AGEING

# The impact of shrinking telomeres


BANANASTOCK

Shortening of telomeres to a critical length triggers a DNA-damage response that contributes to ageing. A new study using a mouse model of accelerated telomere shortening reveals specific transcriptomic and epigenetic changes that provide clues to how telomere shortening is linked to ageing.

The Terc telomerase component and the TRF2 telomere-binding protein are implicated in the maintenance of telomeres. Schoeftner and colleagues made mice that are deficient for *Terc* and carry a *TRF2* transgene that is expressed in epithelia. Because it is inserted into the copy of the X chromosome that is inactivated in females, expression of the TRF2 transgene is an indicator of loss of X inactivation.

The authors looked at successive generations of these mice and found a gradual increase in TRF2 expression in females, which was correlated with progressive telomere shortening and the onset of ageing-associated skin phenotypes. Although the initiation of X inactivation is normal in these mice, its maintenance is perturbed, which suggests that telomere dysfunction leads to the relaxation of X chromosome inactivation, which in turn allows TRF2 transgene expression.

Using cells from the same transgenic model, the authors showed that telomere shortening is correlated with lower levels of transcription of telomeric non-coding RNAs, also known as TERRAs. In addition, the normal accumulation of these non-coding RNAs near to the inactive X chromosome was disrupted. A similar disruption in the accumulation of these transcripts — but not in their expression — was seen in wild-type fibroblasts that were exposed to radiation. This finding suggests that the DNA damage induced by telomere shortening may lead to alterations in nuclear organization, which may also contribute to epigenetic changes.

Transcriptomic analyses revealed that progressive telomere shortening correlates with increasing changes in transcription from all chromosomes and, importantly, there was no bias towards genes located near to telomeres. In particular, overexpression of TRF2 seems to cause the upregulation of genes involved in cell-survival pathways and a loss of the ability to upregulate genes that are involved in DNA-damage repair — a finding that may account for the DNA-damage sensitivity and premature ageing seen in mice with severe telomere dysfunction.

By linking the DNA damage that is triggered by critically short telomeres with changes in X chromosome inactivation and in the expression of genes that are involved in specific cellular functions, these findings help to fill in the gaps in our understanding of how telomere shortening and ageing are related.

*Louisa Flintoft*

**ORIGINAL RESEARCH PAPER** Schoeftner, S. *et al.* Telomere shortening relaxes X chromosome inactivation and forces global transcriptome alterations. *Proc. Natl Acad. Sci. USA* 3 Nov 2009 (doi:10.1073/pnas.0909265106)