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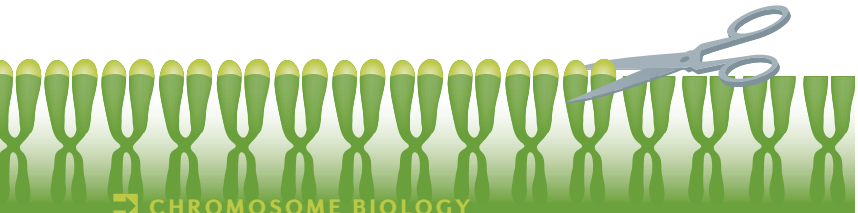

CHROMOSOME BIOLOGY

TZAP trims telomeres

The length of telomeres must be maintained within an optimal range to prevent cancer and to control lifespan. A new study published in *Science* reports the characterization of a protein that is necessary for regulating telomere length.

Li *et al.* identified the zinc finger protein ZBTB48 as a telomere-associated factor and renamed it telomeric zinc finger-associated protein (TZAP). In human cells, TZAP localized mostly to telomeres at levels similar to those of telomeric repeat-binding factor 1 (TRF1), which is a component of the telomere protection complex shelterin. TZAP neither interacted with shelterin components nor was it dependent on them for binding to telomeres. Swapping the DNA-binding domain of the shelterin component TRF2 with the terminal three zinc finger domains of TZAP revealed that TZAP can bind to telomeric repeats directly.

To test if TZAP and shelterin compete for telomere binding, the authors overexpressed TZAP or TRF2 and found that overexpression of TRF2 reduced TZAP localization at telomeres. A comparison of two HeLa cell clones with very different telomere lengths (~5 kb versus ~20 kb) revealed that TZAP did not localize to short telomeres, but it did localize to long telomeres, where the density of shelterin is low. An inverse correlation between telomere length and TZAP localization at telomeres was confirmed in a wide range of cell lines.

So, what role does TZAP have in telomere length regulation? Overexpression of TZAP caused a progressive reduction in telomere length and the accumulation of telomere-free chromosome ends. This finding indicates that TZAP promotes rapid telomere shortening — known as telomere trimming — which leads to the accumulation of extrachromosomal telomeric DNA (ECT-DNA). TZAP overexpression did indeed lead to the accumulation of ECT-DNA, whereas reducing TZAP levels resulted in cells with notably longer telomeres and less ECT-DNA.

Thus, TZAP binds to long telomeres and mediates their trimming, thereby restricting aberrant telomere lengthening that is associated with chromosome instability and disease.

Eytan Zlotorynski

> “TZAP binds to long telomeres and mediates their trimming”

ORIGINAL ARTICLE Li, J. S. Z. *et al.* TZAP: a telomere-associated protein involved in telomere length control. *Science* http://dx.doi.org/10.1126/science.aah6752 (2017)

FURTHER READING Maciejowski, J. & de Lange, T. Telomeres in cancer: tumour suppression and genome instability. *Nat. Rev. Mol. Cell Biol.* http://dx.doi.org/10.1038/nrm.2016.171 (2017) | Lazzerini-Denchi, E. & Sfeir, A. Stop pulling my strings — what telomeres taught us about the DNA damage response. *Nat. Rev. Mol. Cell Biol.* **17**, 364–378 (2016)