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REVIEW

Cytomegalovirus in human brain tumors: Role in pathogenesis and potential treatment options

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Abstract

During the last years increasing evidence implies that human cytomegalovirus (CMV) can be attributed to human malignancies arising from numerous tissues. In this perspective, we will review and discuss the potential mechanisms through which CMV infection may contribute to brain tumors by affecting tumor cell initiation, progression and metastasis formation. Recent evidence also suggests that anti-CMV treatment results in impaired tumor growth of CMV positive xenografts in animal models and potentially increased survival in CMV positive glioblastoma patients. Based on these observations and the high tumor promoting capacity of this virus, the classical and novel antiviral therapies against CMV should be revisited as they may represent a great promise for halting tumor progression and lower cancer deaths.

Key words: Cytomegalovirus; Oncovirus; Glioblastoma; Medulloblastoma; Brain tumor

Core tip: Cytomegalovirus (CMV) has recently been detected in several human cancers. These findings have raised several concerns whether this virus is the cause or a passenger during oncogenesis. Here we discuss the pathogenesis behind CMV infection, its potential as an onco- or oncomodulatory-virus and possible modes of medical interventions.

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HUMAN CYTOMEGALOVIRUS

Cytomegalovirus (CMV) is a common virus belonging to the herpesvirus family[1], which infects 70%-100% of the world's population. After a primary infection that is generally mild or asymptomatic in the immunocompetent host, this virus establishes latency and persistence in myeloid lineage cells, and periodic asymptomatic reactivations are believed to occur during life[1] without clinical signs of infection. However, in individuals with a suppressed immune system, CMV may cause life-threatening infections. Despite a good prophylaxis and surveillance program for early detection of reactivation of CMV in transplant patients, these infections remain to be a clinical problem both as an acute infection as well as a cause of long-term complications. Patients who have had CMV infections in the post-transplant period are at higher risk of developing acute and chronic rejection, cardiovascular diseases, bacterial and fungal infections, post-transplant diabetes and some malignancies[2-5]. These conditions are mainly believed to be mediated by indirect effects of CMV[4], as the virus has been difficult to detect in affected organs at time of diagnosis[6]. However, more recently, the use of sensitive techniques for detection of CMV demonstrate that the presence of CMV in kidney grafts is associated with decreased organ function and graft survival[7,8], suggesting that this virus causes direct, in addition to indirect effects, in the graft.

Emerging evidences also suggest that CMV is highly prevalent in patients with breast, colon, and prostate cancer, rhabdomyosarcoma, hepatocellular cancer, salivary gland tumors, neuroblastoma and brain tumors[9-25]. Over 90% of these tumors have been shown to be positive for CMV proteins and nucleic acids as determined by methods including in situ hybridisation, PCR, electron microscopy, DNA and RNA sequencing, immunostaining of tissue specimens, flow cytometry analyses of tumor cells from surgical resections and western blot analysis. Also most neoplastic cells in sentinel lymph nodes of > 90% of breast cancers have been shown to be CMV positive[26] as well as 98% of brain metastases of colon and breast cancers contain CMV proteins and/or nucleic acids[27]. In sharp contrast, CMV proteins are not detected in healthy tissues surrounding CMV positive tumors or metastases. These observations suggest that this virus does not represent an epiphenomenon of CMV positive tumors, but rather that it may directly aid in tumor progression or even in the initiation and cancer development. As CMV proteins are mainly confined to metastatic cells in metastases of breast and colon cancer[26,27], CMV may be maintained within cells that initiate the development of the metastasis. However, the role of CMV in tumor initiation, progression and metastasis formation needs to be further thoroughly examined in depth since some researchers have failed to detect CMV in tumors[28-33]. This causes confusion in the field and voices have been raised that the presence of CMV in tumors is false and based on artefact data. However, stimulation of dendritic cells with glioblastoma tumor lysates leads to expansion of CMV specific T cells in glioblastoma patients and CMV pp65 specific T cells can kill autologous glioblastoma cells *in vitro*. This suggests that CMV epitopes are present in glioblastoma tumors[34,35]. The inconsistency in the detection of CMV in tumors samples between laboratories is most likely due to differences in the sample preparations, control specimens and sensitivity of the methods employed for the detection of CMV nucleic acids or proteins. Therefore studies to search for CMV in tumors should be based on techniques that have been developed and proven to work in tumor specimens.

