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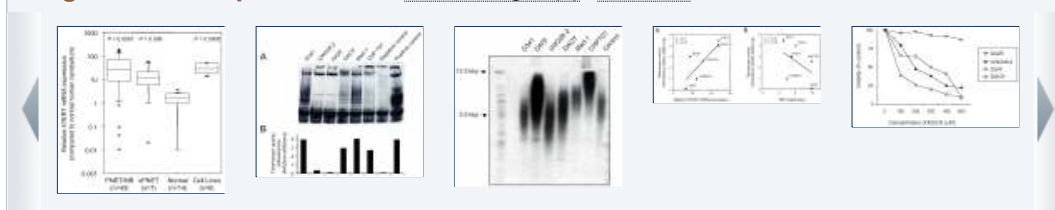
Telomere maintenance in childhood primitive neuroectodermal brain tumors.

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Abstract

Primitive neuroectodermal tumors (PNETs), including medulloblastoma (PNET/MB) and supratentorial PNET (sPNET), are the most common malignant brain tumors of childhood. The stabilization of telomere lengths by telomerase activation is an important step in carcinogenesis and cell immortalization. Epigallocatechin gallate (EGCG), the major polyphenol in green tea, is a telomerase inhibitor with antiproliferative and anticarcinogenic effects against different types of cancer. In this study, we used real-time reverse transcriptase-polymerase chain reaction to measure the mRNA expression of the human telomerase reverse transcriptase (hTERT) in 50 primary PNET samples (43 PNET/MB, 7 sPNET), 14 normal human brain samples, and 6 human PNET cell lines. Compared to normal human cerebellum, 38/50 (76%) primary PNET samples had \geq 5-fold upregulated hTERT mRNA expression. We then examined PNET cell lines for telomerase activity using a quantitative telomeric repeat amplification protocol (TRAP), and for telomere length using terminal restriction fragment analysis. While a positive correlation between hTERT mRNA expression and telomerase activity was detected in PNET cell lines, no correlation was found between telomerase activity and telomere length. Treatment of PNET cell lines with EGCG resulted in a dose-dependent inhibition of telomerase activity at micromolar levels. Although EGCG displayed strong proliferation inhibitory effects against TRAP-positive PNET cell lines, it had no significant effect against TRAP-negative D425 cells. These results provide evidence for a possible role of telomerase in the pathogenesis of most PNETs and indicate that subsets of PNETs maintain telomere length by alternative mechanisms. Inhibition of telomerase function represents a novel experimental therapeutic strategy in childhood PNETs that warrants further investigation.

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