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Researchers unlock secret of deadly brain cancer's 'immortality'

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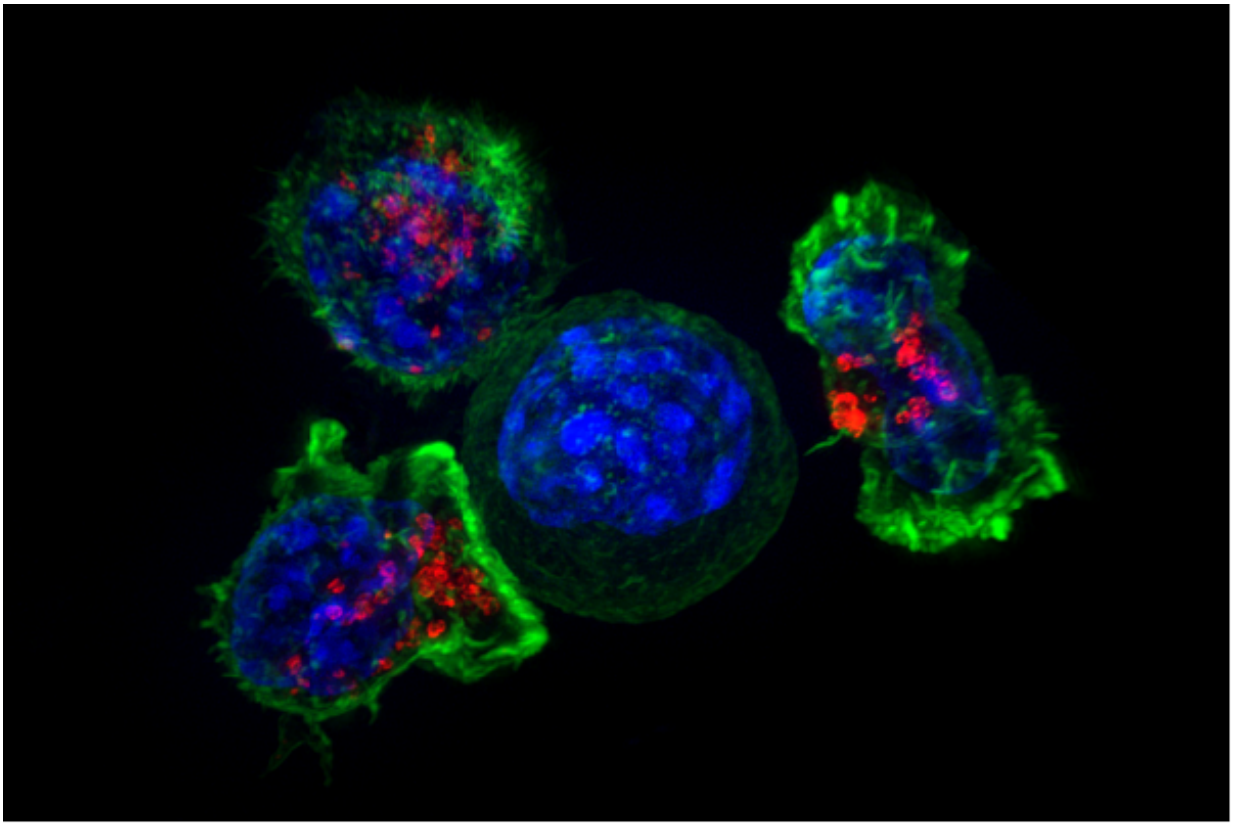

Killer T cells surround a cancer cell. Credit: NIH

UC San Francisco researchers have discovered how a mutation in a gene regulator called the *TERT* promoter—the third most common mutation among all human cancers and the most common mutation in the deadly

brain cancer glioblastoma—confers "immortality" on tumor cells, enabling the unchecked cell division that powers their aggressive growth.

The research, published September 10, 2018 in *Cancer Cell*, found that patient-derived glioblastoma cells with *TERT* promoter mutations depend on a particular form of a protein called GABP for their survival. GABP is critical to the workings of most cells, but the researchers discovered that the specific component of this protein that activates mutated *TERT* promoters, a subunit called GABP-ß1L, appears to be dispensable in normal cells: Eliminating this subunit using CRISPR-based gene editing dramatically slowed the growth of the human cancer cells in lab dishes and when they were transplanted into mice, but removing GABP-ß1L from healthy cells had no discernable effect.