HUMAN MALIGNANT BRAIN TUMORS; GLIOBLASTOMA AND MEDULLOBLASTOMA

Human brain tumors are diverse neoplasms that currently include more than 120 different clinopathological entities[36]. Glioblastomas and medulloblastomas are the most frequently occurring malignant brain tumors in adults and children, respectively. Gliomas accounts for approximately 75% of all primary brain tumors, whereas medulloblastoma is the most common solid childhood tumor[37,38]. The median age of diagnosis of gliomas is 64 years whereas for medulloblastomas about 99% of the tumors are detected in early childhood or adolescence[36,39].

Gliomas are histopathologically classified as ependynomas, astrocytomas, oligodendrogliomas and mixed oligo-astrocytomas and graded with regard to malignancy as Grade Ⅰ-Ⅳ. Grade Ⅲ (anaplastic astrocytomas) and Ⅳ gliomas [glioblastoma (GBM); glioblastoma multiforme] account for approximately 82% of cases and are considered malignant or high-grade gliomas[39]. The current standard of care for malignant gliomas includes surgical resection, radiation therapy with concomitant and adjuvant chemotherapy[40]. Despite aggressive treatment approaches, the median survival for patients diagnosed with Grade Ⅳ glioblastoma is 16 to 19 mo with 25%-30% of the patients alive 2 years after treatment[41].

Malignant gliomas are heterogenous tumors with different clinical and molecular signatures. Glioblastomas have been divided into four molecular subtypes characterized by abnormalities in *PDGFRA*/*IDH1*, *EGFR*, and *NF1* that represent the proneural, classical and mechencymal subtypes, respectively[42]. In addition, a fourth transcriptional subtype termed neural subtype is characterized by high expression of neural markers like *NEFL*, *GABRA1*, *SYT1*, and *SLC12A5*[42]. Many of the molecular abnormalities overlap between the different glioblastoma subtypes and additional rare mutations and chromosomal aberrations have been described, adding to the heterogeneity of glioblastomas. Cells of origin for glioma are not clearly identified but neural stem cells and oligodendrocyte precursor cells that both derive from a neuroepithelial cell, have been suggested[43].

Medulloblastomas are also a compilation of molecular and clinical diverse tumor types that arise either in the cerebellum or brainstem[44]. These tumors are

highly malignant and current treatment of patients with medulloblastoma consists of surgery, whole brain and spinal cord radiation (in patients above 3 years) and aggressive chemotherapy, sometimes followed by stem cell transplantation[44]. Even though long-term survival among medulloblastoma patients is 60%-70%, the patients frequently experience disease or treatment related complications including developmental, neurological, neuroendocrine, and psychosocial deficits[45]. Although medulloblastomas contain significantly less mutations than adult cancers[46], specific subsets have been identified and aberrant expression of key molecules regulating developmental signaling cascades, oncogenic drivers and mutations in tumor suppressor genes, have been described, such as alterations of the Shh and Wnt signaling pathways, overexpression of MYC, MYCN and activation of growth factor independent 1 family proto-oncogenes, GFI1 and GFI1B by enhancer hijacking[44,47-49]. However, since many medulloblastoma tumors have no apparent mutations of any known cancer gene, it has been suggested that epigenetic changes or other etiological factors including infections also may be responsible for tumor initiation and progression[9,44,46,50].

