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Activation of telomerase by human cytomegalovirus.

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BACKGROUND: The mechanism by which human cytomegalovirus (HCMV) stimulates oncogenesis is unclear. Because cellular immortalization and transformation require telomerase activation by expression of the telomerase reverse transcriptase (hTERT) gene, we examined the role of HCMV in telomerase activation. **METHODS:** Normal human diploid fibroblasts (HDFs) and human malignant glioma (MG) cell lines were infected with HCMV or transfected with expression vectors encoding HCMV immediate early (IE) antigen 72 or 86. hTERT expression and promoter activity and telomerase activity were evaluated using reverse transcription-polymerase chain reaction, a luciferase reporter assay, and a telomeric repeat amplification protocol, respectively. hTERT promoter occupancy by the transcription factor Sp1, IE antigens, and histone deacetylases (HDACs) was assessed by chromatin immunoprecipitation. hTERT and IE protein expression in human primary glioblastoma multiforme (GBM) was determined immunohistochemically. All statistical tests were two-sided. **RESULTS:** In telomerase and hTERT-negative HDFs, HCMV infection induced constitutive hTERT expression and telomerase activation. The hTERT promoter activity in HDFs and MG cell lines was statistically significantly enhanced by HCMV in a dose-dependent manner (mean luciferase activity [arbitrary units] in control HDFs and in HDFs infected with HCMV at multiplicities of infection [MOIs] of 0.1 = 6 and 521, respectively, difference = 515, 95% CI = 178 to 850; mean activity at MOI of 1 and 10 = 8828 and 59,923, respectively; $P < .001$ comparing control with HCMV-infected cells at all MOIs). Ectopic expression of HCMV IE-72 protein also stimulated hTERT promoter activity in HDFs. HCMV-mediated transactivation of the hTERT gene was dependent on the presence of Sp1-binding sites in the hTERT promoter and was accompanied by increases in Sp1 binding, acetylation of histone H3, and a reduction in HDAC binding at the core promoter. In specimens of GBM, HCMV IE and hTERT proteins were colocalized in malignant cells and their levels paralleled each other. **CONCLUSIONS:** HCMV activates telomerase in both HDFs and malignant cells. These findings begin to reveal a novel mechanism by which HCMV infection may be linked to or modulate oncogenesis through telomerase activation.

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