Roundworms offer new insights into Bardet-Biedl syndrome

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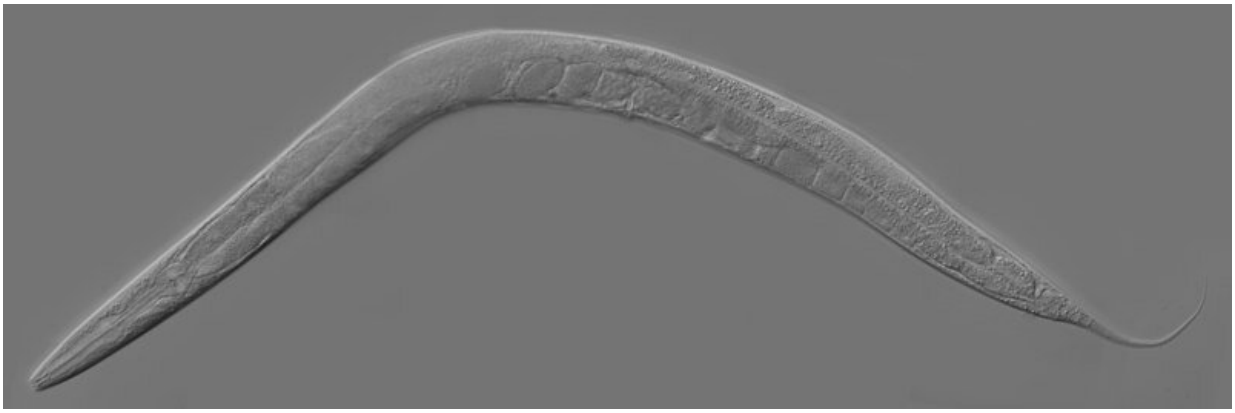

Caenorhabditis elegans. Credit: Kbradnam/Wikimedia Commons, CC BY-SA 2.5

Scientists have identified a new role for a protein complex at the center of a human genetic disorder called Bardet-Biedl syndrome, or BBS, for which there is currently no cure.

Bardet-Biedl syndrome arises when the BBSome protein complex malfunctions. Because the BBSome regulates the form and function of cilia, the hair-like structures on the surface of cells, BBS has been classified as a disease of the cilia.

But the wide spectrum of symptoms associated with BBS—the most

common of which is vision loss, as well as obesity, extra fingers or toes and kidney malfunction—have led to hypotheses that the cause of the syndrome may not lie solely within the cilia.

In a new study published in *Developmental Cell*, a team from the University of Michigan Life Sciences Institute now offers the first known direct evidence for these hypotheses. Their findings demonstrate that the BBSome operates outside of cilia to support sight, at least in one common model species.

The discovery began when scientists in the lab of LSI faculty member Shawn Xu were investigating how tiny roundworms called Caenorhabditis elegans can sense light despite having no eye-like organs. Because C. elegans have a simple and well-mapped nervous system, the Xu lab uses them as a model to understand the fundamental biology behind various forms of sensation.

The team performed a genetic screen, a process of introducing random mutations to identify which genes are required for a given biological process, to find the genes involved in the worms' ability to respond to light. Most of the mutations that caused worms to stop sensing light turned out to be in the BBSome. And, like the progressive vision loss that BBS patients experience, the worms with BBSome mutations progressively lost the ability to sense light as they aged.

Through a series of several more experiments, the team discovered that the BBSome plays a role in light sensation independent of its role in the cilia. In one scenario, they mutated C. elegans to remove all cilia; in a second experiment, they left the cilia on the worms but prevented the BBSome from getting to the cilia. In both cases, the worms were still able to sense light, so long as the BBSome functioned in the rest of the cell.

"It's a great demonstration of the power of model organisms," said Xinxing Zhang, a postdoctoral researcher in the Xu lab and the study's lead author. "Cilia are essential for most organisms. But we can remove cilia from the C. elegans and they still survive, allowing us to uncover this unexpected role for the BBSome completely independent of the cilia."

Xu's lab previously discovered that C. elegans sense light through a receptor protein called LITE-1 that sits at the surface of neurons and sends signals to the central nervous system to respond to the light (in the worms' case, by moving away from it).

In this latest study, the team found that when BBSome malfunctions within the cell, LITE-1 receptors are pulled back into the cell from the surface and then broken down, preventing the worms from sensing light.

In a second genetic screen, the scientists discovered that the process of degrading LITE-1 is controlled through another protein called DLK. The BBSome prevents DLK from starting a chain reaction that inappropriately breaks down LITE-1.

Both BBSome and DLK are conserved in humans, and the researchers were able to show that BBSome similarly blocks DLK expression in human cells. They believe that this BBSome–DLK–photosensor pathway could be involved in the vision loss that is so prominent in patients with Bardet-Biedl Syndrome.

"Because BBS is known to be caused by defects in the BBSome, there has been a longstanding assumption that the disorder must be tied to the cilia," said Xu, who is also a professor of molecular and integrative physiology in the U-M Medical School. "We are not disputing that BBS is tied to defects in the cilia. We are just offering direct evidence that the BBSome can also function outside of cilia, and it has a role there

related to light sensation. Perhaps this can broaden the view of how to develop treatments for BBS."

More information: A cilia-independent function of BBSome mediated by DLK-MAPK signaling in C. elegans photosensation, *Developmental Cell* (2022). DOI: 10.1016/j.devcel.2022.05.005. www.cell.com/developmental-cel … 1534-5807(22)00333-1

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