

RESEARCH HIGHLIGHT

Telomerase turns telomere dysfunction from bad to worse

Sahn-Ho Kim, Evelyn R Barrack and G Prem Veer Reddy

Asian Journal of Andrology (2012) 14, 665–666; doi:10.1038/aja.2012.37; Published online: 7 May 2012

Telomere integrity is critical for proliferation and survival of cells. Telomere dysfunction, often resulting from telomere attrition, causes genomic instability leading to cell death or malignant transformation. Telomerase is essential for maintaining telomere length and to immortalize cancer cells. While telomere shortening is evident in early stages of prostate cancer,¹ the role of telomere dysfunction and telomerase in the development and progression of prostate cancer is largely unknown. A recent study from DePinho's laboratory published in the March 2nd issue of *Cell* suggests that whereas telomere dysfunction-induced chromosome aberrations that occur in the absence of telomerase are tumorigenic, the manifestation of full malignant phenotype requires telomerase reactivation in prostate cancer-prone mice.²

The multiple rounds of proliferation required over a lifetime of tissue renewal lead to progressive shortening of telomeres during each round of DNA replication, due to the end-replication problem.³ Since proliferative cells, as compared to germ or stem cells, contain insufficient telomerase to restore shortened telomeres, telomeres ultimately reach a critical length that leads to telomere dysfunction. Telomere dysfunction is a condition in which telomere capping proteins (shelterin) are no longer able to protect telomere DNA from being mistakenly recognized as DNA double-strand breaks by checkpoint signaling, which triggers cell growth arrest.⁴ However, cells with defective checkpoint signaling, e.g., inactive p53, continue to divide and, as a result, acquire chromosome rearrangements, deletions and amplifications that cause widespread apoptosis. Some cells can avert apoptosis and undergo malignant

transformation.^{5,6} Short but functional telomeres in such malignant cells are then maintained by telomerase that is markedly increased during malignant transformation.⁷ Compared to normal tissue, prostate cancer has much shorter telomeres and markedly elevated telomerase activity, suggesting a potential role of telomere dysfunction and telomerase reactivation in prostate cancer.⁸ However, the recent study of Ding *et al.*² provides direct evidence for a role of telomere dysfunction and telomerase reactivation in prostate cancer development and progression.

Ding *et al.*² used two distinct telomerase (mTert) defective mouse models derived from prostate cancer-prone mice with conditional androgen receptor (AR)-dependent knockout of Pten and p53 (*PB-Pten*^{-/-}/*p53*^{-/-}), to define the role of telomere dysfunction and telomerase reactivation in prostate cancer development and progression. One of these mouse models has telomerase knockout (*mTert*^{-/-} *PB-Pten*^{-/-}/*p53*^{-/-}) and the other is engineered to conditionally express telomerase upon AR-dependent Cre-mediated excision of an intronic Lox-Stop-Lox (LSL) cassette (*LSL-mTert PB-Pten*^{-/-}/*p53*^{-/-}). As illustrated in **Figure 1**, observations made using these mice are quite exciting. Whereas *PB-Pten*^{-/-}/*p53*^{-/-} mice develop bulky, rapidly progressive, and locally invasive non-metastatic tumors, as previously described,⁹ the tumors that are formed in *mTert*^{-/-} *PB-Pten*^{-/-}/*p53*^{-/-} mice are on average smaller and 55% fail to progress beyond high-grade prostatic intraepithelial neoplasia. Thus, despite telomere dysfunction-mediated genome instability, ongoing telomere erosion thwarts growth and progression of tumors by increasing apoptosis and decreasing proliferation of tumor cells in telomerase-deficient *mTert*^{-/-} *PB-Pten*^{-/-}/*p53*^{-/-} mice. By contrast, tumors formed in telomerase reactivated *LSL-mTert PB-Pten*^{-/-}/*p53*^{-/-} mice, which experience

telomere dysfunction prior to telomerase reactivation, are not only bulky, rapidly progressive and locally invasive as in parental *PB-Pten/p53* mice, but are also capable of metastasizing to bone in 25% of mice. Collectively, these observations provide direct evidence for the prevailing dogma that while telomere dysfunction-mediated chromosome instability contributes to cancer-relevant genome rearrangement, the manifestation of a malignant phenotype additionally requires telomerase for stabilization of telomeres.

