World Academy of Science, Engineering and Technology
International Journal of Bioengineering and Life Sciences
Vol:9, No:04, 2015

New Roles of Telomerase and Telomere-Associated Proteins in the Regulation of Telomere Length

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Abstract : Telomeres are specialized structures at chromosome ends consisting of tandem repetitive DNA sequences [(TTAGGG)n in humans] and associated proteins, which are necessary for telomere function. Telomere lengths are tightly regulated within a narrow range in normal human somatic cells, the basis of cellular senescence and aging. Previous studies have extensively focused on how short telomeres are extended and have demonstrated that telomerase plays a central role in telomere maintenance through elongating the short telomeres. However, the molecular mechanisms of regulating excessively long telomeres are unknown. Here, we found that telomerase enzymatic component hTERT plays a dual role in the regulation of telomeres length. We analyzed single telomere alterations at each chromosomal end led to the discoveries that hTERT shortens excessively long telomeres and elongates short telomeres simultaneously, thus maintaining the optimal telomere length at each chromosomal end for an efficient protection. The hTERT-mediated telomere shortening removes large segments of telomere DNA rapidly without inducing telomere dysfunction foci or affecting cell proliferation, thus it is mechanistically distinct from rapid telomere deletion. We found that expression of hTERT generates telomeric circular DNA, suggesting that telomere homologous recombination may be involved in this telomere shortening process. Moreover, the hTERT-mediated telomere shortening is required its enzymatic activity, but telomerase RNA component hTR is not involved in it. Furthermore, shelterin protein TPP1 interacts with hTERT and recruits it on telomeres to mediate telomere shortening. In addition, telomere-associated proteins, DKC1 and TCAB1 also play roles in this process. This novel hTERT-mediated telomere shortening mechanism not only exists in cancer cells, but also in primary human cells. Thus, the hTERT-mediated telomere shortening is expected to shift the paradigm on current molecular models of telomere length maintenance, with wide-reaching consequences in cancer and aging fields.

Keywords : aging, hTERT, telomerase, telomeres, human cells
Conference Title : ICB 2015 : International Conference on Biology
Conference Location : Paris, France
Conference Dates : April 27-28, 2015