

Progression of retinal disease linked to cell starvation

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Rods and cones coexist peacefully in healthy retinas. Both types of cells occupy the same layer of tissue and send signals when they detect light, which is the first step in vision. The incurable eye disease Retinitis Pigmentosa, however, reveals a codependent relationship between the two that can be destructive. When flawed rods begin to die, otherwise normal cones follow them to the grave, leading to blindness. A new study might explain why.

Data published online in *Nature Neuroscience* Dec. 7 suggest the cones are starving to death. As rods disappear, the structure of the retina breaks down. This might disrupt the connections between the cones and their source of nutrients.

"This is the first study linking cone death in Retinitis Pigmentosa to a metabolic problem that suggests starvation," says senior author Constance Cepko, an HMS professor and investigator with Howard Hughes Medical Institute. "If we can find a way to supply nutrients to the cones, we might be able to preserve daylight vision in patients."

Active in bright light, cones allow us to perceive color and fine details. Conversely, rods allow us to see in dim light. The untrained eye cannot distinguish between the two types of cells, which grow side-by-side. Both rods and cones have a protrusion that has many membranous discs, resembling a stack of cookies. A cone stack is half the height of a rod stack. Stacks emanating from both types of cells get clustered together, like Oreos on a plate. The entire plate gets covered in "plastic," with the

flexible plastic reaching down to touch each stack. In the eye, this plastic consists of a giant retinal pigment (RPE) cell, which supplies nutrients to the rods and cones on its plate.

With this structure in mind, researchers have proposed a variety of hypotheses to explain the loss of cones in patients with mutations in rod-specific genes. For example, some teams have suggested that rods produce a chemical cones need to survive. But the data didn't quite fit the proposed models.

Cekpo's team took a fresh approach to the problem. Postdoctoral researcher Claudio Punzo gathered four strains of mice, each with a different rod-specific mutation and a different rate of disease progression. He discovered an interesting pattern. Cone death always began after the major phase of rod death.

Punzo analyzed gene expression before and after this point in each strain. During the cone death phase, 230 genes were always expressed at higher levels. Sleuthing revealed that 34.9 percent of those play a role in cellular metabolism, including 12 genes in the insulin/mTOR pathway.

mTOR serves as a signaling hub, gathering information about the environment and helping the cell to decide whether it has enough nutrients to make new proteins. Punzo now had a lead. Further experiments suggested the cones weren't getting enough glucose. Not only did they express high levels of a protein that allows the cell to take up more glucose, but the cones survived longer when Punzo tricked them into thinking they had enough glucose by injecting the mice with insulin.

"Apparently, the cones caught onto our trick," says Punzo. "After surviving longer than usual, they started to die in droves."

Cepko and Punzo say the new hypothesis makes sense. Rods outnumber

cones by more than 20 to 1. The RPE cells sag when too many rods disappear, as the plastic over that plate of Oreo cookies droops when too many stacks are missing. The structural change likely disturbs the contacts between RPE cells and cones, impeding the flow of nutrients to the cones.

"This points us in a new direction," says Cepko. "We're currently exploring ways to boost nutrient levels in the cones. Perhaps someday we can help Retinitis Pigmentosa patients maintain their daylight vision for at least a bit longer than they otherwise would."

Source: Harvard Medical School

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