Nature Reviews Molecular Cell Biology | AOP, published online 25 September 2013; doi:10.1038/nrm3678

TELOMERES

Plan B for staying long

CORBIS

Although telomeres were originally thought to be transcriptionally silent, it has now emerged that they are transcribed into telomeric repeat-containing RNAs (TERRAs). It had been postulated that these non-coding RNAs form RNA–DNA hybrids, which Luke and colleagues now confirm. Their study also reveals that these structures have a role in telomere length maintenance.

Previous work had shown that dysregulated TERRA transcription and localization affects telomere length, so the authors sought to determine a role for TERRA in telomere length maintenance *in vivo* in budding yeast. First, they confirmed that RNA–DNA hybrids are formed at telomeres and that reduction of TERRA levels results in decreased numbers of these hybrids. These structures are known to be removed by the RNase H enzymes RNase H1 and RNase H2; indeed, RNAse H mutants had 80% more RNA–DNA hybrids at telomeres than wild-type yeast cells.

Notably, analysis of telomere length showed that cells lacking RNase H and telomerase (the enzyme that adds telomeric repeats to chromosomes, which is absent from most human somatic cells but present in budding yeast) had longer telomeres than cells lacking telomerase alone. Moreover, RNase H- and telomerase-null cells accumulated RNA–DNA hybrids, which correlated with delayed onset of senescence. Consistent with this, overexpression of RNase H1 in yeast cells resulted in accelerated senescence.

Because RNA–DNA hybrids are rich in R-loops, which are prone to engaging in homologous recombination, the authors postulated that, in the absence of RNase H and telomerase, these structures might promote homologous recombination-mediated telomere elongation. Indeed, telomeres of cells overexpressing RNase H1 showed reduced sequence divergence, which is indicative of impaired homologous recombination. Furthermore, telomeres that had reduced TERRA and RNA–DNA hybrid levels also showed decreased sequence divergence compared with an unmodified telomere.

The increased recombination induced by R-loops is known to depend on Rad52, so the authors examined whether loss of this protein (and thus loss of recombination) would affect telomere length and senescence in RNase H and telomerase mutants. In this case, loss of RNase H no longer resulted in longer telomeres and delayed senescence onset. This indicates that the effect of RNA–DNA hybrids on telomeres depends on the recombination status of the cell, and cells with functional recombination machinery have longer telomeres and increased viability.

So, the findings of this study suggest that in the absence of telomerase, TERRA can promote telomere length maintenance and delay senescence onset by forming RNA–DNA hybrids, which prevent telomere shortening through recombination. The authors propose that this mechanism operates to delay senescence when critically short telomeres arise.

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ORIGINAL RESEARCH PAPER Balk, B. *et al.* Telomeric RNA–DNA hybrids affect telomere-length dynamics and senescence. *Nature Struct. Mol. Biol.* http://dx.doi.org/10.1038/nsmb.2662 (2013)