Wu *et al. Virology Journal* (2025) 22:194
https://doi.org/10.1186/s12985-025-02826-3

Virology Journal

REVIEW Open Access

Role of cytomegalovirus in glioblastoma development: promoter or culprit?

Xiaoxin Wu[1,2*†], Zhengyu Zhang[3†], Liang Zhang[2] and David J Daniels[2,4*]

Abstract
Glioblastoma is the most common primary malignant tumor of the central nervous system, with a median survival of less than two years. While the etiology of glioblastoma is unclear, viral infection has emerged as a potential contributing factor. Cytomegalovirus (CMV) was first reported to be associated with glioblastoma in 2002. Since then, many studies have detected CMV in glioblastoma tissues suggesting it may plays a role in the glioblastoma progression. While there is no direct evidence confirmings CMV as an oncogenic virus, studies have demonstrated that CMV promotes glioblastoma development in cell and animal models, with several CMV-related genes implicated in tumorigenesis. Importantly, adjuvant CMV antiviral therapy has been proven to improve glioblastoma patient survival. This review focuses on clinical studies regarding the relationship between CMV and glioblastoma, the mechanism of CMV in tumorigenesis, advances in animal models of CMV-induced glioblastoma, and key directions for future investigations.

Keywords Glioblastoma, Etiology, Cytomegalovirus, Mechanism, Progress

Introduction

Gliomas are the most common primary malignant tumors of the nervous system [1], with an annual incidence ranging from 4 to 11 per 100,000 individuals in developed countries [2]. The World Health Organization classifies gliomas into grades 1 to 4, with grades 3 and 4 categorized as high-grade gliomas [3]. Among gliomas, glioblastoma has the worst prognosis for patients with a median survival less than two years [4]. Current treatment options for glioblastoma include maximal surgical resection, radiotherapy, and chemotherapy [5]. Despite advances in therapeutic strategies, such as CAR T-cell therapy and immune checkpoint inhibitors, no major breakthroughs have yet been achieved [6, 7]. The onset of glioblastomas are often associated with risk factors, such as ionizing radiation, genetic mutations, chemical toxins, and pathogen infections including viral agents [2]. Yet, the contribution of pathogen infection to glioblastoma etiology remains unclear, particularly regarding whether such infections initiate or promote cellular mutations and/or contribute to tumorigenesis.

The role of pathogens in tumorigenesis, especially viruses, is well established [8, 9]. Common oncogenic viruses in humans include Epstein-Barr virus, hepatitis B virus (HBV), human papillomavirus (HPV), human T-cell lymphotropic virus, hepatitis C virus (HCV),

†Xiaoxin Wu and Zhengyu Zhang are the co-first authors.

*Correspondence:
Xiaoxin Wu
xiaoxinwu@zju.edu.cn
David J Daniels
Daniels.David@mayo.edu
[1]State Key Laboratory for Diagnosis and Treatment of Infectious Diseases, National Clinical Research Centre for Infectious Diseases, the First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou 310003, Zhejiang, China
[2]Department of Neurologic Surgery, Mayo Clinic, Rochester, MN 55905, USA
[3]Medical Records Department, the First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou 310003, Zhejiang, China
[4]Department of Molecular Pharmacology and Experimental Therapeutics, Mayo Clinic, Rochester, MN 55905, USA

Kaposi's sarcoma herpesvirus, and Merkel cell polyomavirus [10]. Hepatitis B virus and HCV are linked to liver cancer [11, 12]. Human papillomavirus can cause cervical, anal, penile, and oropharyngeal cancers [13]. Epstein-Barr virus has been associated with Burkitt's lymphoma, B-lymphoproliferative disorder, Hodgkin's lymphoma, and nasopharyngeal carcinoma [14, 15]. Human T-cell lymphotropic virus is implicated in adult T-cell leukemia/lymphoma [16]. Merkel cell polyomavirus infection can result in Merkel cell carcinoma [17]. Kaposi's sarcoma herpesvirus infection can lead to Kaposi's sarcoma [18]. Over the past two decades, antigens and nucleic acids of several viruses have been detected in glioblastoma tissues, suggesting that viruses may be involved in glioblastoma development [19]. These viruses mainly include herpes virus, polyomavirus and human papillovirus [19]. Whether these viruses play a causative role in glioblastoma remains unclear. Of particular interest is human cytomegalovirus (CMV), a type 5 herpesvirus, which has garnered attention since its presence in glioblastoma tissues was reported in 2002 [20]. Since then, clinical samples and cell and animal models have been investigated to elucidate the role of CMV in glioblastoma development.

