Researchers discover therapeutic target to aid in glaucoma treatment

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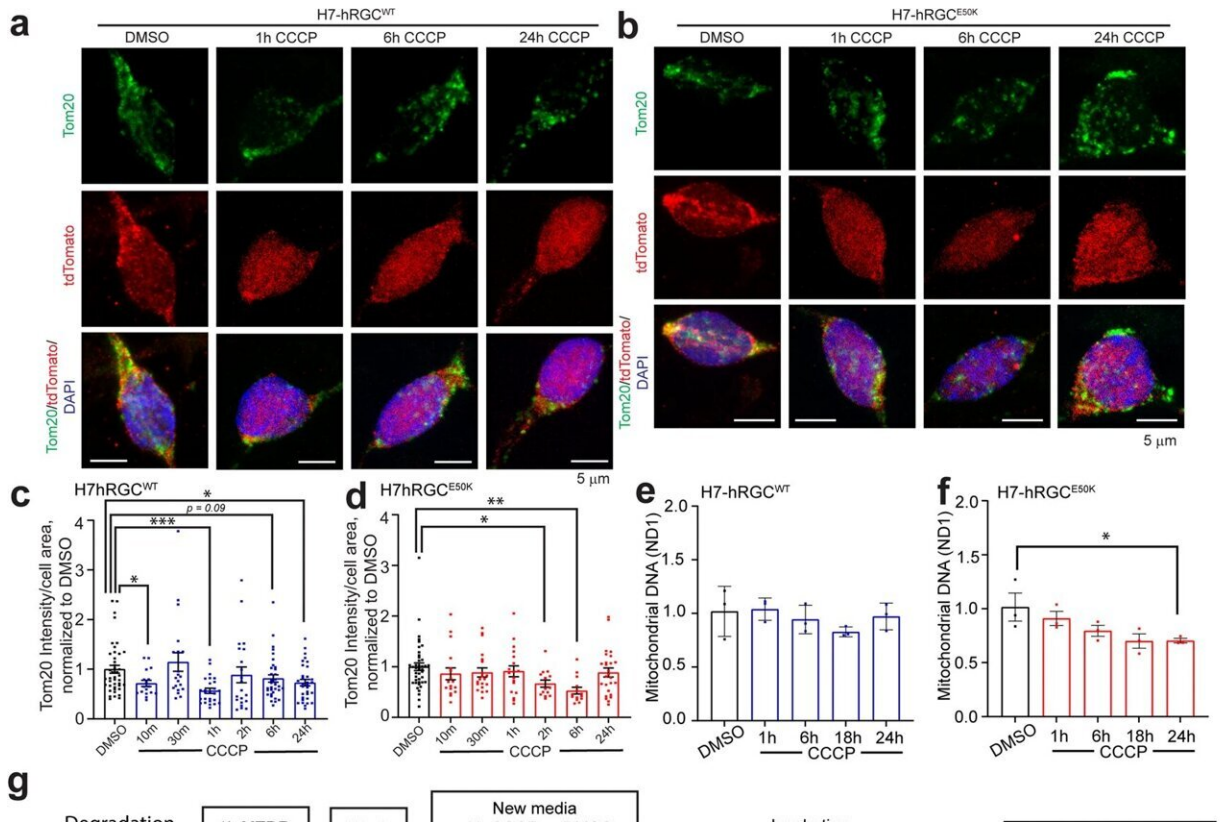

hRGCs maintain mitochondrial mass by simultaneous degradation and biogenesis of mitochondria under damage. **a**, **b** Representative confocal immunofluorescence images of H7-hRGCs against mitochondrial Tom20, tdTomato, and DAPI after indicated 10 µM CCCP treatment timepoints. Scale bars are 5 µm. **c**, **d** Quantification of Tom20 intensity per cell area from sum projections of confocal z-stacks, normalized to corresponding DMSO. *n* = 14–42 cells per condition. **e**, **f** Mitochondrial DNA copy number analyzed by qPCR for mitochondrial ND1 gene relative to nuclear RNase P. Results shown as ΔΔCt

