Different means to the same end: How C. elegans protects its chromosomes

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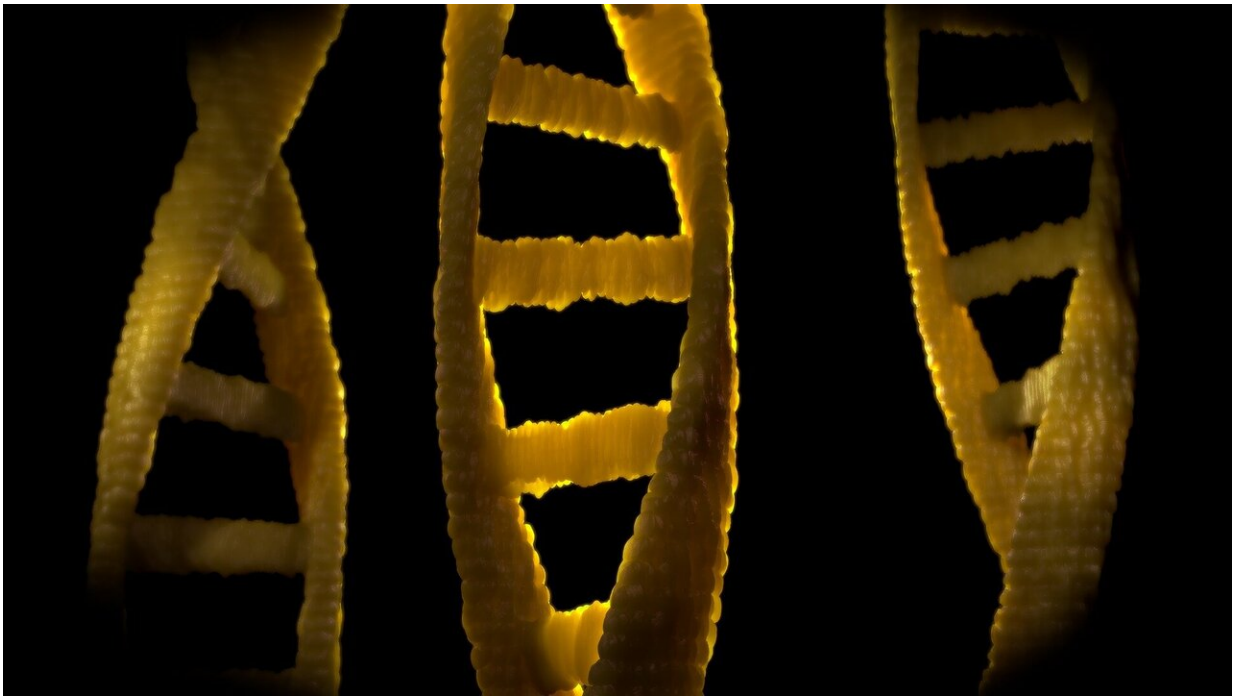

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University of Michigan researchers have discovered that a worm commonly used in the study of biology uses a set of proteins unlike those seen in other studied organisms to protect the ends of its DNA.

In mammals, shelterin is a complex of proteins that "shelters" the ends of our chromosomes from unraveling or fusing together. Keeping

chromosomes from fusing together is an important job: chromosomes carry our body's DNA. If chromosome ends fuse, or if they fuse with other chromosomes, the cell that houses these chromosomes dies.

But not all organisms use the same kinds of proteins to form shelterin. The worm C. elegans has been a powerful model for understanding many types of biological processes, says Jayakrishnan Nandakumar, U-M professor of molecular, cellular, and developmental biology.

Until recently, however, scientists had not identified the proteins that protect the double-stranded DNA ends of their chromosomes, called telomeres. In 2021, Nandakumar's collaborator Hiroki Shibuya and another group independently discovered that proteins in C. elegans, called TEBP-1 and TEBP-2, protected the worm's telomeric ends.

Still, researchers hadn't yet unraveled all of the mysteries of C. elegans shelterin. Proteins can have several parts to them, with each part performing a different function, Nandakumar says. These parts are called "domains," which are named after the function they perform. Researchers weren't sure which domain allowed one TEBP-1 or TEBP-2 molecule to bind to another copy of itself and then which domain bound the proteins to chromosome DNA to help protect it.

Now, Nandakumar and his team have identified the specific domains within TEBP-1 and TEBP-2 proteins that allow them to perform their biological functions. Their findings are published in the *Proceedings of the National Academy of Sciences*.

"There are different means to achieve the same end (the pun is intended). In other words, because of our focus on mammalian telomeres, we tend to bias ourselves in thinking 'our way' is the right way or the only way to solve problems in the cell," he said. "However, the C. elegans example shows us that there are multiple ways to solve the end

protection problem and some of them might be quite different from how humans do it. But as long as they are effective, they are selected for in evolution."

Nandakumar says to think of chromosomes as a shoelace. The ends of your shoelace are coated with a hard plastic shell called an aglet, which protects the lace from unraveling. Humans—and all mammals—have a certain set of proteins that are the primary components of shelterin, the "aglet" of the chromosome.

"Think of these proteins as the plastic aglet that coats the ends of chromosomes to protect them from degradation and preserve their integrity," Nandakumar said. "In C. elegans, TEBP-1 and TEBP-2 protect the chromosome ends."

Now, these proteins, both in mammals and in C. elegans, need a way to bind to each other and then to bind to the chromosome so that they can effectively coat the chromosome end. They do this using what's called a dimerization domain as well as a DNA binding domain part (when two identical protein molecules bind together, researchers say they "dimerize"). In mammals, a domain called "TRFH" dimerizes these proteins, and a different domain called the "myb" domain coats the chromosome ends.

Researchers hadn't yet identified the C. elegans TEBP-1 or TEBP-2 dimerization and DNA binding domains because they were looking for a protein in C. elegans that shared a similar amino acid sequence to the human protein domains—that is, they were looking for a homolog of those proteins. But there wasn't one.

Instead, C. elegans has three copies of something else, something that looks similar to the myb domain on the mammalian proteins. So the research team called them "myb-containing domain," or MCD 1, 2 and

3. A single protein of TEBP-1 and TEBP-2, then, includes three segments: MCD1, MCD2 and MCD3.

The researchers further found that only MCD3 binds DNA. MCD1 and MCD2 look like a DNA binding domain, but instead bind together molecules of TEBP-1 and TEBP-2. MCD1 in one protein binds to MCD1 in the next protein and MCD2 binds to MCD2, allowing the proteins to link up to surround the ends of the chromosomes.

To connect the protein complexes to the telomeres, MCD3 binds to the chromosome DNA. This whole protein is repeated around the entire long end of the chromosome.

Nandakumar says that because you can perform biochemistry and genetics readily with C. elegans, understanding the protein complexes that protect its telomeres will help researchers use it as a model organism for studying telomere biology.

"Protecting the telomeres of your DNA—every eukaryote has to do it, meaning that a worm has to somehow figure that out. Humans have to figure it out. Yeast has to figure it out. It's a universal problem," Nandakumar said.

"Generally, in evolution, you would use that same strategy in different species. If something is working, if you have a solution to a problem, why not reuse it? I think the cool thing is, you can have multiple solutions to the problem."

More information: Nandakumar, Jayakrishnan et al, Caenorhabditis elegans telomere-binding proteins TEBP-1 and TEBP-2 adapt the Myb module to dimerize and bind telomeric DNA, *Proceedings of the National Academy of Sciences* (2024). DOI: 10.1073/pnas.2316651121. doi.org/10.1073/pnas.2316651121

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