Ding *et al.*² further studied the relevance of the observations made using telomerase-deficient prostate cancer-prone mouse models to human prostate cancer. They compared somatic copy number aberrations (sCNAs) in the tumors of telomerase-reactivated *LSL-mTert PB-Pten*^{-/-}/*p53*^{-/-} mice to those seen in human prostate tumors.¹⁰ Twenty-two of the 94 sCNAs in mouse tumors were syntenic with human sCNAs that are enriched in several cancer-relevant genes. One such gene, *SMAD4*, which belongs to the TGF- β signaling pathway and is one of the most frequently altered signaling pathways in patients with bone metastasis, is lost in *LSL-mTert PB-Pten*^{-/-}/*p53*^{-/-} primary tumors (25% of which metastasized to bone). The significance of *SMAD4* deletion was further validated by the observation that prostate cancer that develops in *SMAD4* knockout *PB-Pten*^{-/-}/*p53*^{-/-} mice metastasizes to bone. Thus, telomere dysfunction-mediated gene aberrations in genetically engineered telomerase-deficient mouse models may be relevant to prostate cancer development and progression in humans.

Although telomere dysfunction is a common consequence of aging-related progressive shortening of telomeres, acute telomere dysfunction can also result from the disruption of telomere capping shelterin proteins. For instance, deletion of wild type or overexpression of dominant-negative forms of

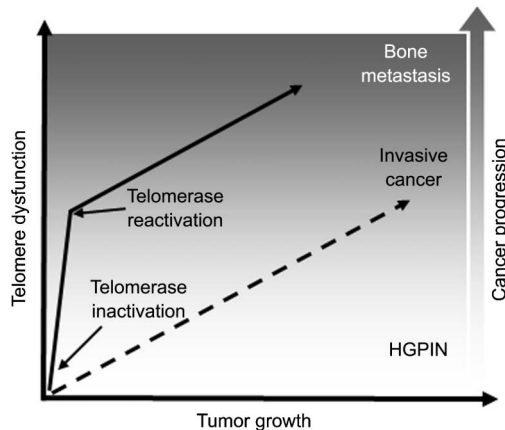


Figure 1 Model depicting the effect of telomere dysfunction on tumor growth and prostate cancer progression in the presence and absence of telomerase. Telomerase activity allows growth and progression of prostate cancer in *PB-Pten/p53* knockout mice (dotted line). In the absence of telomerase, tumor growth and progression are constrained by telomere dysfunction. Telomerase reactivation allows the proliferation of cells with telomere dysfunction-induced genomic instability and gene aberrations that are capable of metastasizing to bone. HGPIN, high grade prostatic intraepithelial neoplasia.

shelterin proteins, such as telomeric repeat-binding protein 2 (TRF2)¹¹ or TRF2- and TRF1-interacting nuclear protein 2 (TIN2),¹² leads to telomere dysfunction. In addition to shelterin proteins, there are several non-shelterin proteins that are associated with telomeres and disruption of these proteins can also result in acute telomere dysfunction. For example, in prostate cancer cells AR is associated with telomeres and AR-antagonist Casodex induces telomere dysfunction.¹³ At present, the biological consequence of such

acute telomere dysfunction in prostate cancer progression is known. The genetically engineered telomerase-defective prostate cancer-prone mouse models described in the study of Ding *et al.*² offer attractive models to investigate the effect of acute telomere dysfunction-mediated genome instability on the growth and progression of prostate cancer. Such studies in mice with and without telomerase may also provide insights into effective ways to use telomerase-targeted therapies for the treatment of prostate cancer.

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