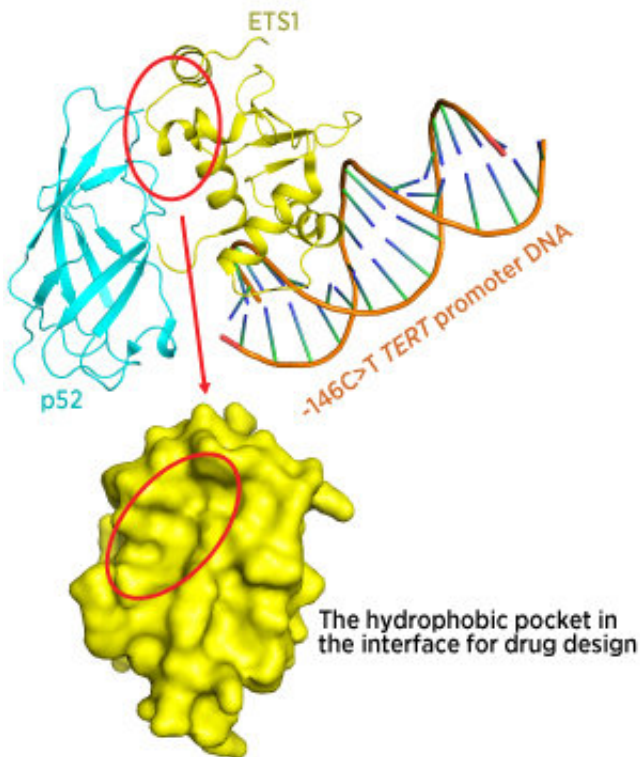


# Controlling the gene for the 'immortalizing enzyme'

November 16 2018



Molecular strand and surface outline representations of the structure of the complex between two proteins (p52 and ETS1) that can reactivate the TERT gene's mutated DNA, with a possible site to target with drugs circled. Credit: A\*STAR Institute of Molecular and Cell Biology

Revealing how a gene is activated in cancer cells to produce an enzyme that helps the cells thrive could lead to new treatments.

"We are investigating one of the most fundamental questions in [cancer biology](#)," says lead researcher, Haiwei Song from the A\*STAR Institute of Molecular and Cell Biology. The team has been studying the [molecular mechanisms](#) that underpin a genetic malfunction found in up to 95 per cent of human cancers. Their findings could lead to new treatments.

Together with colleagues in France, the team has examined processes that activate the gene coding for a protein known as "the immortalizing enzyme." The dramatic name recognizes the enzyme's ability to allow [cancer cells](#) to survive and multiply, in defiance of normal controls on cell growth.

The enzyme, more formally known as telomerase reverse transcriptase (TERT), maintains regions of DNA called telomeres found at the end of chromosomes, which naturally shorten as cells age and die. This maintenance is essential for cells, such as stem cells, that must survive to build healthy bodies.

But the reactivation of the gene for TERT in cells where it should normally be shut down is one of the central processes that allows cancer [cells](#) to multiply into life-threatening tumors. This undesirable reactivation can be caused by mutations in regions of DNA that control the activity of TERT's gene, which enable a complex of two regulatory proteins to bind to the mutated DNA and switch on the TERT gene activity.

The A\*STAR researchers made and analyzed crystals of the complex between the two proteins and the mutated DNA. This revealed the precise structure of the complex (see image) and details of the mechanism behind its effect.

The research also showed that one of the proteins of the complex can

interfere with cell signaling systems to reactivate the TERT gene even without binding to DNA.

"This was a surprise," says Song, especially as it may mean that many other [genes](#) could potentially be activated in a similar way.

"We plan to use our understanding of this system to make new drugs," says Song. He explains that one option is to find [small molecules](#) that inhibit the reactivation of the TERT gene, for example, by binding to the proteins or the DNA involved. Liver cancer may be the first target, as this often involves mutations in the TERT gene that take effect in the early stages of tumor development.

**More information:** Xueyong Xu et al. Structural basis for reactivating the mutant TERT promoter by cooperative binding of p52 and ETS1, *Nature Communications* (2018). [DOI: 10.1038/s41467-018-05644-0](https://doi.org/10.1038/s41467-018-05644-0)

Provided by Agency for Science, Technology and Research (A\*STAR), Singapore

Citation: Controlling the gene for the 'immortalizing enzyme' (2018, November 16) retrieved 9 April 2024 from <https://phys.org/news/2018-11-gene-immortalizing-enzyme.html>

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