

TELOMERES AND TELOMERASE

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Telomeres, consisting of simple repeated DNA sequences together with bound protein factors at the ends of chromosomes, make "caps" that protect and stabilize chromosomes. Without telomeric DNA and its special way of replicating, chromosome ends dwindle away as cells divide. Counteracting this shortening, telomerase replenishes the DNA at telomeres, and can thereby counteract cell senescence. Telomerase is strongly active in most human cancers, where it has a major known function of replenishing telomeric DNA and maintaining cell immortality. However, human cancer cells also responded rapidly to abruptly reducing the level of telomerase RNA, and even without detectable bulk telomere shortening and uncapping, distinct cellular/transcriptional responses were elicited^{1,2}. These distinctive alterations in the gene-expression profiles were predicted to diminish cancer progression or malignancy^{2,3}. To explore possible mechanisms underlying these effects, we have examined telomere structure in cancer cells under different telomerase manipulation regimes. Cultured human cells lacking various DNA damage checkpoints were found to harbor a class of highly truncated telomeres (which we name "t-stumps"), present at unprecedented abundance⁴. The t-stumps defined a minimal telomeric unit stable in cancer cells that is stabilized by high levels of telomerase components.

Although telomerase activity is normally kept in check in adult human cells, throughout life a certain level of telomerase is still required for replenishment of tissues, such as the immune system. Recent findings have highlighted the importance of sufficient telomerase for both telomere protection and telomere length maintenance, with haploinsufficiency for telomerase RNA component increasing cancer risks. We found that low telomerase in white blood cells in humans is associated with six of the known major risk factors for cardiovascular disease⁵, including forms of chronic psychological stress⁶.

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