Research shows how protein component that enables cell replication gets ferried to chromosome tips

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Stem cells are special. Nestled in muscle and skin, organ and bone, they bide their time over years or decades until called to replace damaged or lost tissue. One secret to their longevity is an enzyme called telomerase, which stills the relentless ticking of the molecular clock that limits the life span of other cells.

This cellular fountain of youth prevents the progressive shortening of the tips of our chromosomes that occurs with each cell division. But the presence of telomerase can be a double-edged sword: The same activity that ensures long life for stem cells can also keep a cancer cell dividing long after its aging neighbors have thrown in the towel. Conversely, a malfunction can prevent stem cells from doing their job and lead to devastating diseases.

Now, for the first time, researchers at the Stanford University School of Medicine have identified how telomerase is recruited to chromosome ends — and figured out a way to block it.

"If telomerase is unable to maintain the ends of the chromosomes, cells will stop multiplying," said professor of medicine Steven Artandi, MD, PhD. "This would be advantageous in cancer cells, but in normal stem cells it can cause severe dysfunction and lead to diseases such as pulmonary fibrosis, aplastic anemia and a genetic condition called dyskeratosis congenita. We want to understand how telomerase works,

and to develop therapies for cancer and these other diseases."

Artandi is the senior author of the research, which will be published Aug. 3 in *Cell*. He is also a member of the Stanford Cancer Institute. Graduate student Franklin Zhong is the first author of the study.

Telomerase is normally expressed in adult stem cells and immune cells, as well as in cells of the developing embryo. In these cells, the enzyme caps off the ends of newly replicated chromosomes, allowing unfettered cell division. Without telomerase, cells stop dividing or die when the ends — called telomeres — fall below a minimum length. Unfortunately, the enzyme is also active in nearly all cancer cells.

Earlier research in Artandi's lab identified a protein called TCAB1 that brings the telomerase complex (actually a large clump of many proteins) to a processing area in the cell's nucleus called a Cajal body. But no one knew how the complex was then ferried to the ends of telomeres, and research was stymied by the complex's large size, multiple components and relative scarcity.

"This problem has been really intractable," said Artandi. "The enzyme is extremely hard to study. But we've now found that telomerase is recruited to the telomeres through an interaction with a protein called TPP1 that coats the ends of chromosomes." What's more, the researchers have identified the exact region of TPP1 to which telomerase binds — a section called an OB-fold.

"When we mutated this site in TPP1," said Artandi, "we blocked the interaction between the two proteins and prevented telomerase from going to the telomeres. And when we interfered with this interaction in human cancer cells, the telomeres began to shorten." The researchers are now assessing whether the life span of the cancer cells, and their ability to divide unchecked, will also be affected by the treatment.

To confirm their finding, Artandi and his colleagues used cells from patients with pulmonary fibrosis — a debilitating scarring or thickening of lung tissue associated with telomerase mutations. The disease had been troubling to researchers and clinicians, however, because the patients' mutated telomerase seemed to be fully active when tested in the laboratory. Zhong and Artandi found that the disease-associated mutations occurred in the portion of telomerase that interacted with TPP1, and interfered with their binding. As a result the enzyme, although active, couldn't get to where it was needed.

"It was impossible to even begin to understand this mechanism before we knew how these two molecules interact," said Artandi. "But now that we're getting a handle on this, we can begin to think about developing inhibitors — maybe in the form of peptides or small molecules — that can mimic this disruption. This could be very valuable in cancer therapies."

Provided by Stanford University Medical Center

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