Gene therapy slows vision loss in mouse models of retinal degeneration

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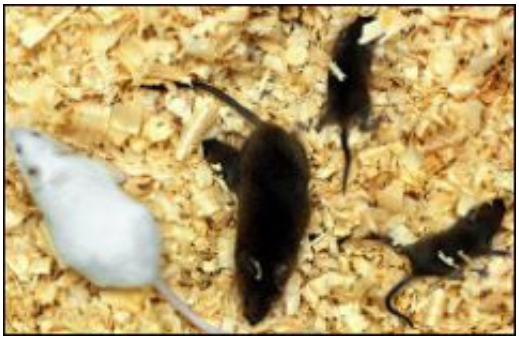

Researchers have developed an antioxidant gene therapy that slows cone-cell death and prolongs vision in mouse models of retinal degeneration.

Led by Harvard Medical School geneticist Connie Cepko and postdoctoral researcher Wenjun Xiong, the research team hopes the work will one day lead to new treatment options for people with inherited progressive blindness, such as retinitis pigmentosa, as well as other diseases involving oxidative damage.

"People who have inherited disease genes that lead to blindness know it's inevitable: They will lose vision. We don't have good therapies in almost any case for them," said Cepko, the Bullard Professor of Genetics and Neuroscience at HMS. "We're studying how these diseases cause

photoreceptor cells to die and whether there's a way to save them."

Photoreceptor cells include the rods and cones that allow us and many other animals, including mice, to sense light and translate it into signals for the brain to interpret. In diseases like retinitis pigmentosa (RP), excess oxygen damages these cells. Cepko and her team investigated whether they could at least slow down, if not prevent, vision loss in laboratory mice by boosting the cells' own antioxidant powers.

"We asked, 'Do the photoreceptors live longer and can the mice see better?'" Cepko said. "We were happy to find that yes, they could. We're excited to explore whether this might work across species and ultimately in humans."

The therapy also slowed the death of retinal ganglion cells in a mouse model of nerve crush injuries, which mimic human conditions such as glaucoma and spinal cord injury. This suggests gene therapy may be useful for combating oxidative damage in different kinds of cells in the eye and beyond, the authors said.

The findings were published March 23 in the *Journal of Clinical Investigation*.

Booster shot

Scientists have seen that oxidative damage occurs in retinal degeneration , but they haven't been able to combat it.

"People have tested small-molecule antioxidant treatments—taking high doses of antioxidants every day—in clinical trials. But the results haven't been really promising," said Xiong, who is first author of the paper.

Such treatments could be failing because the blood-retinal barrier prevents antioxidants from reaching the eye, or for other reasons, said Cepko. Delivering high doses of antioxidants to the whole body also risks side effects, because oxidation plays a role in many normal biological processes.

Cepko's team wanted to develop a therapy that would circumvent those problems. First, they aimed to boost antioxidant activity not by feeding mice antioxidants but by providing extra copies of genes that fight oxidative damage. To achieve this, they delivered those genes (packaged in a viral shell) directly into the mice's eyes.

"This gives us a more directed and potent way to regulate the oxidation," said Cepko.

Three (kinds of) blind mice

The researchers chose three types of laboratory mice, each of which had one of the hundreds of different gene mutations that cause RP in humans. The mice represented fast, moderate and slow rates of retinal degeneration.

The team tested several kinds of antioxidant genes separately and together in each mouse model "to try to save as many cones as possible," said Xiong.

One pair of genes makes enzymes called SOD2 and catalase that sweep out particular reactive oxygen species from cells. Another two genes, Nrf2 and PGC1a, are transcription factors that turn on hundreds of other genes, including many antioxidant genes.

"There are advantages and disadvantages in using the enzymes or the master transcription switches," said Xiong. "As far as we know, there

hasn't been a study before to compare their effectiveness in animal models of human diseases."

Nrf2 worked best. Cone cells lived longer and retained their normal shapes longer in eyes treated with Nrf2 than in untreated eyes. To test whether that meant better vision, the team put the mice in chambers with visual stimuli and tested their reactions.

"Mice that are blind won't respond. Mice with some vision will," said Cepko.

Nrf2 indeed slowed down vision deterioration. At the therapy's peak effectiveness, vision in the mice's treated eyes was twice as good as in the untreated eyes.

SOD2 and catalase combined were also effective. But to the researchers' surprise, PGC1a didn't prolong cone cells' survival. In fact, it accelerated their death.

There is already a large amount of PGC1a in photoreceptor cells. The researchers wonder whether adding more through their gene therapy may have overwhelmed the cells.

None of the treatments was able to cure the mice of their blindness.

Overall, however, "This makes us hope that developing antioxidant gene therapies may be a way to treat human patients," said Xiong.

Nrf2 alone, and SOD2 and catalase together, similarly improved retinal ganglion cell survival in the mouse model of nerve crush.

Of human blindness

The study showed that one gene therapy can work for three different RP mutations in mice. The researchers hope this means it will also work for some or all of the other mutations that cause RP and other retinal degeneration diseases in people—and beyond. That could include neurodegenerative diseases, macular degeneration, spinal cord injury and amyotrophic lateral sclerosis (ALS).

"We think the vectors will probably work to reduce oxidation in any kind of cell," said Cepko.

The therapy has a lot going for it. The viral shell used to deliver the genes, adeno-associated virus or AAV, has been shown to be safe for use in human eyes.

Still, it takes many steps to translate findings from mice to people.

"Mice have a short lifespan and rapid onset of blindness; they're protected for a couple of months. Humans need protection over decades," said Cepko. "I don't know how to extrapolate from the time span we saw in the mouse to what we'd like to see in humans."

Human eyes are also 10 times bigger than mouse eyes. And timing of delivery will have to be tested. Most people don't know they have retinal degeneration until their rods are already dead and their cones are dying.

Cepko and team are looking at other strategies they can combine with antioxidant gene therapy, such as optogenetic therapy or stem cell therapy.

"My gut feeling is we will need a combination therapeutic to give long-lasting photoreceptor survival," she said. "It will be a long road, and it will take more basic science to figure out which genes and which animal models to use."

More information: "NRF2 promotes neuronal survival in neurodegeneration and acute nerve damage" *J Clin Invest.* DOI: 10.1172/JCI79735

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