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Neural Tumor-Initiating Cells Have Distinct Telomere Maintenance and Can be Safely Targeted for Telomerase Inhibition.

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Abstract

PURPOSE: Cancer recurrence is one of the major setbacks in oncology. Maintaining telomeres is essential for sustaining the limitless replicative potential of such cancers. Because telomerase is thought to be active in all tumor cells and normal stem cells, telomerase inhibition may be nonspecific and have detrimental effects on tissue maintenance and development by affecting normal stem cell self-renewal. **Methods:** We examined telomerase activity, telomere maintenance, and stem cell maturation in tumor subpopulations from freshly resected gliomas, long-term, primary, neural tumor-initiating cells (TIC) and corresponding normal stem cell lines. We then tested the efficacy of the telomerase inhibitor Imetelstat on propagation and self-renewal capacity of TIC and normal stem cells in vitro and in vivo.

RESULTS: Telomerase was undetectable in the majority of tumor cells and specific to the TIC subpopulation that possessed critically short telomeres. In contrast, normal tissue stem cells had longer telomeres and undetectable telomerase activity and were insensitive to telomerase inhibition, which results in proliferation arrest, cell maturation, and DNA damage in neural TIC. Significant survival benefit and late tumor growth arrest of neuroblastoma TIC were observed in a xenograft model ($P = 0.02$). Furthermore, neural TIC exhibited irreversible loss of self-renewal and stem cell capabilities even after cessation of treatment in vitro and in vivo.

CONCLUSIONS: TIC exhaustion with telomerase inhibition and lack of telomerase dependency in normal stem cells add new dimensions to the telomere hypothesis and suggest that targeting TIC with telomerase inhibitors may represent a specific and safe therapeutic approach for tumors of neural origin. *Clin Cancer Res*; 17(1); 111-21. ©2011 AACR.

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