Protein plays unexpected role protecting chromosome tips

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This is Sharon Dent, Ph.D., professor in M. D. Anderson's Department of Biochemistry and Molecular Biology. Credit: M. D. Anderson

A protein specialist that opens the genomic door for DNA repair and gene expression also turns out to be a multi-tasking workhorse that protects the tips of chromosomes and dabbles in a protein-destruction complex, a team lead by researchers at The University of Texas M. D. Anderson Cancer Center reports in the Aug. 13 edition of *Molecular Cell*.

"Instead of being a really important tool dedicated just to regulation of

gene transcription, Gcn5 is more like a Swiss Army knife that performs different functions depending on what needs to be done in the cell," said senior author Sharon Dent, Ph.D., professor in M. D. Anderson's Department of Biochemistry and Molecular Biology.

The researchers document a chain of events that starts with depletion of Gcn5, which leads to decreased activity by another protein that protects yet a third protein from destruction. That last protein, TRF1, protects telomeres, dense structures at the end of chromosomes which, like the compressed plastic tips on the ends of a shoelace, keep the chromosome ends intact.

Variation in the gene that expresses the middle protein in this model, ubiquitin specific protease 22 (USP22), is part of an 11-gene signature associated with highly metastatic cancers and poor prognosis, the authors note.

"Our results indicate that the Gcn5 complex regulates not just gene transcription but also protein stability," Dent said. "They also suggest that the role of USP22 in highly aggressive cancers might be due to these new functions."

Telltale telomere damage

Chromosomes are made of DNA that is tightly intertwined with proteins called histones to form chromatin. Chromatin is a condensed structure that forms a natural barrier inhibiting access to DNA. Gcn5 was previously known for its role in a complex of proteins that loosens chromatin to allow access to DNA by the cell's DNA repair machinery and by transcription factors that launch the process of gene expression.

"Years ago a student in my lab found that mice deficient in Gcn5 died early during embryonic development," Dent said. "The reason they died,

in part, was that telomeres were fusing together. There was no reason to think Gcn5 would have anything at all to do with telomeres, so these fusions were quite puzzling."

Clues for protein's role in metastatic cancer

While Dent and colleagues attacked the problem, a research group elsewhere discovered that USP22 is active in the same protein complex in which Gcn5 operates. USP22 protects proteins by pealing off ubiquitin molecules that attach to the proteins and mark them for destruction by the proteasome complex.

A literature review showed that TRF1 carries a ubiquitin mark that makes it vulnerable to degradation by the proteasome.

"TRF1 normally resides at the telomeres and tells the cell that this is a normal chromosome end and you should leave it alone," Dent said. "If you don't have enough TRF1, the cell now thinks these chromosomal ends are abnormal and tries to fix them when they shouldn't be fixed."

Putting it all together, the team hypothesized that USP22 protects telomeres by knocking ubiquitins off of TRF1, sparing it from destruction. "Our model is of a pathway in which depletion of Gcn5 reduces USP22 activity, causing greater TRF1 ubiquination, which leads to TRF1 destruction and that leads to telomere problems," Dent said.

In the *Molecular Cell* paper, the researchers show that depletion of Gcn5 leads to chromosomal fusion and damage in mouse embryonic cell lines and also reduces the level of TRF1. They then demonstrate that USP22 interacts with TRF1 and is required for that protein to remain stable. Additional experiments identified ubiquitin removal is the mechanism by which USP22 protects TRF1.

Dent and colleagues continue to look for new proteins and cellular processes that are impaired in cells lacking GCN5 or USP22. "There must be a reason why USP22 is over expressed in highly metastatic cancers and we are encouraged that we will be able to provide important clues for this process," Dent said.

Source: University of Texas M. D. Anderson Cancer Center (news : web)