Human CMV infection is typically asymptomatic affecting up to 40–95% of the global population [10]. Numerous clinical studies have detected CMV nucleic acids or proteins in glioblastoma samples, suggesting that CMV may be involved in the initiation and/or progression of glioblastoma [1, 20]. Some studies have also reported that co-treatment with antiviral drugs such as valganciclovir showed improvement of overall patient survival [21–27]. While human CMV has been shown to promote tumor cell development and metastasis [28], the exact mechanism of CMV in glioblastoma remains to be elucidated. This review summarizes findings from epidemiological studies based on clinical samples, the role of CMV-targeted adjuvant therapy in glioblastoma in the past two decades, the tumor-promoting effect of CMV demonstrated in cell models and underlying progress in animal models of CMV-induced glioblastoma, and key areas for future research.

Clinical studies on the relationship between CMV and glioblastoma

Since the detection of CMV in glioblastoma tissues in 2002, the relationship between CMV and glioblastoma has garnered significant attention from clinicians and researchers [20]. Numerous investigations have been conducted to explore this association; however, the findings have been inconsistent [29]. While many studies have reported the presence of CMV proteins and nucleic acids in glioblastoma tissues [30–32], others have failed to detect any [33–35]. Several factors may be attributing to the inconsistency including CMV may not be present in all glioblastoma cases, the CMV genome may degrade over time in paraffin-embedded specimens, and the limitations of CMV detection techniques, which may necessitate the selection of suitable antibodies or optimization of detection methods [20, 36]. Some comprehensive reviews and meta-analyses have reported that CMV nucleic acids and proteins are detectable in over 63% of patients with cancer [1]. Although glioblastoma and CMV are closely related, most current studies have focused on detecting viral proteins or nucleic acids. However, viral proteins and nucleic acids can only suggest the presence of infection but cannot prove viral replication and activity. Measuring viral load in clinical samples and detecting CMV in serum samples may further clarify the role of CMV activity in glioblastoma [37]. Some studies have reported high viral loads of CMV in clinical samples and performed viral isolation, confirming the presence of live viruses in glioblastoma tissues [38, 39]. These isolated viruses were used to construct models that provided preliminary evidence of a relationship between CMV and glioblastoma [40]. Future clinical research should incorporate large-scale detection of viral proteins, nucleic acids, and viral load, followed by viral isolation and model validation to determine whether CMV plays a causative role in glioblastoma.

Findings from CMV-targeted adjuvant therapies also support a potential association between CMV and glioblastoma. For example, patients with low-grade CMV infection have longer overall survival than those with high-grade infection [41], suggesting that control CMV infection could be a novel therapeutic target for patients with glioblastoma. In 2013, Cecilia Söderberg-Nauclér et al. published a retrospective study involving 50 patients with glioblastoma who received valganciclovir as an adjuvant to standard therapy. The patients demonstrated significantly higher survival rates than the matched controls with similar disease stages, surgical resection grade, and baseline treatment. Patients who received valganciclovir treatment beyond six months achieved a two-year survival rate of 90% and a median overall survival of 56.4 months [23]. Giuseppe Stragliotto, et al. reported that valganciclovir treatment, when added to standard therapy, improves the outcomes of newly diagnosed glioblastoma patients [25, 42]. They further demonstrated the positive effect of valganciclovir in secondary glioblastoma. Eight patients treated with valganciclovir showed a significant increased median overall survival after progression to secondary glioblastoma compared with controls (19.1 versus 12.7 months) [26]. In another study, the addition of valganciclovir to bevacizumab slightly improved median overall survival in patients with recurrent glioblastoma compared with those receiving bevacizumab alone [24]. Patients who received valganciclovir as an add-on to their second- or third-line therapy after

recurrence also exhibited significantly improved survival rates than the controls [27]. A recent meta-analysis of five randomized controlled trials with over 600 patients demonstrated that ganciclovir significantly improved glioblastoma 2-year and 4-year survival rate by 20% [43]. This warrant further case studies or large-scale clinical trials to clarify the relationship between CMV and glioblastoma, as well as the underlying mechanisms.

While antiviral therapies provide evidence for CMV's involvement in glioblastoma and improved patient prognosis [44], it remains unclear whether CMV promotes glioblastoma development or acts as a causative agent. In patients with glioblastoma, radiotherapy and chemotherapy may reactivate latent CMV infection [45, 46]. Valganciclovir therapy may be effective in treating encephalitis symptoms and modifying the clinical course of the disease, thereby potentially influencing prognosis. Once reactivated, CMV may affect tumor aggressiveness and promote recurrence by influencing multiple cancer hallmarks. Isolating and characterizing CMV strains from patients will be critical to determining the direct role of CMV strains in brain cancer.

