

ALAN MEEKER
GU Pathology

Direct In Situ Analysis of Telomere Lengths in Primary Prostate Cancer and Prostate Cancer Metastases

Alan K. Meeker^{1,2}, Jessica L. Beckman-Hicks¹, Christina J. Bennett¹, Helen Fedor¹, and Angelo M. De Marzo^{1,2}

¹Department of Pathology, ²Department of Urology, The Johns Hopkins University School of Medicine, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins Baltimore, MD.

Telomere shortening initiates chromosomal instability in the absence of senescence and DNA damage checkpoints. Recently, application of a fluorescence in situ hybridization technique (TELI-FISH) for direct assessment of telomere lengths to prostatic intraepithelial neoplasia (PIN), revealed that telomere shortening is a highly prevalent somatic genomic alteration, strongly suggesting that telomere length abnormalities play a role in driving malignant transformation in the prostate.

Studies on telomere lengths in clinically manifest prostate cancers have typically relied upon relatively insensitive and cumbersome Southern blot methodologies. Here, we apply TELI-FISH to tissue micro arrays containing primary prostate cancers and metastases in order to directly examine, in detail, their telomere length phenotypes.

For high-grade prostatic adenocarcinoma we find that 97% (n=37) display abnormally short telomeres when compared to adjacent stromal cells and/or matched, normal-appearing prostatic epithelium from the same case. In only a single case (3%) were tumor telomeres within the normal range. In this series we find no evidence for widespread telomere elongation, despite the fact that approximately 85% of primary prostate cancers possess detectable telomerase activity. Overall, telomere lengths were consistent between different tissue cores from the same tumor sample. Significant regional or gland-to-gland telomere length heterogeneity was observed in 7 (19%) of the cases.

For prostate cancer metastases, 84% (n=37) exhibit only abnormally short telomeres. Two cases (5%) display telomere lengths equal to or greater than normal, while 4 cases (11%) show heterogeneity of telomere lengths, ranging from markedly short to normal.

CONCLUSION:

These results indicate that the short telomere phenotype acquired early during prostate carcinogenesis (PIN stage) is maintained in the vast majority of primary prostate cancers and metastases, despite the fact that telomerase activity is measurable in most prostate cancers. We propose that prostate cancer telomerase activity acts only to maintain telomere length, thereby allowing continuous tumor cell proliferation, but without net telomere elongation.

The finding of homogeneous, markedly short telomeres in the majority of primary prostate cancers, as well as in metastases, suggests that therapeutic modalities based on telomerase-inhibition may be particularly effective in treating this disease.

References:

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