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Retinal photoreceptors use dual pathways to tell brain 'I've seen the light'

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Working with mammalian retinal cells, neuroscientists at Johns Hopkins Medicine have shown that unlike most light-sensing cells (photoreceptors) in the retina, one special type uses two different

pathways at the same time to transmit electrical "vision" signals to the brain. The work also reveals that such photoreceptors, according to the researchers, may have ancient origins on the evolutionary scale.

This and other findings, published in *PNAS*, "shed scientific as well as literal light" on a decades-long mystery about how such cells work, the researchers say.

The new research was co-led by King-Wai Yau, Ph.D., professor in the Department of Neuroscience at the Johns Hopkins University School of Medicine, and postdoctoral fellow Guang Li. King's previous work led to advances in understanding how light-sensing cells in the mammalian eye transmit signals to the brain, findings that may eventually help scientists learn why people without sight can still sense light.

In animals, including humans, photoreceptors (light-sensing cells) called rods and cones are located in the retina, a tissue layer at the back of the eye that responds to light. The rods and cones analyze visual signals that are transmitted via electrical signals to the brain, which interprets what is "seen."

Another type of photoreceptors in the retina, called intrinsically-photosensitive retinal ganglion cells (ipRGCs), use long protrusions (axons) that form the optic nerve to convey visual signals from rods and cones. The ipRGCs also perform other functions, such as setting the body's light-driven circadian rhythms and distinguishing contrast and color.

It has been known that photoreceptors in animals detect light by using a signaling pathway named for the cell's origin. Photoreceptors of "microvillous" origin, similar to those in the fruit fly eye, use the enzyme phospholipase C to signal light detection—whereas photoreceptors of ciliary origin, such as those in our rods and cones, use a cyclic-nucleotide

pathway.

To signal light detection, most photoreceptors use either the microvillous or ciliary pathway, not both. However, in experiments to further understand how ipRGCs work, Yau's team found that ipRGCs use both pathways at the same time.

The researchers discovered this by exposing ipRGCs to brief pulses of bright light. In those conditions, the microvillous signaling pathway produces faster electrical responses and precedes, with some overlap, a slower response by the ciliary pathway.

Yau's team found that all six subtypes of ipRGCs use both microvillous and ciliary signaling mechanisms—although at different percentages—at the same time.

The Johns Hopkins team also found that while most photoreceptors using the ciliary signaling pathway use a particular cyclic nucleotide, cGMP, as the signaling messenger, ipRGCs use another, cAMP, which is similar to that of jellyfish, an animal much older on the evolutionary scale. This suggests that ipRGCs may have an ancient origin.

Other Johns Hopkins researchers who contributed to this study are Lujing Chen and Zheng Jiang.

More information: Guang Li et al, Coexistence within one cell of microvillous and ciliary phototransductions across M1- through M6-IpRGCs, *Proceedings of the National Academy of Sciences* (2023). DOI: 10.1073/pnas.2315282120

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