Mechanism of CMV in tumor development

Currently, most evidence indicates that CMV promotes tumor development; however, it has not been conclusively proven to be an oncogenic virus [47]. Cytomegalovirus can promote tumor development through multiple mechanisms (Fig. 1), including inhibiting tumor suppressor genes expression, promoting angiogenesis, enhancing tumor stem cell stemness, modifying the tumor microenvironment, promoting epithelial-mesenchymal transition (EMT), and inhibiting apoptosis (Table 1). Cytomegalovirus-infected glioma cancer stem cells can produce CMV interleukin-10 (IL-10), which can induce monocytes expressing immune suppressor B7H1 and secreting vascular endothelial growth factor, transforming growth factor-beta (TGF-β), and CMV immediate-early protein (IE), thereby facilitating glioblastoma invasion [48]. Cytomegalovirus infection rapidly activates receptor tyrosine kinase and AKT signaling pathways, promoting glioblastoma multiforme (GBM) cell invasiveness via focal adhesion kinase (FAK) activation [49]. CMV can also upregulate stemness regulators such as SOX2, phosphorylated-STAT3 (p-STAT3), and BMX in glioma stem-like cells (GSC), thereby promoting their survival, stemness,

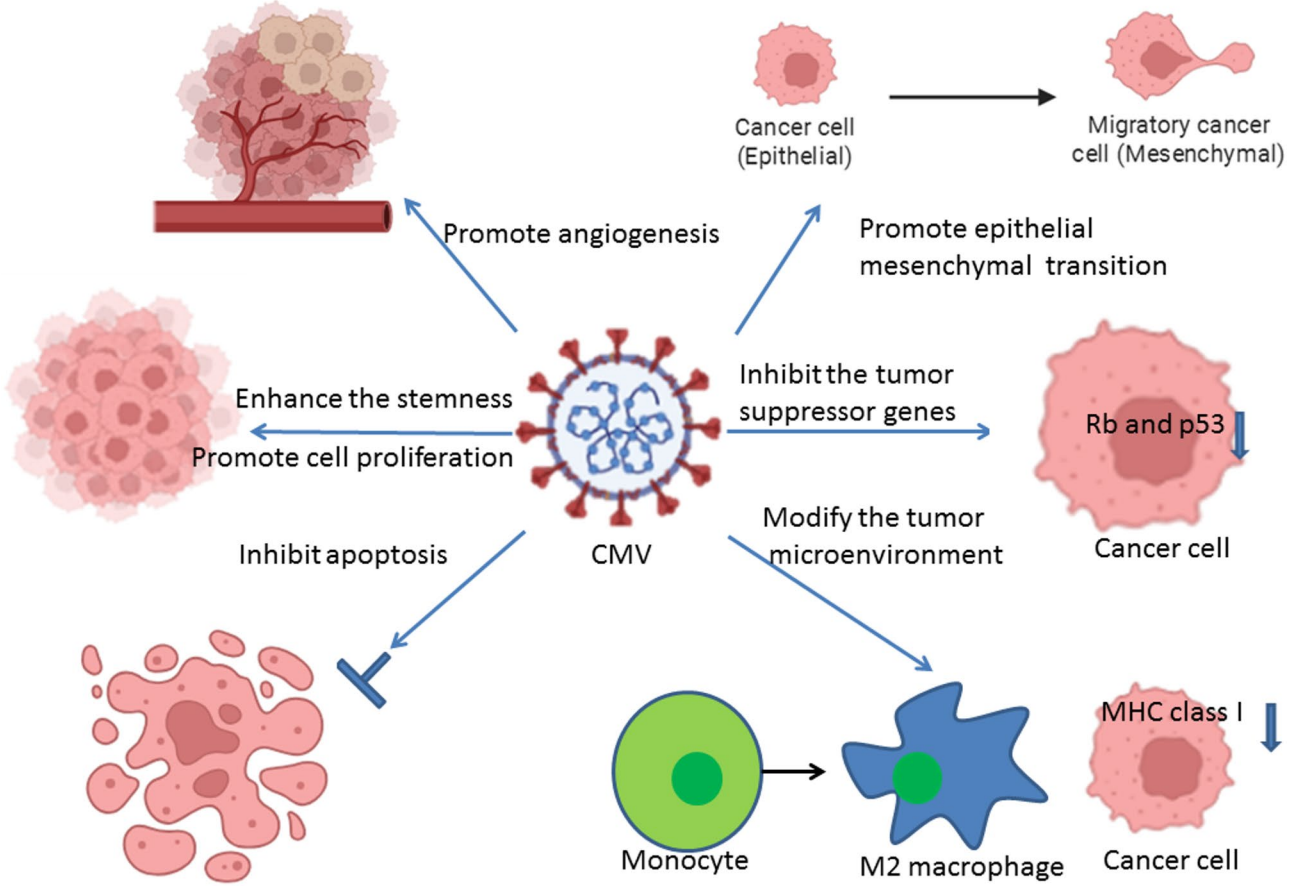

Fig. 1 Schematic diagram of the mechanisms by which cytomegalovirus promotes glioblastoma growth. CMV: Cytomegalovirus, MHC: Major histocompatibility complex. Created in BioRender. Wu, X. (2025) https://BioRender.com/t8sq5xn

