The long reach of telomeres

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The primary purpose of telomeres is to protect chromosome ends from erosion during cell division cycles. New observations suggest an additional function for telomeres, namely in gene silencing via formation of long-range chromatin interactions.

Chromosome ends are a danger to cells. The termini of chromosomes are difficult to faithfully replicate, and, because they resemble broken DNA, their presence may tempt cells to activate DNA damage response (DDR) pathways, leading to untimely cell cycle arrest and cell death. Cells use telomeres to eliminate these threats. The repetitive telomere sequences are replenished at each cell cycle by telomerase, and triggering of the DDRs is prevented by a protective protein complex that masks the chromosome ends and suppresses DNA damage signaling. These protective functions of telomeres have long been considered their only mechanisms of action. A study by Robin et al. (2014) in this issue of Genes & Development now demonstrates a novel role for telomeres in gene regulation.

Telomeres are characterized by a distinct chromatin environment (Blasco 2007). In mammals, telomeres themselves are made up of 3–20 kb of AT-rich repeats flanked by subtelomeric regions extending up to 300 kb into the chromosome. Telomeric chromatin is marked by numerous specific telomere-binding proteins, which recruit the H3K9me3/SUV3–9/HP1 (heterochromatin protein 1) machinery, which establishes and maintains the telomere chromatin structure via spreading of heterochromatin from the chromosome end into the subtelomeric regions (Blasco 2007). Given the repressive nature of heterochromatin, it was not entirely surprising to find that genes in proximity of telomeres are silenced. This effect is referred to as the telomere position effect (TPE) (Gottschling et al. 1990, Tham and Zakian 2002). The degree of repression declines with distance from the telomere, as demonstrated by insertion of reporter genes at increasing distances from the telomere, and in mammalian cells appears to be limited to ~100 kb (Kulkarni et al. 2010).

The new study by Robin et al. (2014) now shows that telomeres can affect gene expression over much larger distances than previously recognized and that they do so by a novel mechanism involving chromatin looping rather than heterochromatin spreading. The investigators discovered this mechanism by mapping chromatin interactions of telomeres using a variant of the Hi-C [chromosome capture followed by high-throughput sequencing] method to detect chromatin interactions in three-dimensional (3D) space. Robin et al. (2014) performed high-density mapping of interactions in a 20-Mb region on human chromosome 6 and identified several megabase-sized loops between the telomeres and distal target genes. This association was validated using fluorescence imaging, which demonstrated that these interactions occurred in a large fraction of cells, suggesting wide prevalence in the population. These observations suggest that telomeres fold back onto chromosomes and regulate gene expression. In reference to conventional TPE caused by heterochromatin spreading, the investigators refer to this phenomenon, due to chromatin looping, as TPE over long distances (TPE-OLD).

These long-range interactions of telomeres with target genes appear functionally important, as indicated by a global gene expression analysis that revealed >140 genes within 10 Mb of several telomeres whose expression was affected by telomeres. Despite this finding, it remains to be seen how pervasive TPE-OLD is. The investigators used microarray analysis for their global expression studies, and subtelomeric regions are notoriously underrepresented on these arrays, allowing for the possibility of many more TPE-OLD-regulated genes in the genome. On the other hand, some of the observed misregulation may be due not to loop formation but secondary effects of some of the affected genes. Systematic mapping of telomeric long-range interactions and comparison with comprehensive gene expression analysis should reveal how broadly this mechanism is used in gene regulation and whether all or only some chromosome ends use it.

Importantly, using a novel system in which telomere length can be controlled by eliminating telomerase activity
at different times of clonal growth, Robin et al. (2014) show that long-range telomere interactions are lost as telomeres shorten. This observation points to a potential regulatory role of TPE-OLD on these genes. This finding is of interest and has potential clinical implications given the role of telomeres in disease, particularly cancer, and aging, since telomeres generally shorten in those conditions. A precedent exists for disease-relevant control of gene expression via aging-related telomere shortening, since telomere length-dependent effects on gene expression have been demonstrated for DUX4 and FRG2 in facioscapulohumeral muscular dystrophy (Stadler et al. 2013). While no functional commonalities among the TPE-OLD-regulated genes were noted by Robin et al. (2014), it will be interesting to determine whether any of the TPE-OLD-controlled genes are of relevance to cancer and aging.

How TPE-OLD exactly works is not clear yet. It is possible that gene activation via the telomeres occurs similar to enhancer–promoter interactions by facilitating recruitment of transcription factors (Calo and Wysocka 2013). On the other hand, gene repression may be brought about by superposition of the repressive chromatin environment near telomeres onto target genes in a process similar to that seen in position effect variegation (Elgin and Reuter 2013). Initial observations by the investigators also suggest that other mechanisms may be at work, since no accumulation of the H3K9me3/Suv3–9/HP1 machinery and no chromatin compaction, which are frequently seen in persistently repressed genome regions, were found. Future work will be required to delineate the molecular basis of TPE-OLD.

The results may also have implications for how we think about the previously described TPE mechanism in which silencing of telomere-proximal genes appeared to be a default process and a byproduct of the heterochromatin structure of telomere ends. The existence of discrete telomere loops over several megabases suggests that telomere-mediated gene control events may be regulated, raising the prospect that conventional TPE is also under regulatory control. Interestingly, discontinuities in TPE had previously been described and attributed to the presence of boundary elements and insulators, offering the potential for regulatory input (Fourel et al. 1999).

Telomeres are commonly assumed to only function in protecting the structure of chromosome ends and controlling the proliferation potential of cells. When telomeres become too short, they trigger proliferation arrest and replicative senescence via activation of DNA damage signaling. A final, particularly interesting question that arises from these studies is whether the effects on distal genes occur prior to telomeres reaching the threshold below which senescence pathways are activated. If so, telomeres would be not only guardians of the genome but also its regulators.

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