Human Cytomegalovirus US28 Found in Glioblastoma Promotes an Invasive and Angiogenic Phenotype.

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Abstract
Human cytomegalovirus (HCMV) infections are seen often in glioblastoma multiforme (GBM) tumors, but whether the virus contributes to GBM pathogenesis is unclear. In this study, we explored an oncogenic role for the G protein-coupled receptor-like protein US28 encoded by HCMV that we found to be expressed widely in human GBMs. Immunohistochemical and RT-PCR approaches established that US28 was expressed in ~60% of human GBM tissues and primary cultures examined. In either uninfected GBM cells or neural progenitor cells, thought to be the GBM precursor cells, HCMV infection or US28 overexpression was sufficient to promote secretion of biologically active VEGF and to activate multiple cellular kinases which promote glioma growth and invasion, including phosphorylated STAT3 and e-NOS. Consistent with these findings, US28 overexpression increased primary GBM cell invasion in Matrigel. Notably, this invasive phenotype was further enhanced by exposure to RANTES/CCL5, a US28 ligand, associated with poor patient outcome in GBM. Conversely, RNAi-mediated knockdown of US28 in human glioma cells persistently infected with HCMV led to an inhibition in VEGF expression and glioma cell invasion in response to CCL5 stimulation. Analysis of clinical GBM specimens further revealed that US28 co-localized in situ with several markers of angiogenesis and inflammation, including VEGF, p-STAT3, COX2 and e-NOS. Taken together, our results indicate that US28 expression from HCMV contributes to GBM pathogenesis by inducing an invasive, angiogenic phenotype. Additionally, these findings argue that US28-CCL5 paracrine signaling may contribute to glioma progression and they suggest that targeting US28 may provide therapeutic benefits in GBM treatment.

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