Medulloblastomas have been linked to disordered mechanisms of normal development and medulloblastoma cells retain many features resembling precursor cells of the embryonic brain. Approximately half of these tumors contain abnormal activation of the developmental signalling cascades, Shh and Wnt[51,52]. Moreover, activation of the PI3K/Akt signalling pathway has been shown to be important for initiation and proliferation of medulloblastoma[53-55]. Molecular analysis have shown that there are four major medulloblastoma subgroups (Wnt, Shh, Group 3 and Group 4[44]). These subgroups are distinct in tumor cell histology and biology and exhibit divergent clinical phenotypes. Different subtypes of medulloblastoma are also believed to have distinct cellular origins. One subtype originates from cerebellar granule neural precursor cells located in the external granular layer of the cerebellum as a result of aberrant Shh signalling[56,57]. A subpopulation of cells from these tumors is positive for the progenitor markers Math1 and CD15[58]. A different medulloblastoma subtype arises outside the cerebellum, likely from cells of the dorsal brainstem and is dependent on Wnt signalling. These tumors contain aberrantly proliferating Zic (+) precursor cells[59]. Finally, evidence of a third medulloblastoma subtype deriving from CD133-positive (Prom1) cerebellar stem cells has also been proposed. These tumors contain elevated Myc expression[60,61].

Many malignant gliomas and medulloblastomas are hence thought to initiate from precursors cells within the CNS by sequential and cumulative genetic alterations or developmental errors[43,49,62]. Rare hereditary syndromes including Cowden, Turcot, Li-Fraumeni, tuberous sclerosis, neurofibromatosis and schwannomatosis have been associated with increased risk of glioma, whereas increased risk of medulloblastomas have been observed in individuals with Turcot, Gorlin and Li-Fraumeni syndromes[62]. However, the etiology behind the vast majority of gliomas and medulloblastomas still remain largely unknown and no fundamental environmental factors, except ionizing radiation that is associated with increased risk for glioma development, has been convincingly demonstrated[37]. On the other hand, it seems to be a strong inverse relationship between atopic diseases and glioma[63]. Both glioblastomas and medulloblastomas express high levels of cyclooxygenase-2 (COX-2) that catalyzes conversion of arachidonic acid to prostaglandins and other eicosanoids with concomitant secretion of proinflammatory prostaglandin E_2 (PGE_2)[64-66]. In gliomas, the level of COX-2 expression is directly correlated to glioma grade and associated with shorter survival in glioblastoma patients[65]. Non-steroidal anti-inflammatory drugs, capable of inhibiting cyclooxygenase, significantly suppress the growth of glioblastoma and medulloblastoma in preclinical models[9,64,66]. Also, short-term use (< 10 years) of anti-inflammatory medication is associated with a protective effect against glioblastoma[67]. Taken together, this suggests that brain tumors are at least partly dependent on an inflammatory microenvironment in order to proliferate and progress.

An inflammatory microenvironment can be induced directly by tumor cells through activation of oncogenes that activate transcriptional programs leading to the production of pro-inflammatory eicosanoids, cytokines and chemokines that attract different immunological cells to the surrounding tumor microenvironment. Inflammation in the tumor microenvironment can also be caused indirectly by viral and microbial infections, autoimmune diseases, and dietary products[68]. Tumor-related inflammation is hence important for tumor cells to sustain a proliferative state, escape apoptosis and enhance angiogenesis, metastasis and suppression of the immune system[68].

CMV'S POTENTIAL ROLE IN BRAIN TUMORS: CMV PROTEINS CONFER BOTH ONCOMODULATORY AND ONCOGENIC FUNCTIONS

In the light of the above description of the phenotypic and molecular diversity of gliomas and medulloblastomas, and their different sites of origin in the brain, it is interesting to note that most of glioblastomas and medulloblastomas appear to be CMV positive. The presence of CMV proteins in medulloblastoma and glioblastoma hence raise questions whether this virus plays an important role in tumor initiation and/or progression of these tumors. CMV is not a typical oncogenic virus, but CMV proteins provide many mechanisms that can promote tumor biology relevant mechanisms. During the evolution, there has been a strong evolutionary pressure on CMV to cope with and survive the attacks by the immune system and to create efficient virus factories. CMV was believed to encode for approximately 180 proteins, of which only about 45 have been estimated to be essential for virus replication[69-72]. A more recent study based on ribosomal

profiling suggests that 751 unique CMV proteins are translated in infected cells[73]; if true, this virus is far more complex than previously appreciated. However, regardless of the exact number of CMV proteins that are encoded by this virus, the vast majority of CMV proteins must confer other functions during the virus life cycle than ensuring replication and formation of new virus particles. Several CMV encoded proteins can under certain circumstances initiate cellular transformation or through other ways aid in tumour development and provide mechanisms representing the cornerstones of hallmarks of cancer[74].

