



## CONSEQUENCES OF TELOMERE SHORTENING IN THE MOUSE PROSTATE GLAND

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Telomeres are highly repetitive, non-coding DNA segments located at chromosome ends. Telomeres, together with the telomeric-binding protein complex Shelterin, protect chromosomes by providing DNA that can be lost without losing any genes during DNA replication. DNA replication does not completely synthesize the ends of both strands of linear DNA due to the mechanism of synthesis of the lagging strand, shortening chromosomes by 50-200 base pairs after each round of replication. Without telomeres, continuing chromosomal erosion can affect DNA that encodes for genes, leading to deletion mutations. Telomeres also stabilize chromosome ends, thus critically shortened telomeres also pose a threat to chromosomal stability by enhancing the risk of chromosomal end-to-end fusion and subsequent breakages during mitosis, leading to translocations and large-scale deletions, abnormalities commonly seen in cancer. In keeping with this, shortened telomeres in prostate epithelial cells have been linked to prostate cancer. We hypothesized that short, dysfunctional telomeres play a causal role in the disease. To test this hypothesis, we expressed a telomere-specific endonuclease in mouse prostate glands and examined its effect on telomere length using fluorescent *in situ* hybridization. We demonstrated that expression of telomeric endonuclease activity in prostate epithelial cells results in critically short telomeres. These mice will be monitored for the emergence of abnormalities in prostate histomorphology in an otherwise wild type background and in a mouse strain with forced overexpression of the human MYC oncogene. We predict that if our hypothesis is correct, we will see the appearance of early prostate cancer lesions in the wild type setting and accelerated tumorigenesis in the setting of MYC overexpression.