Table 1 Mechanisms by which cytomegalovirus and its products contribute to glioblastoma development

Virus or viral products	Target gene or signaling pathway	Effect on host	Reference
CMV IL-10	Upregulation of VEGF and TGF-β	Enhances migration of gCSCs	[48]
CMV	Activation of PI3K/AKT, PLCγ, and FAK pathways	Increases migration of glioma cell	[49]
CMV	Upregulation of SOX2, p-STAT3. and BMX	Promotes survival, stemness, and proliferation of GSC	[50]
CMV	Activation of NF-κB signaling and c-MET	Promotes growth of GBM cells in vitro and in vivo	[51]
CMV	Upregulation of Endocan, IL-6, and arginase-2	Contributes to glioma progression	[52, 53]
CMV	Upregulation of ATF5 and Bcl-2	Inhibits apoptosis in GBM cell	[54, 55]
CMV	Activation of RIP2/ NF-κB, N-cadherin, and vimentin Downregulation of E-cadherin	Induces EMT and enhances cell migration and invasion in glioma cells	[56, 57]
CMV-miR-UL112-3p	Inhibits tumor suppressor candidate 3 gene expression	Promotes cell proliferation, clone formation, migration, and invasion	[58]
miRNA CMV70-3P	Increases expression of cellular SOX2	Increases GBM CSC stemness	[59]
CMV	Induces the PDGFD expression	Promotes murine GBM growth and angiogenesis	[60]
IE-72	Increases hTERT promoter activity	Cellular immortalization and transformation	[64]
IE1	Increases Sox2 and Nestin	Promotes stemness properties in GBM in vitro and in vivo	[65]
IE1	Reduction of Rb and p53 family proteins and induction of PI3K/AKT	Induces cellular proliferation	[66]
IE1	Downregulation of GFAP, TSP-1, and p53	Promotes the development of glioma	[67]
IE2	Suppresses GFAP	Increases glioma cell malignancy	[68]
IE72 and IE86	Degradation of connexin 43 and disrupt gap junction communication	Promotes the invasiveness of glioma cell	[69]
IE86	Upregulating heterogeneous nuclear ribonucleoprotein A2B1	Promotes migration of GBM cells and inhibits the apoptosis of GBM cells	[70, 71]
pp71	Activation of NF-κB signaling and upregulation of SCF	Contributes to the aggressive phenotype of glioma	[72, 73]
pp71	Downregulation of MHC class I proteins	Promotes immune suppression	[74]
gB	Binds to PDGFRA and activation of PI3-K/AKT	Promotes glioma cell invasion	[75, 76]
U28	Activation of NF-κB and IL-6-JAK1-STAT3	Promotes GBM cell proliferation	[77]
U28	Upregulation VEGF, p-STAT3, and e-NOS	Accelerates GBM cell growth and invasion	[78]–[81]
U28	Activation of S1P signaling and STAT3, AKT, and cMYC	Stimulates proliferation and survival of GBM cell	[82]
U28	Activation of HIF-1α and pyruvate kinase M2	Increased cell proliferation and metabolic reprogramming	[83]
US33	Activation of STAT3 and cAMP-responsive element	Aggravates GBM tumor growth	[84, 85]
CMV	Increases phosphorylated STAT3	Promotes glioma progression in a mut3 mouse model	[86]

CMV: Cytomegalovirus, VEGF: Vascular endothelial growth factor, TGF-β: Transforming growth factor-β, gCSCs: Glioma cancer stem cells, PI3K/AKT: Phosphatidylinositol-3 kinase/Protein Kinase B, PLCγ: Phospholipase Cγ, FAK: Focal adhesion kinase, SOX2: Sex determining region Y-box 2, p-STAT3: Phosphorylated signal transduction and activators of transcription-3, BMX: Bone marrow X-linked kinase, GSC: Glioma stem-like cells, NF-κB: Nuclear factor kappa-B, GBM: glioblastoma, c-MET: Cellular-mesenchymal epithelial transition factor, ATF5:Activating transcription factor 5, Bcl-2: B-cell lymphoma-2, RIP2: Receptor-interacting protein 2, EMT: Epithelial–mesenchymal transition, PDGFD: Platelet Derived Growth Factor D, hTERT: human telomerase reverse transcriptase, Rb: retinoblastoma, GFAP: glial fibrillary acidic protein, TSP-1: thrombospondin-1, SCF: stem cell factor, MHC: Major histocompatibility complex, gB: glycoprotein B, PDGFRA: platelet derived growth factor receptor alpha, e-NOS: endothelial nitric oxide synthase, S1P: sphingosine-1-phosphate, cMYC: Cellular myelocytomatosis oncogene homolog, cAMP: cyclic adenosine monophosphate, mut3 mouse model: GFAP-cre; $Nf1^{loxP/+}$; $Trp^{53-/+}$ genetic mouse model

