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Telomerase enzyme structure provides significant new target for anti-cancer therapies

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Inappropriate activation of a single enzyme, telomerase, is associated with the uncontrollable proliferation of cells seen in as many as 90 percent of all of human cancers. Since the mid-1990s, when telomerase was first identified in human tumors, scientists have eyed the enzyme as an ideal target for developing broadly effective anti-cancer drugs.

Now, researchers working at The Wistar Institute have brought this goal closer by deciphering the three-dimensional structure of a domain, or region, of the telomerase molecule essential for the activity of the enzyme. The findings, published November 13 in the journal *Structure*, may help scientists develop strategies to design the first direct inhibitors of telomerase.

Telomerase also has been shown to play a central role in normal aging, and the new study may shed light on that vital life process as well. The potential for creating new cancer treatments, however, is the most important immediate implication of the study.

“Knowing the physical structure of this complex will give pharmaceutical companies a direct target for designing drugs that disrupt a mechanism that telomerase uses to assemble itself,” says Emmanuel Skordalakes, Ph.D., an assistant professor in the Gene Expression and Regulation Program at Wistar and senior author on the study. “Such drugs could well have significant anti-cancer activity.”

Telomerase is essential for normal cell division and survival, and has been associated with aging and cancer. In humans, the usual role of telomerase is to add multiple repeats of a short length of DNA to the ends of chromosomes, known as telomeres, thus preventing damage and the loss of genetic information during DNA replication. It performs this critical service in developing embryos and in a few specialized cell lines, including stem cells.

In normal adult cells, however, telomerase is switched off almost entirely to prevent the dangers of runaway cell proliferation. This lack of telomerase activity is also associated with normal aging and underlies a seminal observation known as the Hayflick limit. At Wistar in the 1960s, Leonard Hayflick, Ph.D., noted that cells in culture divide only about 50 times before dying. Later, scientists tied this effect to the shortening of telomeres with each cell division when telomerase is no longer active in the cell.

Cancer cells, however, often regain the ability to produce telomerase, permitting them to replicate indefinitely. Though scientists have sought ways to inhibit this enzyme, a lack of detailed information on the enzyme's structure has hindered progress.

Prior studies have shown that telomerase is made up of multiple protein components and a stretch of RNA that is used as a template to create the short DNA repeats that are added to the ends of chromosomes. In order for telomerase to function, the RNA and protein components of telomerase must interact to form a stable complex capable of DNA replication. This interaction occurs mainly on the so-called TRBD domain, which plays an essential role in complex formation and full assembly of the enzyme.

"Studies show if you delete the TRBD domain from telomerase, the enzyme is inactive because it can no longer assemble with RNA,"

Skordalakes says. “Without the RNA, the enzyme can no longer replicate telomeres.”

To get a clear view of this interaction, Skordalakes and co-workers obtained the three-dimensional structure of TRBD using X-ray crystallography, a technique that analyzes the diffraction patterns of X-rays beamed at crystals of a molecule to determine the molecule’s atomic structure.

Their studies reveal that the TRBD domain is shaped like a boomerang, with a structural organization that leads to the formation of a narrow well-defined pocket on the surface of the protein that enables the enzyme to bind the single-stranded RNA used as a template for the DNA repeats.

A second RNA-binding site is formed by a large cavity that serves as an extension of the single-strandedRNA-binding pocket. The extent of these RNA interactions indicates the important role of this domain in stabilizing the complex, Skordalakes says.

Source: The Wistar Institute