Featured Highlight

Landmark Study Opens Door to New Cancer, Aging Treatments

Researchers at The Wistar Institute used the NSLS to decipher the structure of the active region of telomerase, an enzyme that plays a major role in the development of nearly all human cancers. The landmark achievement opens the door to the creation of new, broadly effective cancer drugs, as well as anti-aging therapies.

Researchers have attempted for more than a decade to find drugs that shut down telomerase—widely considered the No. 1 target for the development of new cancer treatments—but have been hampered in large part by a lack of knowledge of the enzyme's structure.

The findings, published online August 31 in *Nature*, should help researchers in their efforts to design effective telomerase inhibitors, says Emmanuel Skordalakes, assistant professor in Wistar's Gene Expression and Regulation Program, who led the study.

"Telomerase is an ideal target for chemotherapy because it is active in almost all human tumors, but inactive in most normal cells," Skordalakes says. "That means a drug that deactivates telomerase would likely work against all cancers, with few side effects."

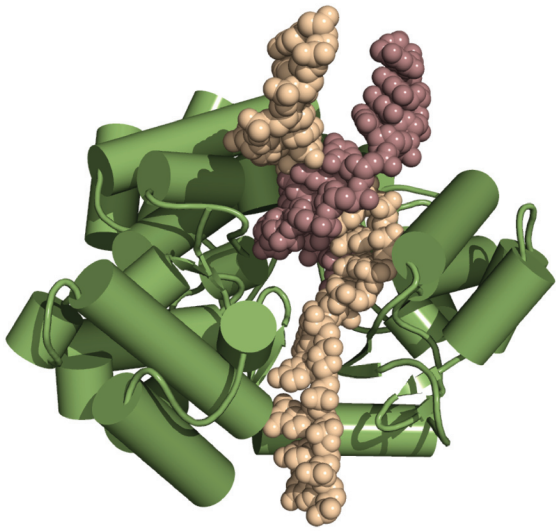
The study elucidates the active region of telomerase and provides the first full-length view of the telomerase molecule's critical protein component. It reveals surprising details, at the atomic level, of the enzyme's configuration and how it works to replicate the ends of chromosomes—a process critical to both tumor development and the aging process.

Achieving immortality

In humans, telomerase adds multiple repeats of a short DNA sequence to the ends of chromosomes, known as telomeres, thus preventing damage and the loss of genetic information during cell division.

When telomerase is dormant, telomeres shorten each time a cell divides, leading eventually to genetic instability and cell death. By preserving chromosomes' integrity, telomerase allows cells to continue living and dividing. The enzyme is active in cells that multiply frequently, such as embryonic stem cells, but is switched off almost entirely in normal adult cells to prevent the dangers of runaway cell proliferation.

Cancer cells, however, often regain the ability to activate telomerase, which has been implicated in 90 percent of human tumors. The enzyme permits cells to replicate indefinitely and achieve the cellular "immortality" that is the hallmark of cancer. Deactivating telomerase would stop tumor growth.



Model of the atomic structure of telomerase, solved by Emmanuel Skordalakes, Ph.D., a researcher at The Wistar Institute. Shown are the molecule's protein component (in green) in complex with RNA (in beige) and DNA (in red). (Image courtesy of The Wistar Institute)

In addition to its role in cancer, telomerase holds significant implications for the development of therapies to combat aging and other age-related diseases. Finding ways to activate telomerase under controlled conditions and allow some cells to begin dividing again could result in healthier, younger-looking tissue that lives longer.

An elusive enzyme

Telomerase is a complex structure made up of multiple protein domains and a stretch of RNA, which contains the template the enzyme uses to synthesize telomeres.

Last year, Skordalakes and his team solved the structure of a key segment of the molecule—the so-called TRBD domain, where RNA binding occurs. However, the complexity of telomerase has proved a roadblock to determining the enzyme's overall architecture—a goal pursued by researchers worldwide for more than 15 years.

To perform the necessary studies, scientists first must gather large quantities of the enzyme in a specific conformation. Because the complex structure of telomerase most likely allows it to change configuration, that process has been challenging, Skordalakes says.

To find sufficient quantities of the enzyme for the study, Skordalakes and his team looked beyond commonly relied-on sources such as humans and yeast. By screening a wide variety of organisms, including protozoa and insects, they discovered that a gene from the red flour beetle could produce telomerase in copious amounts, and a stable form.

"That was really the breakthrough," Skordalakes says. "Once we found that the gene from this organism expressed the protein in the quantities we needed, we were able to move quickly."

The researchers used x-ray crystallography at NSLS beamline X6A, a technique that analyzes the diffraction patterns of x-rays beamed at crystals of a molecule, to determine the three-dimensional structure of the enzyme's active region—the catalytic component called telomerase reverse transcriptase protein, or TERT.

The study revealed surprising features, including the fact that the molecule's three domains are organized into a doughnut shape, an unexpected configuration. Knowledge of the structure allowed the researchers to create a model of the enzyme's function.

"It's extremely exciting," Skordalakes says. "For the first time, we can see how telomerase assembles at the end of chromosomes to initiate telomere replication."

Looking ahead

Skordalakes plans to further study TERT and search for new telomerase inhibitors that could become cancer therapies. He also will look at modifying existing drugs. Previous attempts to target telomerase have fallen flat, but knowledge of the enzyme's structure will help researchers to determine the limitations of existing agents and make them more effective.

Skordalakes began his studies of telomerase when he joined The Wistar Institute in 2006 and established his first laboratory. "I've always been interested in understanding, on a molecular level, the function of protein nucleic acid assemblies and using that information in the treatment of human disease," he says. "Telomerase, because of its important role in cancer and aging, was an obvious target for me."

He says though the process was frustrating at times, his team was determined to solve the structure. "It required a lot of perseverance and effort, but we really wanted to do this," he says.

Wistar's Andrew J. Gillis and Anthony P. Schuller assisted with the study.

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