and proliferation [50]. Cytomegalovirus infected GBM tumor cells leads to NF-κB activation and the subsequent upregulation of the proto-oncogene c-MET, which promotes GBM growth [51]. Other studies indicate that CMV contributes to glioma progression by upregulating endocan, IL-6, and arginase-2 [52, 53]. Cytomegalovirus infection also increases ATF5 expression and the Bcl-2/BAX ratio, blocking apoptosis in glioblastoma cells [54, 55]. Cytomegalovirus infection also induces EMT and enhances cell migration and invasion in glioma cells by activating the RIP2/NF-κB signaling pathway, downregulating the expression of the epithelial cell marker (E-cadherin), and upregulating the expression of mesenchymal cell markers (N-cadherin and vimentin) [56, 57]. Cytomegalovirus-encoded miRNAs has also shown to promote glioma. For example, miR-UL112-3p regulates GBM pathophysiological processes by suppressing tumor suppressor candidate 3 expression [58], while miRNA CMV70-3P increases GBM cancer stem cell stemness by upregulating cellular SOX2 [59]. In a mouse model, CMV

induced PDGFD expression, thereby increasing pericyte recruitment and angiogenesis [60].

Cytomegalovirus gene products have been implicated in cell cycle dysregulation, apoptosis inhibition, enhanced cell migration and invasion, and angiogenesis [61, 62]. Specific viral gene products may influence key oncogenic signaling pathways involved in glioma progression [63]. Direct CMV infection increases glioblastoma cell migration and hTERT levels. Cytomegalovirus IE-72 may drive mitogenesis and cellular immortalization via hTERT upregulation [64]. Cytomegalovirus IE1 promotes GBM stemness, cell cycle progression, and survival by increasing SOX2 and Nestin levels [65]. Upon PI3-K/AKT pathway activation, the CMV IE1 gene product can activate Rb and p53 tumor-suppressor proteins in some GBM cells [66]. CMV IE1 gene product can also downregulate glial fibrillary acidic protein and thrombospondin-1 [67]. Cytomegalovirus IE2 has also been found to suppress glial fibrillary acidic protein expression, which declines with increasing glioma malignancy [68]. Moreover, CMV IE72 and IE86 can cause Cx43 degradation, resulting in the disruption of gap junctional intercellular communication (GJIC) in glioblastomas. GJIC degradation, which occurs at an earlier stage of tumor development, contributes to gliomagenesis [69]. Furthermore, CMV IE86 promotes GBM cell migration and inhibits apoptosis by upregulating heterogeneous nuclear ribonucleoprotein A2B1 [70, 71].

Cytomegalovirus pp71, encoded by the UL82 gene, can activate the NF-κB signaling pathway and an important angiogenic pathway. In adult neural progenitor cells and glioma cells, pp71 expression induces stem cell factor (SCF) expression in an NF-κB-dependent manner. In vivo, pp71 expression in human GBM cells may contribute to endothelial cell migration and angiogenesis, features typically associated with an aggressive tumor phenotype [72, 73]. Additionally, pp71 expression in GBM cells promotes immune suppression by reducing cell-surface expression of MHC class I proteins [74]. Cytomegalovirus glycoprotein B (gB) directly binds to PDGFRA and induces downstream activation of the oncogenic PI3-K/AKT pathway, thereby promoting glioma cell invasion [75, 76].

US28 is a constitutively active G-protein-coupled receptor that upregulates multiple oncogenic signaling pathways, including the JAK/STAT3 pathway. A study demonstrated that US28 activates the IL-6-JAK1-STAT3 signaling axis via NF-κB activation, which leads to IL-6 production [77]. US28 expression induces COX-2 expression through NF-κB activation, thereby driving the production of VEGF [78]. In GBM cells, human CMV infection or US28 overexpression is sufficient to promote the secretion of biologically active VEGF and activate multiple cellular kinases that facilitate glioma growth and invasion, such as p-STAT3 and endothelial nitric oxide synthase [79–81]. Another study demonstrated that US28 stimulates glioblastoma cell proliferation and survival by initiating S1P signaling, resulting in the concurrent activation of STAT3, AKT, and c-MYC [82]. Moreover, US28 can mediate HIF-1α and pyruvate kinase M2 expression, which drives cell proliferation, angiogenesis, and metabolic reprogramming [83]. US33, which is a viral G protein-coupled receptor, contributes to CMV-mediated STAT3 activation and can aggravate glioblastoma tumor growth in orthotopic glioblastoma xenograft models [84, 85].