The concept of a role of CMV in cancer is not new. Already in the 1970's, Fred Rapp's group reported the frequent presence of CMV in prostate cancer, and isolated a virus strain from tumors that was oncogenic *in vitro* and in immunodeficient mice[75]. However, in several later studies, CMV failed to transform normal human cells, wherefore this virus was not considered to be oncogenic. The classical view implies that oncoviruses encode gene products that can induce cellular transformation under certain circumstances, *e.g.*, HPV, SV40, EBV, Hepatitis B and adenoviruses. For CMV, the term oncomodulation has instead been proposed to describe the indirect influence of CMV on tumorigenesis (reviewed in[6,76,77]). Oncomodulation is defined as the ability to promote, in an appropriate genetic environment supplied by tumor cells, an oncogenic process characterized by disruptions in intracellular signalling pathways, transcription factors and tumor suppressor proteins. For example, CMV proteins control the cell cycle, induce telomerase activity, inhibits apoptosis, induce angiogenesis and cellular migration and hence provide oncomodulatory mechanisms[76-79]. Furthermore, CMV proteins can promote stemness by blocking cellular differentiation and interact with the DNA damage response pathway to alter the cell cycle (reviewed in[77]). CMV proteins induce expression of oncogenes, control expression of tumor supressors, induce specific chromosomal breaks and p53 mutations, inhibit DNA repair mechanisms, control epigenetic functions and cellular proliferation[80-82], and provide immune evasion strategies[83-85].

Experimental data also suggest that CMV can be oncogenic. A gene region of the CMV genome, the transforming region Ⅱ (mtrⅡ), a 980-bp sequence, was first shown to transform rodent fibroblasts[86-90]. Expression of the CMV proteins IE72 or IE86 together with the adenovirus E1A protein can induce cellular transformation through a "hit and run" mechanism[91]. The CMV IE proteins can bind to p53, Rb and degrade p21, and thereby modulate cell cycle regulation, induce telomerase activity[78] and downregulate tumor suppressor proteins, which may aid in oncogenic transformation[77]. The CMV protein US28, a G coupled chemokine receptor homologue, has several characteristics resembling a viral oncoprotein[92-95]. Expression of US28 in NIH3T3 cells renders them tumorigenic upon injection in nude mice[94,95], which involves induced COX-2 expression and VEGF production[95]. Furthermore, transgenic mice expressing US28 only in intestinal epithelial cells developed intestinal adenomas and adenocarcinomas[92], by inhibiting glycogen synthase 3β (GSK-3β) activity, resulting in an accumulation of β-catenin and increased expression of Wnt target genes involved in the control of cell proliferation[92]. US28 also induces STAT3 phosphorylation through IL-6 production, which correlates with poor survival in GBM patients[93]. Analysis of clinical GBM samples *in situ* showed co-localization of US28 with phosphorylated STAT3, COX-2, VEGF and e-NOS, and US28 can induce cellular migration *in vitro*, which suggests that US28 may contribute to tumour invasiveness and angiogenesis *in vivo*[77,93,96]. CMV protein expression in mucoepidermoid cancer also correlated with activation of known oncogenic pathways such as EGFR, ERK and amphiregulin, and protein expression was related to severity[97]. These experimental data suggest a direct molecular link between the expression of US28 and tumorigenesis. In addition, US28 has also been shown to activate the transcription factor nuclear factor B (NF-Kβ), a critical regulator of immunity, stress responses, apoptosis, cellular differentiation and migration[96].

