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Starving Cells May Be Responsible for Loss of Color Vision in Retinitis Pigmentosa

Even when a person experiences starvation, he doesn't think to start eating himself. But that's exactly what cells do when they are starved. Now, Howard Hughes Medical Institute researchers report that one of the reasons that the cells responsible for color vision die off in people with retinitis pigmentosa may be that the cells nibble themselves to death when starved of nutrients.

This finding helps to explain what drives the disease, which affects about one in 3,000 people in the United States. It also points toward possible new treatments, said Constance Cepko, an HHMI investigator at Harvard Medical School. Cepko is the senior author of a December 7, 2008, *Nature Neuroscience* article describing the research. Claudio Punzo, a postdoctoral fellow in Cepko's lab, performed most of the experiments described in the article.

In their experiments, Punzo and Cepko tracked changes in the retinal cells and some of the biochemical events that might lead to the death of rod and cone cells in genetically engineered mice that have a disease similar to retinitis pigmentosa. Rods and cones are specialized light-sensitive nerve cells that line the retina. They collect light and then send nerve signals that the brain interprets as vision. Rods mediate black and white vision and are used mainly at night. During the day, humans depend on cones for color vision.

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- Constance L. Cepko

In people with the genetic mutations that cause retinitis pigmentosa, rods and cone cells die. Usually the rods die first and the cones die later, leading to severe vision impairment. "People can get by reasonably well without rods," said Cepko. "They just don't have night vision. The real loss of quality of life happens when the cones die. The cones are the cells we use in bright

light--they give us color vision and they give us high acuity vision.”

In most cases of retinitis pigmentosa, the inherited genetic defects that cause the disease are only seen in the rod cells. That is, the cone cells don't need the genes that have been mutated. So researchers did not understand why the cone cells also die. “Yes, it's true their neighbors--the rods--are dying,” said Cepko. “That doesn't necessarily mean they have to die too. But they do.”

To find out why, Punzo and Cepko studied four different strains of genetically engineered mice. Each strain develops retinitis pigmentosa at a different rate, but each loses its rods before losing its cones. The researchers looked for commonalities in the retinas of the four types of mice, trying to find molecular changes that stood out as the cones began to die.

“We asked, ‘What features do these four different mutant mice have in common when cones are starting to die?’ It's a needle in the haystack question, and we were hoping we could make the haystack a little smaller,” said Cepko.

The researchers used RNA microarrays to measure how much of each gene is expressed inside the cone cells. With the help of Karl Kornacker at Ohio State University, who performed some of the statistical analyses, they found that genes involved in basic cellular metabolism started to go haywire as the cones began to die. In particular, they noticed changes in a lynchpin complex called mTOR--a group of proteins that acts as a hunger gauge for the cell. Clues from mTOR and related genes told the researchers that the cone cells were starving. They likely lacked glucose, and in turn they began to eat themselves, a process called autophagy.

“The cell is hungry and it doesn't have enough nutrition. So it goes through a self-digestion process,” said Cepko. “That's sort of a last ditch effort. Cells can't do that for very long, or they'll die.”

To see if they could reverse the death of cone cells, the researchers gave some of the mice extra insulin, a signal that tells cells there's plenty of glucose around. As a comparison, they depleted insulin in other mice. The cone cells survived longer than usual in the mice that received extra insulin, and those cells died faster in the mice lacking insulin. These experiments suggested that the researchers were on the right track and that the cone cells' lack of nutrition might lead it down a self-destructive path, said Cepko.

Despite the results of these studies, Cepko is not proposing that insulin injections should be a treatment for retinitis pigmentosa. This is because the cone cells die eventually, even in mice given extra insulin. “Insulin temporarily fools the cells and maybe slows down their self-digestion,” said Cepko. “The cells live a little longer, but the long-term problem--the lack of nutrition--has not been addressed.”

Cepko thinks that other co-factors, such as oxygen radicals, may also contribute to the death of the cone cells. “Our evidence points toward lack of nutrition being a major problem in the cone cells,” she said. “But until we can actually save the cones by addressing the nutrition problem--and save them in a real long-term way--I can't know how important it is relative to other possible factors.”

Cepko's lab is now trying to sort out why the cone cells don't receive the nutrition they need. They're focusing on a structure called the retinal pigment epithelium, which contains cells that feed nutrients to rods and cones. When the rod cells die--there are many more rods than cones-- the support cells of the retinal pigment epithelium collapse and become misshapen. This may explain the fundamental nutrition problem, said Cepko.

She hopes that other researchers take note of their findings. “The exciting thing for us is that this is a new idea, these are new therapeutic targets that could lead to new treatments,” she said.