Cytomegalovirus has shown to facilitate glioblastoma progression in a genetically engineered mouse model [86] (Fig. 2). Perinatal infection of these mut3 mice with mouse CMV led to a significant reduction in survival rates due to accelerated tumorigenesis. Mouse CMV infection increased p-STAT3 levels in neural stem cells prior to glioma onset [86]. However, current studies are limited to tumor cells and animal models and thus only demonstrate that CMV infection promotes tumor development [87].

Animal model for CMV-induced glioblastoma

To demonstrate the role of CMV in glioblastoma, the virus should first be isolated. Even within the same CMV species, different strains exhibit different characteristics [38]. Ideally, CMV should be isolated directly from glioblastoma cells, as this will be required for subsequent experiments. However, only one research team has succeeded in its isolation [38]. To validate the oncogenic potential of CMV, the virus should exhibit transforming potential in human cells in vitro and induce tumors in animal models, and this tumorigenesis should be preventable by viral neutralization. Georges Herbein et al. have made significant contributions promoting this research. They have isolated three CMV clinical strains from glioblastoma tissues. The strains can transform primary human astrocytes into CMV-elicited glioblastoma cells (CEGBCs). When xenografted into mice, the CEGBCs formed glioblastoma-like tumors [40]. Cytomegalovirus nucleic acids and proteins were detected in CMV-derived xenografts for up to two months post-engraftment, further indicating a potential link between CMV persistence and tumor progression. Future studies should characterize the differences between CEGBCs, primary glioblastoma cell lines, and glioblastoma tissues at the gene level and evaluate whether complete transformation from human astrocytes to glioma cells is possible.

To date, no CMV oncogene has been definitively linked to glioblastoma, highlighting the need for further investigations. For example, HBV-transgenic mice expressing HBV pre-S, S, and X proteins spontaneously developed liver cancer during their lifespan [88]. Similarly, HPV E6

