

Researchers unmask proteins in telomerase, a substance that enables cancer

20 March 2008

One of the more intriguing workhorses of the cell, a protein conglomerate called telomerase, has in its short history been implicated in some critical areas of medicine including cancer, aging and keeping stem cells healthy. With such a resume, telomerase has been the subject of avid interest by basic scientists and pharmaceutical companies alike, so you'd think at the very least people would know what it is.

But researchers have been frustrated in their attempts to find the proteins that make up this complex. They know that it's a behemoth of an enzyme and is made up of more than just the two components they've gotten their hands on in the past. They also know what it does: it maintains the cell's genetic material in fetal cells, normal adult stem cells and in cancer cells.

What they don't know is what other proteins make up the massive telomerase complex. Until now, that is.

Researchers at Stanford University School of Medicine have identified two new proteins that make up the telomerase complex and have a lead on several more. This is the first significant step toward understanding the makeup of telomerase since 1999. The discovery of these two proteins provides new targets for cancer treatments, the researchers said.

"It's so surprising that we are discovering new components of this enzyme almost ten years after it was discovered," said Steven Artandi, MD, PhD, assistant professor of medicine and senior author of the study. The work will be published in the March 21 issue of *Cell*.

Telomerase is best known for its role in maintaining the cell's genetic material, the chromosomes. Every time a person's cell divides, it makes a second copy of the 46 chromosomes, then sends one copy to each of the two resulting

cells. As that copying process proceeds, each replication snips a bit off the protective tips of the chromosomes, called telomeres. Those ever-shortening chromosomes are one reason cells age. After a lifetime of cells dividing, the telomeres dwindle down to a length that eventually triggers the cell to stop replicating altogether or die.

Cancerous cells overcome that lifespan limitation by making telomerase, which repairs those snipped chromosome ends. Without shortening, the cells can divide forever. Telomerase is normally active in fetal cells, then shortly after birth it is turned off in all cells except normal tissue stem cells and some immune cells.

Since telomerase's discovery in cancerous cells in 1994, the idea has been that if a drug could block telomerase, chromosomes in those cancerous cells would eventually grow shorter and the cells would age and die just like any other cell in the body. But without knowing what proteins make up telomerase it's hard to design a drug to block it.

In the study, Artandi and first author Andrew Veneicher, an MD/PhD student, describe two protein components of telomerase. They also show that disabling one of the proteins brings telomerase to a grinding halt. Although the work was done in cells in a lab dish, the findings suggest that a drug blocking that protein may be a useful tool against cancer.

Artandi said one problem with studying telomerase is that it's available in such small quantities. Growing huge vats of cancer cells in the lab still only results in miniscule amounts of protein. Until recently, no technology was sensitive enough to analyze proteins at such minute levels.

"Many technical advances feed into our ability to make this discovery," Artandi said.

Artandi and his colleagues at the National Cancer

Institute and Washington University School of Medicine took advantage of new technologies to get around the quantity problem. They chopped the massive telomerase complex into tiny protein pieces, then sent those pieces through a sensitive device that detected the pieces and compared the protein sequence to a genetic database that could match the snippet to a particular gene.

With the gene in hand, the researchers could find the protein made by that gene. They also used genetic trickery to disable one of the proteins, which prevented the telomerase from working. Artandi said the next step is to find small molecules that can block that newly discovered protein in cancerous cells. He's also trying to identify a handful of additional proteins that seem to be part of the telomerase complex.

Source: Stanford University Medical Center

APA citation: Researchers unmask proteins in telomerase, a substance that enables cancer (2008, March 20) retrieved 13 October 2022 from <https://medicalxpress.com/news/2008-03-unmask-proteins-telomerase-substance-enables.html>

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