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Overlooked cell key player in preventing age-related vision loss

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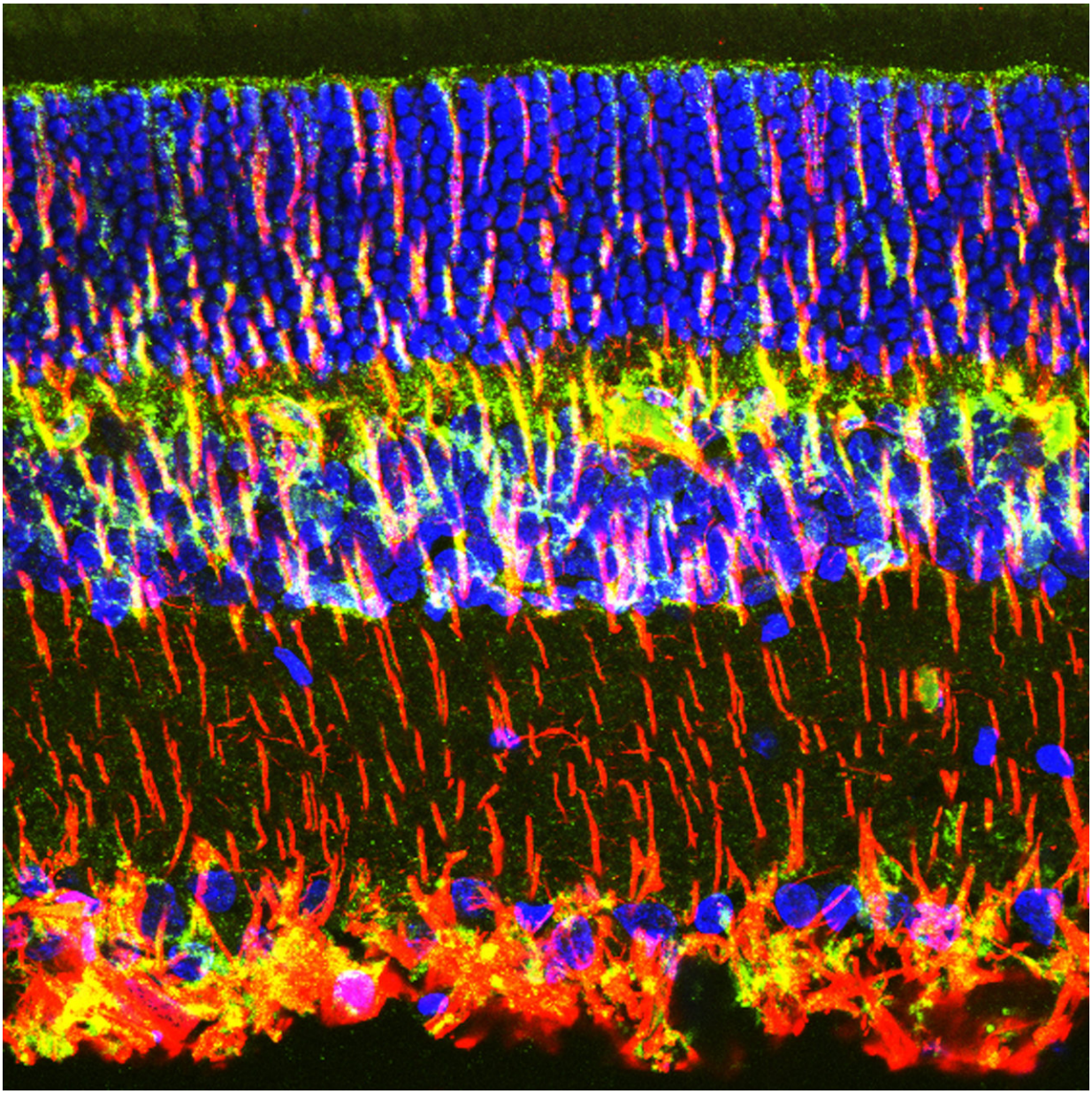

Retinas are built of a stack of neurons that transmit signals from the photoreceptors to the brain. These neurons and the synapses between them are supported by long, tree-shaped cells called Müller glia (in green), which may provide a new therapeutic target for treating degenerative eye diseases. Credit: Sehwon Koh, Duke University

Duke researchers have pinpointed a new therapeutic target for macular degeneration, an eye disease that affects over 10 million Americans and is the leading cause of blindness in adults over 60.

Clinical trials have shown that injection of human umbilical stem cells, or hUTC, into the retina helps preserve and restore vision in macular degeneration patients. However, the underlying mechanisms behind the therapy remain unknown.

The findings, published online in the *Journal of Neuroscience*, show that hUTC treatment preserves the function of a retinal cell called the Müller glia in rats with degenerative vision loss.

"This provides strong evidence that Müller glia are important therapeutic targets for treating degenerative eye diseases," said Sehwon Koh, Ph.D., who is the lead author of this paper and a postdoctoral fellow in the laboratory of Cagla Eroglu, Ph.D., an associate professor of cell biology and neurobiology at the Duke University Medical Center. This research was carried out in collaboration with Janssen Research & Development, LLC.

Retinas are built of a stack of different types of neurons, each connected by synapses that transmit signals from photoreceptors to the brain. Long, tree-shaped cells called Müller glia span the entire thickness of the retina, wrapping their branches around neurons to support their health

and encourage the development of synapses.

Macular degeneration involves both the death of photoreceptor neurons—the classic rods and cones that capture light and convert it into an electric signal—and the loss of neural synapses within the retina.

Though age is the biggest risk factor for macular degeneration, genetics, race and lifestyle choices such as smoking also play a role.

The Duke scientists first examined the retinas of young rats that were genetically predisposed to an eye disease which causes progressive blindness similar to a disorder called retinitis pigmentosa in humans. They found that the neural synapses within the retina began to deteriorate even before the photoreceptors started to die.

As the number of neural synapses declined, the Müller glia also became sickly, pulling their branches away from neurons and dividing haphazardly.

When the researchers injected human umbilical stem cells behind the retinas of these rats, the Müller glia remained healthy, as did the neural synapses. The treatment succeeded in preserving the majority of the rats' vision and stopped the photoreceptors from dying.

"Previous studies primarily focused on neurons and the retinal pigment epithelium cells as culprits in degeneration," said Eroglu, who is also a member of the Duke Institute for Brain Sciences (DIBS). "Müller glia were not considered an important player in the early stages of retinal degeneration and were not thought to be an important target for hUTC treatment, but our findings suggested otherwise."

To test whether the Müller glia were truly the key players in the synaptic loss, the team used a gene-editing technique to remove a specific gene

from Müller glia cells. Deleting this gene is known to cause retinal degeneration, but its function in Müller glia has never been explored.

Without this gene, the Müller glia were defective and bore striking similarities to those in rats that had developed retinitis pigmentosa. In addition, the neural connections within retinas of these rats were malformed, mimicking the problems seen in early stages of retinal degeneration.

"What we are seeing here is that Müller glia are important players in retinal health," Eroglu said. "They are impaired in disease, and effective cellular therapies should target not only other retinal cell types but these cells as well."

More information: Sehwon Koh et al, Subretinal Human Umbilical Tissue-Derived Cell Transplantation Preserves Retinal Synaptic Connectivity and Attenuates Müller Glial Reactivity, *The Journal of Neuroscience* (2018). DOI: 10.1523/JNEUROSCI.1532-17.2018

Provided by Duke University