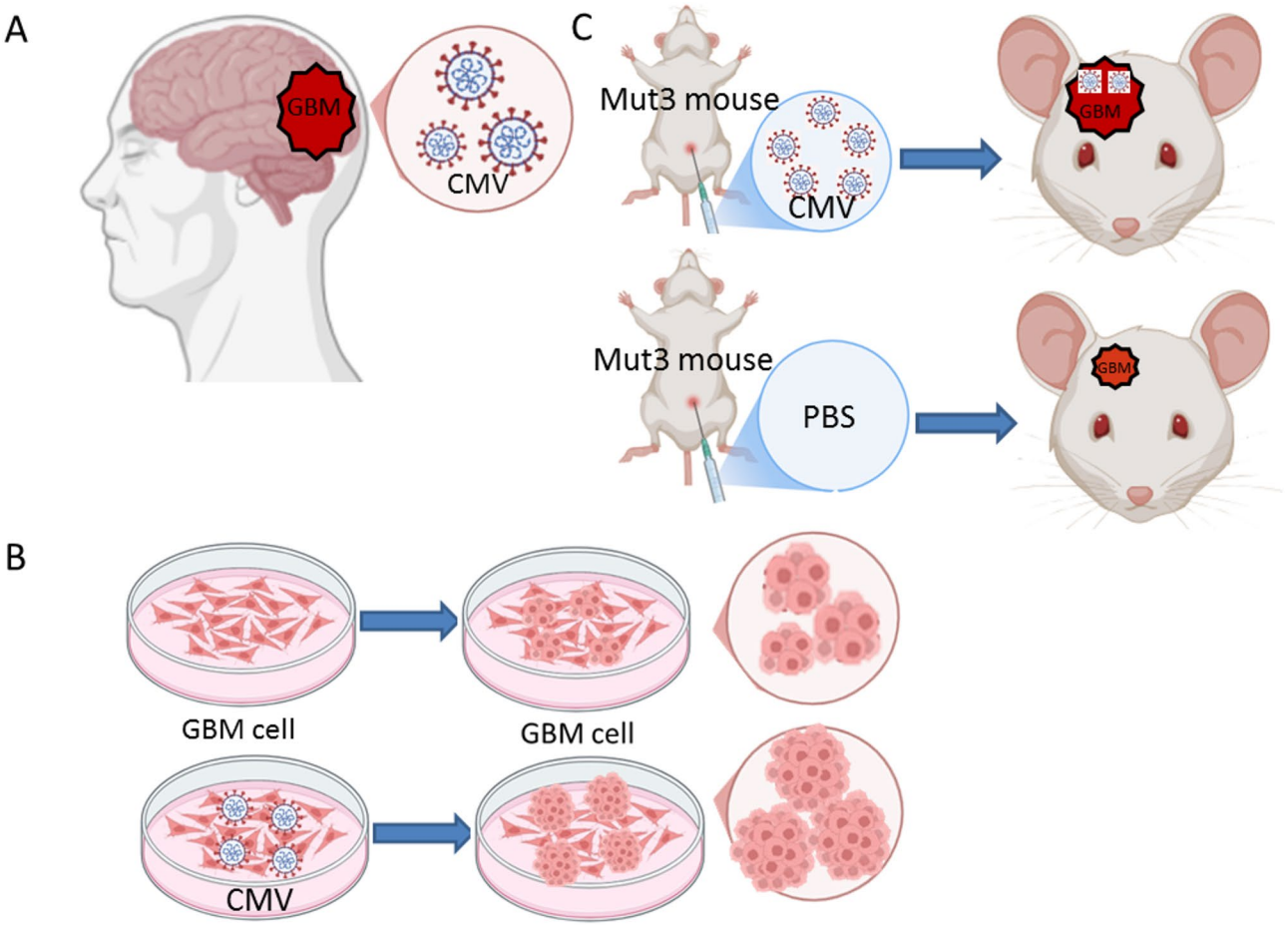

Fig. 2 Several lines of evidence support the role of cytomegalovirus in promoting glioblastoma development. **A**: Cytomegalovirus is detected in the tumors of patients with glioblastoma. **B**: CMV promotes glioblastoma progression in cell culture models. **C**: CMV promotes glioblastoma progression in a genetically engineered mouse model. Mut3 mouse: GFAP-cre; $Nf1^{loxP/+}$; $Trp^{53-/+}$ genetic mouse. CMV: Cytomegalovirus, GBM: Glioblastoma multiforme. Created in BioRender. Wu, X. (2025) https://BioRender.com/qqzub37

and E7 oncogenes are critical to tumorigenesis and have been validated in murine models [89]. To establish CMV as a causal agent in glioblastoma, it is essential to identify the key genes and develop murine tumor models that recapitulate their oncogenic activities (Fig. 3).

Key directions for future investigations

Based on current clinical studies and in vitro and animal studies, CMV demonstrates a robust association with glioblastoma development. While CMV has been demonstrated to promote glioblastoma progression, definitive evidence linking CMV to glioblastoma etiology remains lacking, necessitating future investigations [90–92]. Establishing causality requires transitioning from correlative evidence to mechanistic validation, including the development of stable animal models and the identification of viral oncogenes [93]. Primarily, clinical research should include detailed patient data and pay more attention to tumor characteristics (primary versus recurrent), treatment history (chemotherapy and/or radiotherapy), and signs of infection or encephalitis. Such information is crucial for evaluating the role of CMV in tumor initiation and/or progression. Neuro-oncologists should continue investigate the clinical relationship between CMV and glioblastoma and the prognostic significance of antiviral therapy. Importantly, virologists and neuro-oncologists need to collaborate more to form research consortia to facilitate the collection of fresh or frozen glioblastoma and blood samples to ensure the preservation of viral nucleic acids and viral activity. Virus isolation should be prioritized for samples with high viral titers. After isolation, virus identification and research should be conducted to clarify the characteristics of the virus and study the effects of the virus on cell proliferation and tumorigenicity. The isolated virus should also be used for in vivo models. Comparative analysis with patients' tumor cell lines and tissues should be performed at the transcriptomic level to assess whether tumorigenesis has occurred. Furthermore, CMV vaccines should be