More recently, the microenvironment at the tumor site and the potential close connection to inflammation has received increasing attention, and there seems to be a close link between inflammation and tumor development. COX-2 and PGE_2 are over-expressed in a number of different cancers and high COX-2 expression is often correlated with poor prognosis[66,98]. CMV infection induces COX-2 and 5-lipoxygenase (5-LO) expression and mediate production of PGE_2 and leukotrienes that are both potent inflammatory mediators[99,100]. PGE_2 also induces cellular proliferation, angiogenesis, inhibition of apoptosis and stimulation of invasion, and can contribute to the generation of a tumour promoting inflammatory microenvironment[98]. Interestingly, we observed a clear association between CMV protein expression and COX-2 expression in medulloblastoma, suggesting that CMV may control COX-2 expression in these tumors[9]. Viruses could also by their sole presence induce an immune response through expression of non-self peptides to T cells and create an inflammatory microenvironment.

Epithelial cells can undergo a transition into mesenchymal cells [epithelial to mesenchymal transition (EMT)], involving a series of events resulting in the loss of cell-to-cell contacts and dramatic remodelling of the cytoskeleton. In addition to its role in normal physiological development, recent data implicates a role for EMT and mesenchymal to epithelial transition (EndoMT) in tumor pathology, particularly in regards to metastatic capacity of epithelial tumors. A major factor that regulates the EMT process is transforming growth factor beta (TGFβ). CMVs ability to induce TGFβ provides a role of this virus to facilitate the EMT process[101]. In support of this hypothesis, CMV infected epithelial cells treated with TGFβ *in vitro*, were shown to undergo morphologic and transcriptional changes similar of EMT; this also occurred in uninfected cells[102]. CMV infected epithelial cells can also activate extracellular latent TGFβ1 through induction of metalloproteinase 2 (MMP-2), which was proposed to be mediated by the CMV proteins CMV IE72 or IE86[102]. Induced MMP-2 activity could also in theory mediate

degradation of the extra cellular matrix[103], which would further aid in the formation of a metastasis. In addition, CMV US28 can interfere with the activity of expression of GSK3β, which is known to phosphorylate and control the stability of key oncogenic transcription factors such as the Smads and Snail that can trigger an EMT program. Furthermore, virus induced COX-2 expression, and activation of Ras/Erk and PI3K/AKT signalling pathways may further induce and maintain a viscous paracrine loop leading to possible cellular invasion into surrounding stroma.

POTENTIAL TREATMENT OPTIONS TARGETING CMV IN BRAIN TUMORS

We found CMV DNA and proteins in 92% of primary medulloblastoma tumors and in 99% of glioblastomas and also detected the virus in eight of eight examined medulloblastoma cell lines, grown in culture for decades[9]. When the medulloblastoma cells were implanted subcutaneously in immunodeficient mice, all tumors were CMV protein positive; a majority of the tumor cells expressed CMV IE proteins[9]. We found CMV proteins in medulloblastoma cells in culture expressing CD133 and CD15, which are proposed markers of medulloblastoma stem cells. The cancer stem cell hypothesis states that only a subpopulation of cancer cells have self-renewing ability and the capacity to give rise to tumours[104]. Such cancer stem cells or tumour initiating cells (TICs) exhibit an immature phenotype, *e.g.*, expression of pluri-/multipotency associated transcription factors[105], a slower proliferation rate and increased resistance to cancer therapy relative to more differentiated cancer cells[106]. In theory, TICs could either be directly infected by CMV as immature cells or represent a dedifferentiated mature cell with a potential ability to affect tumorigenesis and EMT. CMV infected tumor cells undergoing EMT may detach from adjacent cells and potentially enter the circulation *via* the lymphatic system or the blood stream. It is possible that CMV positive tumor cells in primary breast, prostate and colon tumors can undergo EMT to obtain stem cell characteristics, *i.e.*, a potential TIC/ EMT cell will circulate, undergo the reverse process of EndoMT as metastases are developing in lymph nodes or distant organs such as the brain. If CMV resides in TICs, it would explain why all xenografted tumors were virus positive, although only a minority of medulloblastoma tumor cells in culture expressed CMV proteins[9]. If this holds true, drugs targeting CMV infection may not only be beneficial to inhibit primary tumor growth but may also reduce the capacity of the tumour to become invasive as it may selectively kill the TICs. Such scenario implies that most stages of tumor development, primary growth, migration, invasion, intravasation and potentially metastasis may be sensitive to anti-viral drugs making CMV an ideal target for therapeutic intervention.

