stress, and start forming scar tissue, which hinders rather than supports vision. Problems such as diabetes, can increase ROS levels.

ROS are molecules produced through normal body function such as breathing and cells using energy. The body needs a limited amount of ROS to carry out additional functions, such as cell signaling. Problems, from eye disease to cancer, result when the body's natural system for eliminating excess ROS can't keep up and ROS start to do harm, such as cell destruction.

Normally humans have about 125 million night-vision enabling rods intermingled with about 6 million cones that enable us to respond to light and see color.

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