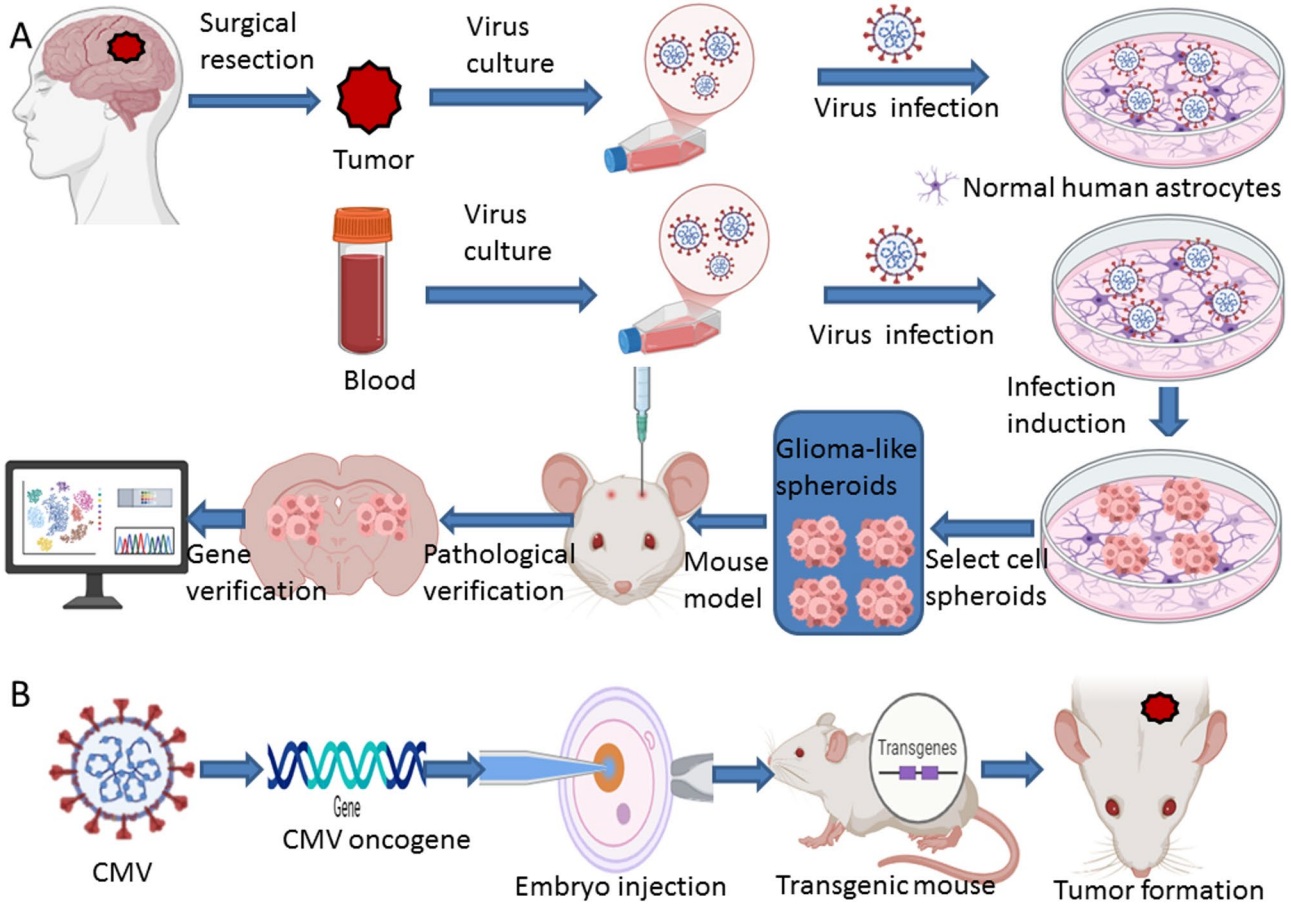

Fig. 3 Schematic of an animal model for cytomegalovirus-induced glioblastoma under ideal conditions. **A**: Schematic of cytomegalovirus culture and in vivo and in vitro induction of glioblastoma diagram. **B**: Diagram of the construction of a cytomegalovirus transgenic mouse model. CMV: Cytomegalovirus. Created in BioRender. Wu, X. (2025) https://BioRender.com/bv3nsvz

developed and tested for their preventive effects against glioblastoma.

Conclusion

Glioblastoma remains a critical oncological challenge affecting human health. Despite advances in treatment modalities, median survival for glioblastoma remains under two years. There are two primary research directions: continued development of treatment strategies and investigation into the cause of glioblastoma. Over the past two decades, increasing evidence has implicated viral involvement, particularly CMV, as a potential driver of glioblastoma development. However, existing data primarily demonstrates that CMV promotes glioblastoma progression. Antiviral therapy as an adjunct therapy for glioblastoma may extend survival and improve quality of life. Additionally, CMV-targeted immunotherapies, such as vaccines, have great prospects for future research.

To date, no direct evidence confirms that CMV can induce glioblastoma. However, CMV has been isolated from glioblastoma tissues, and preliminary in vivo models have been established. Future efforts should prioritize viral isolation and characterization from clinical samples, followed by mechanistic validation using cellular and animal models. With continued efforts, the role of CMV in glioblastoma development may be elucidated.

Acknowledgements
We thank Home for Researchers editorial team (www.home-for-researchers.com) for language editing service.

Author contributions
LZ and XW designed the research. XW and ZZ drafted the manuscript. LZ, XW and DJ Daniels contributed to the critical revision of the manuscript. All authors contributed to the manuscript and approved the submitted version.

Funding
This work was supported by the National Natural Science Foundation Youth Project (82300004) and National Key R&D Program of China (2024YFC2309904 and 2024YFC3506600). The funding sources had no role in the study design; in the writing of the report; or in the decision to submit the paper for publication.

Data availability
All data or related information supporting the conclusions of the review is included in the article.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
We have got the publication licenses for Figs. 1, 2 and 3 from BioRender.

Competing interests
The authors declare no competing interests.

Conflict of interest
The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 2 May 2025 / Accepted: 7 June 2025
Published online: 13 June 2025

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