"These findings suggest that the ß1L subunit is a promising new drug target for aggressive glioblastoma and potentially the many other cancers with *TERT* promoter mutations," said study senior author Joseph Costello, Ph.D., a leading UCSF neuro-oncology researcher.

Immortality is one of the key traits of cancer cells. In contrast to healthy cells, which are strictly limited in the number of times they are able to divide, cancer cells can go on dividing and multiplying forever, in many cases accumulating additional cancer-driving mutations as they go.

Normally, cellular life spans are set by structures called telomeres—protective caps that sit at the ends of chromosomes like the aglets at the end of a shoelace. Telomeres shorten each time a cell divides, until eventually they are too short to protect the DNA any longer, a signal the cell has reached the end of its natural life span and should be retired like a balding car tire.

Tumor cells in most cancers get around this limitation by stealing the secret of immortality from long-lived stem cells, which can divide

indefinitely thanks to a telomere-extending enzyme called telomerase, the discovery of which led to a Nobel prize shared by UCSF's Elizabeth Blackburn, Ph.D. Normally only stem cells are allowed to cheat death in this way, but scientists estimate that as many as 90 percent of human cancers have activated telomerase, many through mutations in *TERT*, one of the two genes that encodes the telomerase complex, which enable them to grow and spread unfettered by the limitations of normal cells.

Efforts to treat cancers with drugs that block telomerase have mostly proven too toxic to patients because they interfere with telomere maintenance in stem cells such as those needed to maintain healthy blood.

But recent research has suggested that more than 50 types of human cancers may be caused not by a defective *TERT* gene itself, but by mutations in the *TERT* promoter—a region of DNA where protein complexes called transcription factors can influence when and how the *TERT* gene is activated. These mutations enable a transcription factor called GABP to bind to the *TERT* promoter and activate it, other studies had found, which was strange because in healthy cells GABP and *TERT* usually have nothing to do with one another.

"This was really intriguing to us," Costello said. "You can't create a drug to target a promoter itself, but if we could identify how GABP was binding to the mutated promoter in these cancers, we might have a remarkably powerful new drug target."

Costello's team, led by graduate students Andrew Mancini and Ana Xavier-Magalhaes, studied human glioblastoma cell lines and primary tumor cells derived from advanced-stage glioblastoma patients and showed that the cells' mutations create two adjacent sequences of DNA in the *TERT* promoter that make a perfect landing pad for a particular form of the GABP transcription factor complex containing four

subunits, one of which was GABP-ß1L.

The researchers showed that this GABP-ß1L-containing form of GABP is required to activate *TERT* and drive cancer growth, but that it appears not to be essential for healthy cells. When the researchers used multiple techniques, including CRISPR-based gene editing, to eliminate the GAPB1L subunit from glioblastoma cells in laboratory cultures, the cells' growth dramatically slowed. The researchers then implanted patient-derived glioblastoma cells into mice and showed that while unedited cells grew aggressively and quickly proved fatal for the animals, cells edited to lack GAPB1L grew much more slowly and were less lethal.

Costello said the next step will be to identify small-molecule drugs that could have a similar effect as the gene editing used in the current experiments, which was performed in collaboration with co-authors Pablo Perez-Pinera, Ph.D., of the University of Illinois, Urbana-Champaign and CRISPR pioneer Jennifer Doudna, Ph.D., of UC Berkeley and the Gladstone Institutes in San Francisco, who is also an adjunct professor of cellular and molecular pharmacology at UCSF.

"In theory what we have now is a therapeutic target that is not *TERT* itself, but a key to the *TERT* switch that is not essential in normal cells," Costello said. "Now we have to design a therapeutic molecule that would do the same thing."

A San Francisco-based company called Telo Therapeutics, founded by Costello and former graduate student Robert Bell, Ph.D., who is also a co-author on the current study, is currently conducting small molecule screens to find such a molecule in partnership with pharmaceutical giant GlaxoSmithKline (GSK).

"It's gratifying that GSK is willing to invest their significant resources

into this early-stage finding," Costello said. "To me, it really speaks to promise of this target for so many different human cancers."

More information: *Cancer Cell* (2018). DOI: 10.1016/j.ccell.2018.08.003

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