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GENOME STABILITY

Specialist responses at telomeres

Cells must ensure that DNA ends at telomeres are not recognized and processed in the same way as damaged DNA, otherwise the DNA repair processes may cause genomic rearrangements such as telomere fusions. Prevention of this genomic instability partly occurs through the protective sequestration of telomeric DNA ends in shelterin multiprotein complexes. Additionally, a new study now shows that when telomeres become deprotected they trigger a specialized form of DNA damage response to minimize the occurrence of rearrangements.

To mimic the stages of telomere deprotection that occur during physiological processes such as replicative senescence, Cesare *et al.* used various short hairpin RNAs (shRNAs) of different potencies to knock down expression of the shelterin component telomere repeat-binding factor 2 (TRF2) in human cells *in vitro*. One of the shRNAs achieved an intermediate stage of deprotection that was sufficient to induce a DNA damage response at telomeres (as shown by staining for the DNA damage response marker γH2AX) but was still able to resist the formation of telomeric fusions and the cytokinesis defects that occurred in cells with more complete TRF2 knockdown.

The authors then characterized how this DNA damage response differed from 'standard' DNA damage responses that would be expected to create telomeric fusions through DNA repair mechanisms involving DNA end joining and recombination. They found that, although activation of the DNA damage response kinase ataxia telangiectasia mutated (ATM) occurred, it failed to phosphorylate and activate its classic downstream substrate checkpoint kinase 2 (CHK2). By contrast, DNA damage induced by ionizing radiation caused the activation of both ATM and CHK2. A further difference was that the telomeric DNA damage response failed to induce the G2/M arrest that occurs following ionizing radiation. Instead, cells proceeded through cell division and arrested in the following G1 phase. This difference may serve to minimize the exposure of telomeres to recombinogenic DNA repair mechanisms, which are most active in the S and G2 phases. Using cells either with or without functional p53 the authors showed that the telomeric DNA damage response requires p53 for the G1 arrest and the maintenance of genomic stability. This potentially explains the known cooperation between telomere dysfunction and p53 loss in driving genome instability and tumorigenesis. The authors also showed that this specialized, CHK2-independent DNA damage response occurs when telomeres become deprotected in settings other than forced TRF2 knockdown, such as during replicative senescence and prolonged mitotic arrest.

It will be interesting to more comprehensively dissect the molecular details of the causes and consequences of this specialized DNA damage response at telomeres.

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ORIGINAL RESEARCH PAPER Cesare, A. J. *et al.* The telomere deprotection response is functionally distinct from the genomic DNA damage response. *Mol. Cell* http://dx.doi.org/10.1016/j.molcel.2013.06.006 (2013)