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CMV and EBV mono- and coinfection as emerging onco-modulators in glioblastoma

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Dear Editor

Glioblastoma (GBM) remains the most aggressive and therapeutically refractory primary malignant brain tumor in adults, with mortality rates that have changed little over the past two decades. While numerous genomic and epigenetic alterations have been identified in GBM, its etiological drivers are still poorly understood. Increasingly, evidence suggests that viral infections -particularly those caused by members of the *Herpesviridae* family- may contribute to GBM pathobiology through *onco-modulatory* mechanisms rather than classical oncogenic transformation. In this context, we draw attention to the potential role of human cytomegalovirus (CMV) and Epstein–Barr virus (EBV) mono- and coinfection as overlooked contributors to GBM aggressiveness.

CMV has been detected in a substantial proportion of GBM tissues, and its gene products are known to modulate a wide array of cellular pathways relevant to tumor progression. CMV-encoded proteins such as IE1, glycoprotein B, and US28 have been shown to activate PI3K/AKT, STAT3, FAK, and hypoxia-related signaling, promoting proliferation, invasion, angiogenesis, and immune evasion. Furthermore, CMV appears capable of inducing telomerase activation in malignant glioma cells, supporting sustained growth and resistance to apoptosis. These findings suggest that CMV does not initiate oncogenesis directly but may enhance the malignant phenotype of GBM cells once tumorigenesis has begun.

EBV, another lifelong persistent herpesvirus with recognized oncogenic potential, has also been detected in GBM tissues. EBV-encoded oncoproteins, especially Latent Membrane Protein 1 (LMP1) and LMP2A, activate multiple cancer-related pathways -including NF-κB, MAPK, PI3K/AKT, and JAK/STAT- resulting in enhanced proliferation, epithelial–mesenchymal transition, inflammatory signaling, and chemoresistance. Although EBV's involvement in GBM is less widely studied than in nasopharyngeal carcinoma or lymphomas, several reports show a statistically significant association between EBV presence and GBM, warranting closer examination.

Importantly, coinfection with CMV and EBV has been documented in multiple clinical contexts. Such dual infections can influence viral reactivation, immune cell differentiation, and cytokine responses, thereby reshaping the tumor microenvironment toward a more permissive, immunosuppressive state. Given that each virus independently modulates key oncogenic pathways, their coexistence in GBM tissue raises the possibility of synergistic or additive effects on tumor biology. For example, both viruses can activate STAT3 and PI3K/AKT signaling, inhibit apoptosis through distinct molecular mechanisms, and enhance invasiveness through modulation of cytoskeletal dynamics and inflammatory mediators. These converging activities could collectively intensify the malignant behavior of GBM cells.

Despite these observations, the mechanistic interactions between CMV and EBV within GBM remain largely unexplored. It also remains unclear whether sequential infection, simultaneous infection, or virus-virus competition influences the extent of oncogenic signaling. Given that antiviral therapies targeting CMV have demonstrated potential survival benefits in some GBM patients, understanding whether EBV or CMV/EBV coinfection contributes to therapeutic resistance is an urgent priority.

We propose that future investigations incorporate models of mono- and coinfection to directly compare their effects on GBM proliferation, apoptosis, invasion, inflammation, and treatment sensitivity. Such studies may uncover viral biomarkers or vulnerabilities that could be exploited therapeutically. Determining whether CMV and EBV act as independent onco-modulators or engage in cooperative interactions could reshape our understanding of GBM pathogenesis and open new avenues for antiviral-based adjunctive therapy.

In conclusion, although the presence of CMV and EBV in GBM has been documented for years, the implications of their coexistence remain insufficiently recognised. A renewed focus on the CMV/EBV coinfection axis may help clarify unresolved questions in GBM biology and contribute to the development of more effective therapeutic strategies.

Acknowledgment

None.

Competing interests

None.

Abbreviations

Glioblastoma: GBM; Cytomegalovirus: CMV; Epstein-Barr virus: EBV; Immediate-Early 1: IE1; Phosphoinositide 3-kinase: PI3K; Protein Kinase B: AKT; Signal Transducer and Activator of Transcription 3: STAT3; Focal Adhesion Kinase: FAK; Latent Membrane Protein 1: LMP1; Latent Membrane Protein 2A: LMP2A; Nuclear Factor kappa-light-chain-enhancer of activated B cells: NF-κB; Mitogen-Activated Protein Kinase: MAPK; Janus Kinase: JAK.

Authors' contributions

The author read and approved the final manuscript. He takes responsibility for the integrity of the data and the accuracy of the data analysis.

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