

Discovery pinpoints new connection between cancer cells, stem cells

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A molecule called telomerase, best known for enabling unlimited cell division of stem cells and cancer cells, has a surprising additional role in the expression of genes in an important stem cell regulatory pathway, say researchers at the Stanford University School of Medicine. The unexpected finding may lead to new anticancer therapies and a greater understanding of how adult and embryonic stem cells divide and specialize.

"Telomerase is the factor that accounts for the unlimited division of cancer cells," said Steven Artandi, MD, PhD, associate professor of hematology, "and we're very excited about what this connection might mean in human disease." Artandi is the senior author of the research, which will be published in the July 2 issue of the journal *Nature*. He is also a member of Stanford's Cancer Center.

In many ways, telomerase is the quintessential molecule of mystery — hugely important and yet difficult to pin down. Telomerase was known to stabilize telomeres, special caps that protect the ends of [chromosomes](#). It stitches short pieces of DNA on these chromosome ends in [stem cells](#) and some [immune cells](#), conferring a capacity for unlimited cell division denied to most of the body's other cells. Its importance is highlighted by the fact that it is inappropriately activated in more than 90 percent of cancer cells, suggesting that drugs or treatments that block telomerase activity may be effective anticancer therapies. However, its vast size, many components and relative rarity — it is not expressed in most of the body's cells — hinder attempts to learn more about it.

Artandi and his lab have spent many years identifying and studying the components of the telomerase complex. In this most recent study, they were following up on a previous finding suggesting that one part, a protein called TERT, was involved in more than just maintaining telomeres. They had discovered that

overexpressing TERT in the skin of mice stimulated formerly resting adult stem cells to divide — even in the absence of other telomerase components. "This was a pretty clear hint that TERT was involved in something more than just telomere maintenance," he said.

Artandi and his colleagues recognized that the cells' response to TERT mimicked that seen when another protein, beta-catenin, was overexpressed in mouse skin. Beta-catenin is a component of a vital signaling cascade known as the Wnt pathway, which is important in development, stem cell maintenance and stem cell activation. Stanford developmental biologist and professor Roeland Nusse, PhD, a collaborator on the current study, identified the first Wnt molecule in 1982.

In this study, Artandi and his colleagues purified the TERT protein from cultured human cells and found that it was associated with a chromatin-remodeling protein implicated in the Wnt pathway. They showed that overexpression of TERT in the presence of the remodeling protein enhanced the expression of Wnt-inducible genes. Finally, they found that TERT is required for mouse [embryonic stem cells](#) to respond appropriately to Wnt signals and that blocking TERT expression impairs the development of frog embryos.

"This is completely novel," said Artandi, who went on to show that TERT physically occupies the upstream promoter regions of the [genes](#). "No one had any idea that TERT was directly regulating the Wnt pathway." He speculates that interfering with the protein's Wnt-associated activity may be a faster way to inhibit cancer cells than blocking telomerase activity, which depends on the gradual shortening of telomeres with each cell division.

"The Wnt pathway and telomerase activity are two separate but coherent functions in stem cell self-renewal and cancer cell proliferation," said Artandi. "Nature evolved a way to connect these two crucial

functions by recruiting a component of telomerase directly into the Wnt pathway." The researchers are now investigating what role TERT may play in normal and cancerous cells.

Source: Stanford University Medical Center ([news](#) : [web](#))

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