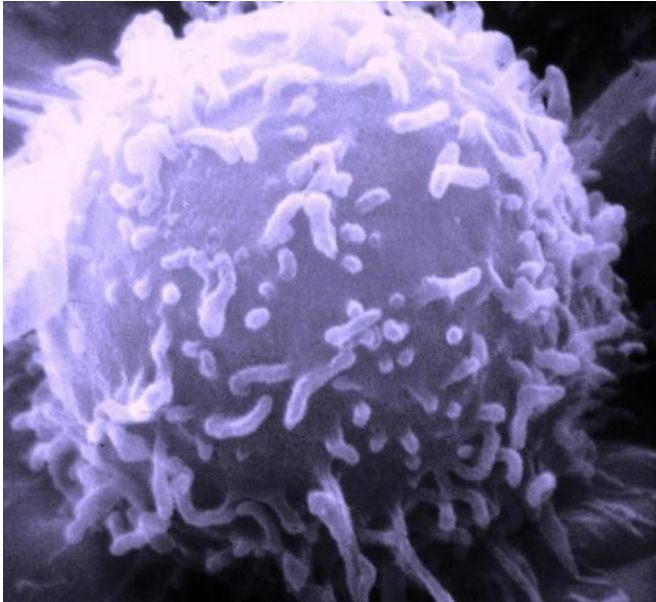# Unraveling the mystery of why cancer cells survive and thrive

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Electron microscopic image of a single human lymphocyte. Credit: Dr. Triche National Cancer Institute

Some cancer cells have a trick up their sleeve to avoid cell death: boosting maintenance of telomeres, the protective "end caps" on chromosomes, and a research team led by Jackson Laboratory (JAX) Professor Roel Verhaak reports in *Nature Genetics* on a newly discovered telomere maintenance mechanism.

The findings open avenues for functional studies that may yield insight into how to steer cancer cells away from immortalizing and back to normal death programming. Moreover, harnessing telomere maintenance mechanisms could be a potential approach to selectively retarding aging. The 2009 Nobel Prize in Physiology or Medicine to Elizabeth Blackburn, Carol Greider and Jack Szostak established the roles of telomeres and telomerase in the aging of cells and organisms.

In most cells, telomeres shorten over time to the point where cell division is no longer possible, leading to cell death. Certain cells, such as stem cells and germ cells, are capable of ongoing division because they contain active telomerase, an enzyme that lengthens telomeres.

It has been long known to researchers that cancer cells reactivate telomerase through telomerase reverse transcriptase (TERT) transcription, but the mechanisms behind this remain elusive.

"These cancer cells are hijacking a mechanism to maintain telomeres, enabling them to continue to divide," Verhaak says.

The researchers scanned 18,430 samples from cancerous and non-neoplastic tissues to determine and compare their telomere lengths and query them for telomerase activity. The analysis, which included samples from 31 different cancer types, showed that telomeres were generally shorter in tumors than in healthy tissues, and longer in soft tissue tumors and brain tumors compared to other cancers.

They found that the majority—73 percent—of cancers expressed TERT (which in turn drives reactivation of telomerase). In addition to the expected mutations and genomic rearrangements driving TERT expression, the researchers discovered an important new mechanism: TERT promoter methylation.

In methylation, clumps of molecules called methyl groups attach to a segment of DNA and can change the activity of that segment without changing its genetic sequence.

Methylation in DNA sequences known as promoters, as the researchers found in most of the cancer samples, typically acts to repress gene transcription, the process of making an RNA copy of a gene sequence. Counterintuitively, Verhaak

says, "we found that TERT DNA promoter methylation resulted in TERT expression. We think that because of the DNA methylation, mRNA transcription-repressing proteins are no longer able to bind."

About 22 percent of the tumor cells lacked detectable TERT expression. "There could be a number of reasons for this," says Floris Barthel, a JAX postdoctoral associate and first author of the study. "Maybe not all tumors harbor immortalized cells with a telomere maintenance mechanism, or there are alternative mechanisms at play, or perhaps TERT expression that falls below the detection threshold we used is still sufficient to maintain telomeres." Future studies are needed to elucidate the telomere maintenance mechanisms, or lack thereof, in these tumors, he notes.

  More information: Systematic analysis of telomere length and somatic alterations in 31 cancer types, *Nature Genetics*, nature.com/articles/doi:10.1038/ng.3781