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"A Role for Telomerase in Normal Somatic Human Cells"

by
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Wednesday, July 6th, 2022
11:00 AM
Cancer Center, G-1196

Join Zoom Presentation:
https://rutgers.zoom.us/j/97808640784?pwd=eFBva3lqeWRZT2dmSkp4UEk0aXZiUT09
Meeting ID: 978 0864 0784
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ABSTRACT

The primary function of telomerase is to extend telomeres at the ends of linear chromosomes. In humans, telomerase activity can be detected in cells of the germ line, stem cells and most cancer cells, yet its expression and activity in the majority of somatic human cells is significantly reduced. Due to this reduced activity, telomeres in somatic human cells progressively shorten with every cell division cycle until they become critically short, forcing cells to enter replicative senescence, an irreversible proliferative arrest. The observations that telomeres shorten after each cell division cycle, together with the fact that telomerase activity is almost undetectable in human somatic cells led to the notion that telomerase lacks a role in these cells.

In this study, we investigate the functions of hTERT, the catalytic component of telomerase, in human somatic cells using sensitive and specific antibodies raised against the C-terminus of hTERT. We were able to detect and immunoprecipitate endogenous hTERT in human cell lines with increased specificity. Immunofluorescence staining of human skin fibroblasts revealed discrete hTERT foci in a fraction of cells, some of which co-localized with telomeres. This characteristic focal staining pattern was more prominent in cells in G2/M-phase, suggesting that hTERT localizes to a few discrete sites in the nucleus after chromosomes had been replicated. In support of this conclusion, we discovered an increase in the number of cells with this distinct hTERT focal staining pattern after cells had been treated with colcemid. Similarly, generating DNA replication stress and double stranded-DNA breaks in human fibroblasts not only increased the percentages of cells displaying discrete hTERT foci, but also increased the percentage of hTERT foci co-localizing with DNA damage response (DDR) factors, including γH2AX and 53BP1 at telomeric sites. More importantly, knocking out hTERT from normal skin fibroblasts using a CRISPR system resulted in proliferative arrest and a senescent phenotype with increased Telomere-dysfunction Induced Foci (TIF) compared to parental cells. Our findings, so far, suggest that hTERT performs specific and necessary functions in human somatic cells, potentially during post-replication processing of telomeres, the DDR and following DNA replication stress.