Hence, regardless if CMV plays a role in the development of tumors, CMV has been detected in brain tumors such as glioblastoma and medulloblastoma and virus infected tumor cells may therefore represent a new target of therapy. In support of this hypothesis, we showed that animals carrying CMV positive human medulloblastoma or neuroblastoma tumors that were treated with anti-CMV drugs had significantly smaller tumors than placebo treated animals[9,107]. A synergistic effect was observed with a COX-2 inhibitor, which resulted in a 72%-97% reduced medulloblastoma tumor growth *in vitro* and *in vivo*[9]. Both COX-1 and COX-2 inhibitors are efficient anti-viral drugs that prevent the replication of CMV[99,108]. Thus, antiviral drugs and COX-2 inhibitors may act synergistically to affect the growth of CMV positive tumors[9]. Interestingly, a number of recent studies demonstrate that Aspirin, a non-selective COX- inhibitor, significantly prevents cancer development and metastases[109-113]. With current data at hand, it cannot be excluded that some of the preventive effect of COX-2 inhibitors involves CMV mediated tumor mechanisms.

Treatment of GBM xenograft tumors with the anti-CMV drug Cidofovir also reduced tumor growth, although a CMV independent mechanism was observed[114]. Importantly, treatment of 50 glioblastoma patients who received anti-CMV treatment as an add-on to standard therapy at Karolinska University Hospital as adjuvant treatment demonstrate a remarkably high survival: the 2 year survival was 70% among 40 patients receiving 6 mo of anti-viral therapy and as high as 90% among patients with continuous treatment (n = 25) compared with 18% in contemporary controls (n = 137); median OS was 56.4 mo compared with 13.5 mo in controls in the latter group ($P < 0.0001$[115]). These observations call for a deeper understanding of CMVs role in cancer and whether this virus is a novel target in anti-cancer therapy. Also, anti-CMV drugs used as an add-on therapy should be further analysed in larger glioblastoma patient populations to give robust statistical data in randomised trials to confirm or dismiss the use of valganciclovir in these patients. The presence of CMV in glioblastoma would also imply that immunotherapy protocols that target CMV epitopes expressed in the tumor can be exploited as cancer therapy[116-118]. Several immunotherapy protocols are currently under evaluation in clinical trials to evaluate different CMV based protocols for glioblastoma patients; these need to also consider the immunosuppressive state of glioblastoma patients.

Several studies indicate that GBM patients exhibit functional impairments of their T cell functions[119,120]. However, polyfunctional CMV specific T cells can be restored by *in vitro* stimulation with CMV antigens and gamma C cytokines. It was recently demonstrated the CMV pp65 specific T cells can kill autologous glioblastoma cells *in vitro*[35], and that immunotherapy using CMV specific T cells was associated with prolonged survival in a single patient[18]. This suggests that adoptive therapy of *in vitro* expanded T cells may be a preferred protocol to be used to overcome the problem of unresponsive T cells *in vivo*, although T cell activation may be possible to overcome by the right stimulus also *in vivo*. Today

two clinical studies are open for enrolment of GBM patients; one is testing genetically modified CMV specific cytotoxic cells for recurrent GBM; a chimeric antigen receptor recognizes human epidermal growth factor receptor 2 coupled to CD28. The other is based on DC vaccination together with a monoclonal antibody against CD25 aimed to inhibit IL-2 signalling. Results from these trials are expected in 2015 and 2016, respectively, and currently results from two other studies that are closed for recruitment are also awaited in the near future. Most likely, future protocols will have to evaluate the effect of immunotherapy in combination with anti-viral therapy for CMV to obtain optimal anti-CMV effects in cancer patients.

CONCLUSION

In summary, emerging data suggest that CMV may play a pathogenic role in cancers of epithelial and neuronal origin. Under such circumstances, anti-viral treatment strategies may provide new options in cancer therapy of CMV positive tumors and metastases to improve patient outcome.

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