Scientists identify key component in cell replication

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Last week, a presidential limousine shuttled Barack Obama to the most important job in his life. Scientists at the Stanford University School of Medicine have now identified a protein that does much the same for the telomerase enzyme — ferrying the critically important clump of proteins around to repair the ends of chromosomes that are lost during normal replication. Without such ongoing maintenance, stem cells would soon cease dividing and embryos would fail to develop.

"This is the first new protein component of telomerase that has been identified in 10 years," said Steven Artandi, MD, PhD, associate professor of hematology. "And it's likely to be a valuable target for anti-cancer therapies."

Artandi is the senior author of the research, which will be published in the Jan. 30 issue of *Science*. Graduate student Andrew Venteicher is the first author. The two collaborated with scientists at the National Cancer Institute-Frederick and the University of Georgia to conduct the research.

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 within a limited number of generations. Unfortunately, the enzyme is also active in many cancer cells. Artandi and his collaborators found that blocking the inappropriate expression of the protein, called TCAB1, in human

cancer cells keeps telomerase from reaching its DNA targets, called telomeres, and may limit the cell's life span.

"There are currently no effective telomerase inhibitors," said Artandi. "We've never really understood before how the enzyme gets to the telomeres; it's been a complete black box. Now we're starting to piece together how it happens, and that gives us more opportunities to interfere with its function."

Telomerase has been subject of intense research for years, but scientists have been stymied by the enzyme's large size and extreme rarity. Few cells in the adult body make the huge protein complex, and even they make only tiny amounts. As a result, only some members have been identified.

"It's been incredibly challenging to figure out all the protein components of telomerase," said Artandi, who refers to the unknown members of the complex as "dark matter." "We know how big the enzyme is, and it's clear that the known components don't add up to the total. Now we've identified one more member."

The researchers used a highly sensitive protein identification technique called mass spectrometry to ferret out TCAB1's presence in telomerase based on its ability to bind to another, known component of the enzyme. Early last year, Artandi's lab used the same technique to identify for the first time two other proteins — pontin and reptin — that are important for assembling the massive complex. This time around they identified TCAB1, a protein of previously unknown function.

Unlike pontin and reptin, TCAB1 is a true component of telomerase. But it's not required for the enzyme's activity. Rather, it recruits the telomerase complex to processing and holding areas in the nucleus of the cell called Cajal (pronounced "cuh-hall") bodies. Like a high-end garage,

Cajal bodies apply the finishing touches to a variety of proteins that use small molecules of RNA to conduct their activities (telomerase, for example, uses an RNA molecule as a template for the DNA chain it tacks onto the ends of chromosomes). When appropriate, TCAB1 then chauffeurs the telomerase complex to the waiting end of a newly replicated chromosome.

"TCAB1 is absolutely necessary for the telomerase to make this jump from Cajal bodies to telomeres," said Artandi. "When we inhibited its activity in human cancer cells, the telomeres grew shorter," implying the cancer cells would die more quickly.

Prior to this study, TCAB1 had no known function. "Andy [Venteicher] found that TCAB1 binds not only telomerase, but also a specific class of small, non-coding RNA molecules that also end up in the Cajal bodies," said Artandi. He added that the protein may be a common biological shuttle responsible for delivering a variety of molecules to their destinations. He and his collaborators plan to continue their study of TCAB1 and also to identify other telomerase components.

"This is a story that's been unfolding over decades," said Artandi. "Telomerase is such a high-priority target for many diseases, but it's hard to attack when you know very little about it. But that's changing now."

Source: Stanford University