fold changes relative to DMSO control for different times points of 10 μM CCCP treatment. *n* = 3, 3 technical repeats averaged for each biological repeat. **g** Schematic of MTDR flow experiments for tracking degrading versus newly synthesized mitochondria. **h** Mitochondrial mass in single cells at different CCCP (10 μM) treatment time points for degradation or **m** different timepoints post CCCP (10 μM) wash for biogenesis were measured by flow cytometer, and the average fluorescence intensity normalized to DMSO was plotted. *n* = 3. **i**, **k** Representative western blot images of LC3B and actin from **i** $hRGC^{WT}$ and **k** $hRGC^{E50K}$ treated with CCCP (10 μM) for the indicated timepoints. **j**, **l** Quantification of the ratio of LC3B-II to corresponding LC3B-I for each condition. *n*⋆ .3 = *p*-value p-value p-value p-value t-test between independent datasets. Error bars are SEM. Credit: *Communications Biology* (2023). DOI: 10.1038/s42003-023-04576-w

Indiana University School of Medicine researchers have identified a new therapeutic target that could lead to more effective treatment of glaucoma.

Glaucoma is a neurodegenerative disease that causes vision loss and blindness due to a damaged optic nerve. More than 200,000 people are affected by glaucoma in the United States each year. Unfortunately, there is currently no treatment. In a newly published paper in *Communications Biology*, researchers found neurons use mitochondria for a steady source of energy, and restoring mitochondrial homeostasis in the diseased neurons can protect the optic nerve cells from being damaged.

"Age-related neurodegenerative disease, which includes glaucoma, Parkinson's disease, and amyotrophic lateral sclerosis (ALS), is the biggest global health problem," said Arupratan Das, Ph.D., assistant professor of ophthalmology and principal investigator of the study.

"The fundamental mechanisms that we discovered can be used to protect neurons in glaucoma and be tested for the other diseases. We have identified a critical step of complex mitochondrial homeostasis process, which rejuvenates the dying neuron, similar to giving a lifeline to a dying person."

The research team, led by Michelle Surma and Kavitha Anbarasu from the Department of Ophthalmology, used induced pluripotent stem cells (iPSCs) from patients with and without glaucoma as well as clustered regularly interspaced short palindromic repeats (CRISPR) engineered human embryonic stem cells with glaucoma mutation.

Using stem cell differentiated retinal ganglion cells (hRGCs) of the optic nerve, electron microscopy and metabolic analysis, researchers identified glaucomatous retinal ganglion cells suffer mitochondrial deficiency with more metabolic burden on each mitochondrion. This leads to mitochondrial damage and degeneration. Mitochondria are the tube like structures in cells which produce adenosine triphosphate, cell's energy source.

However, the process could be reversed by enhancing mitochondrial biogenesis by a pharmacological agent. The team showed retinal ganglion cells are highly efficient in degrading bad mitochondria, but at the same time producing more to maintain homeostasis.

"Finding that retinal ganglion cells with glaucoma produce more adenosine triphosphate even with less mitochondria was astonishing," Das said. "However, when triggered to produce more mitochondria, the adenosine triphosphate production load was distributed among more mitochondrion which restored the organelle physiology. It is similar to a situation where a heavy stone is carried by fewer people versus a greater number of people—each person will have less pain and injury, just like each mitochondrion will have less difficulty and damage."

In the future, Das would like to test if these mechanisms protect the optic nerve in animal models under injury before testing in humans to hopefully lead to new clinical interventions.

More information: Michelle Surma et al, Enhanced mitochondrial biogenesis promotes neuroprotection in human pluripotent stem cell derived retinal ganglion cells, *Communications Biology* (2023). DOI: 10.1038/s42003-023-04576-w

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