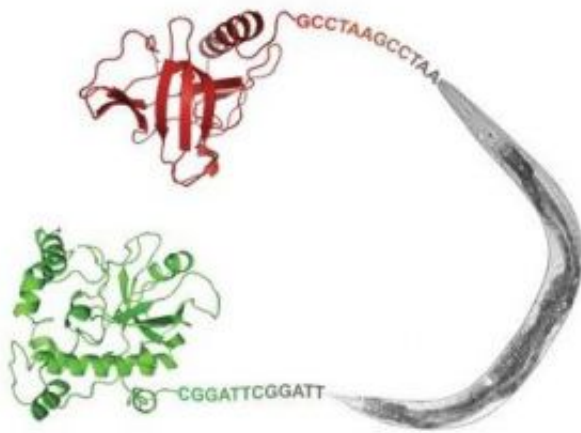


How worms protect their chromosomes: Thereby hangs a surprising tail

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Artistic rendering of *C. elegans* telomeres. Unlike mammals, the tiny roundworm protects the tips of its chromosomes with two different motifs. Credit: Courtesy of Dr. Jan Karlseder, Salk Institute for Biological Studies

A team of scientists at the Salk Institute for Biological Studies has discovered that the roundworm *C. elegans* constructs the protective tips of its chromosomes — known as telomeres — with a little more panache than do mammals, a finding that could deepen our understanding of the interrelationship of aging and cancer.

In a study reported in March 7 issue of the journal *Cell*, researchers in the laboratory of Jan Karlseder, Ph.D., Hearst Endowment Associate Professor of the Molecular and Cell Biology Laboratory, showed that

unlike mammals, who normally terminate both ends of every chromosome with a string of DNA rich in the base guanine (G), *C. elegans* can also decorate a telomere with a different motif, a strand abundant in the base cytosine (C).

Karlseder says discovering this deviation from the standard G-tail issued to mammals was completely unanticipated. “Telomeres protect the ends of chromosomes like a glove,” he said. “In mammals telomeres have a single-stranded overhang with a TTAGGG sequence about 150 bases long. We found that in worms there can also be a single-stranded overhang of a C-containing strand.”

Safeguarding the ends of linear chromosomes is essential for any animal’s survival. “Telomere loss can lead to chromosome fusion,” explained Karlseder. “If that happens when a cell divides its chromosomes could randomly break, leading to a condition known as genome instability, a major cause of cancer.”

Telomeres are the object of intense investigation because these structures represent the physical link between cancer and aging research. Normally, telomeres shorten as cells divide, acting as a kind of cellular clock ticking down a cell’s age: when they shorten to a critical point the cell dies. However, in cancer, the clock runs backwards and telomeres aberrantly elongate, turning what could be a cellular fountain of youth into a potential malignancy.

Karlseder and lead author Marcela Raices, Ph.D., discovered the unique C-tails in collaboration with Andrew Dillin, Ph.D., associate professor in the Molecular and Cell Biology Laboratory. The team first found that not only did worm telomere tails come in two flavors but that each was uniquely attached to the chromosome. Double-stranded DNA terminates with mirror-image ends, like right and left hands. In mammals, G-tails extend from the “right hand”— or 5’ end. But worm C-tails hung off the

DNA “left hand” or 3’ end.

They then identified two novel worm proteins that bound preferentially to either C- or G-tails. They capped the study by showing that worms lacking either protein exhibited abnormal telomeres, suggesting that each protein — like a somewhat similar protein found in mammalian cells — is part of the machinery regulating the length of C- or G-tailed telomeres.

Using roundworms enabled the experimenters to streamline analysis of these proteins in an animal. “*C. elegans* is an established model to study aging,” said Karlseder. “We can screen the whole worm genome relatively cheaply in a few months. The same experiment in human cells would take years and probably ten times the money. We want to exploit the *C. elegans* system and then translate our findings into a human system.”

Raices, a postdoctoral fellow in both the Karlseder and Dillin labs, also praises worms as a model system. “We think that experiments in *C. elegans* will allow us to study differences in telomere replication and processing, questions that have been extremely challenging to investigate in human cells. Telomere regulation is extremely important in many human cancers.”

An obvious question now emerging from the study is whether C-tails are unique to worms or whether they have been overlooked in mammals. “It is premature to think that C-tails do not exist in human cells,” said Karlseder. “We may find them in mammalian cells under certain circumstances, and if so, they could play a role in telomere maintenance and in cancer.”

In fact, some investigators propose to stop a cell from becoming cancerous by blocking the enzyme that synthesizes telomeres. Karlseder

emphasizes that knowing every strategy used by cells to build a telomere is necessary for that approach to work. “Many people in the field think of the overhangs as the most important part of a telomere,” he said. “If we knew how those overhangs were generated and maintained, we could exploit this for cancer therapy.”

Source: Salk Institute

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