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[Clin Cancer Res](#). 2011 Apr 13. [Epub ahead of print]

Glioma-associated cytomegalovirus mediates subversion of the monocyte lineage to a tumor propagating phenotype.

[Dziurzynski K](#), [Wei J](#), [Qiao W](#), [Hatiboglu MA](#), [Kong LY](#), [Wu A](#), [Wang Y](#), [Cahill D](#), [Levine NB](#), [Prabhu S](#), [Rao G](#), [Sawaya R](#), [Heimberger AB](#).

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Abstract

PURPOSE: CMV has been ubiquitously detected within high-grade gliomas, but its role in gliomagenesis has not been fully elicited.

EXPERIMENTAL DESIGN: Glioblastoma multiforme (GBM) tumors were analyzed by flow cytometry to determine CMV antigen expression within various glioma-associated immune populations. The gCSC CMV IL-10 production was determined by ELISA. Human monocytes were stimulated with recombinant CMV IL-10 and levels of expression of p-STAT3, VEGF, TGF-beta, viral IE1 and pp65 were determined by flow cytometry. The influence of CMV IL-10 treated monocytes on gCSC biology was ascertained by functional assays.

RESULTS: CMV demonstrated a tropism for macrophages (M Phi s)/microglia and CD133+ gCSCs within GBMs. The gCSCs produce CMV IL-10, which induces human monocytes (the precursor to the CNS M Phi s/microglia) to assume an M2 immunosuppressive phenotype (as manifested by down modulation of the major histocompatibility complex and costimulatory molecules) while up regulating immune inhibitory B7-H1. CMV IL-10 also induces expression of viral IE1, a modulator of viral replication and transcription in the monocytes. Finally, the CMV IL-10-treated monocytes produced angiogenic VEGF, immunosuppressive TGF-beta, and enhanced migration of gCSCs.

CONCLUSIONS: CMV triggers a feed-forward mechanism of gliomagenesis by inducing tumor-supportive monocytes.

PMID: 21490182 [PubMed - as supplied by publisher]

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