



## Mini-review

## Oncogenic role of cytomegalovirus in medulloblastoma?

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## ABSTRACT

Medulloblastoma is the most common solid tumor among children. Current therapeutic strategies for this malignancy include surgical resection, radiation therapy and chemotherapy. However, these treatments are accompanied with serious side effects such as neurological complications and psychosocial problems, due to the severity of treatment on the developing nervous system. To solve this problem, novel therapeutic approaches are currently being investigated. One of them is targeting human cytomegalovirus in medulloblastoma cancer cells. However, this approach is still under debate, since the presence of cytomegalovirus in medulloblastomas remains controversial. In this review, we discuss the current controversies on the role of cytomegalovirus in medulloblastoma oncogenesis and the potential of cytomegalovirus as a novel (immuno)therapeutic target.

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## Introduction

Amongst children, medulloblastoma is the solid tumor with the highest incidence [1], arising in the cerebellum [2]. The survival rate nowadays is at 60–70% [3], but with very serious sequelae of neurophysiological and psychosocial effects as a result of the treatment [4]. To define the optimal therapeutic strategy for medulloblastomas, the World Health Organization (WHO) classified medulloblastomas into four histological subtypes: classic medulloblastoma, large cell/anaplastic medulloblastoma, desmoplastic/nodular medulloblastoma and medulloblastoma with extensive nodularity [5]. In addition to this classification based on clinicopathological features, a revised classification was proposed based on the molecular profile of the tumor. This classification divides medulloblastomas in 4 molecular distinct subtypes i.e.: WNT-activated medulloblastoma, SHH-activated medulloblastoma (subclassified in two types: *TP53*-wildtype and *TP53*-mutant), group 3 and group 4 medulloblastoma [5].

The human  $\beta$ -herpesvirus cytomegalovirus (HCMV) has been described to play a role as an oncomodulator in the development of different types of cancer [6–8]. Some studies have proposed a role for HCMV in the development of medulloblastoma [9,10]. Others have not been able to detect the presence of this virus in medulloblastoma [11–13]. Thus, the oncogenic role of HCMV is still an ongoing controversy in the literature. In this review, we will discuss the controversy regarding the involvement of HCMV in medulloblastoma, as well as the potential of HCMV-guided (immuno)therapy.

## Medulloblastoma characteristics and subtypes

Medulloblastoma is the most common malignant childhood brain tumor, but it is very infrequent in adults [1]. It is a malignancy that arises in the cerebellum [2]. Even though these patients are subjected to surgery, radiation therapy, and chemotherapy, the overall five-year survival rate still remains around 60–70% [3]. Although the treatment of medulloblastoma has improved during the past few decades due to the intensified therapy, many children still die or suffer severe side effects as a result of the applied therapy. The side effects of the current treatment modalities include neurological dysfunction, endocrine deficits and psychosocial problems, e.g. difficulties in establishing relationships and significant problems in school [4].

In addition to somatic mutations in neural progenitor cells giving rise to medulloblastomas, several hereditary tumor syndromes have been associated with medulloblastomas. The Li-

**Abbreviation index:** APC, Adenomatous Polyposis Coli; CNS, Central Nervous System; COX-2, Cyclooxygenase-2; DC, Dendritic cell; GNPCs, Granule neuron precursor cells; HCMV, Human Cytomegalovirus; IL, Interleukin; PGE<sub>2</sub>, Prostaglandin E<sub>2</sub>; Rb, Retinoblastoma; SHH, Sonic Hedgehog; STAT3, Signal Transducer and Activator of Transcription 3; TCR, T Cell Receptor; VEGF, Vascular Endothelial Growth Factor; WHO, World Health Organization.

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Fraumeni syndrome, an autosomal dominant disorder linked to germ-line mutations in the tumor suppressor gene *TP53*, predisposes patients to cancer development and incidentally they develop a medulloblastoma. In fact, half of the SHH medulloblastomas with *TP53* mutations have a germ-line origin (Li-Fraumeni syndrome) [14]. The Gorlin syndrome, a disorder characterized by alterations in the *PTCH* gene, which encodes the sonic hedgehog (SHH) receptor Patched 1, has also been found to be occasionally related to the development of medulloblastoma. Even though only 1–2% of patients with medulloblastoma suffer from Gorlin syndrome [15], aberrations in the *PTCH* gene occur frequently in SHH medulloblastomas [16,17]. Finally, patients suffering from the Turcot syndrome, which is caused by mutations in the adenomatous polyposis coli (*APC*), *MLH1* or *PMS2* genes, have a significantly increased risk of developing a medulloblastoma as compared to the population [15].

The first consensus stratified medulloblastoma into 4 different subtypes depending on the histology of the tumor: classic medulloblastoma, large cell/anaplastic medulloblastoma, desmoplastic/nodular medulloblastoma and medulloblastoma with extensive nodularity [5]. Consensus that was reached in 2010, classifies medulloblastoma in four subgroups depending on their transcriptome, namely WNT-activated medulloblastoma, SHH-activated medulloblastoma, group 3 and group 4 medulloblastoma [16,18]. In addition to this classification, the current 2016 WHO stratification of medulloblastoma establishes two subtypes of SHH medulloblastoma: *TP53*-mutant and *TP53*-wildtype [5]. Additionally, a recent publication stratifies each of these four medulloblastoma subgroups into different subtypes [19]. These classifications were established to gain better insights into the characteristics of these tumors and their potential treatment options, with the aim of personalized medicine on the horizon, so that each patient can receive the most effective and less harmful treatment.

The first two groups, as their names state, are caused by alterations in the WNT and SHH signaling pathways, respectively, while less is known about the causes underlying group 3 and group 4 medulloblastoma [18]. WNT medulloblastomas may arise from precursor cells within the dorsal brain stem and SHH medulloblastomas have been reported to originate from cerebellar granule neuron precursor cells (GNPCs) [20,21]. Group 3 medulloblastomas also seem to arise from GNPCs, but have distinct differences in the activated pathways when compared to SHH medulloblastomas [22]. Group 3 medulloblastomas express photoreceptor-encoding genes that are typically associated with retinal development, and specifically the expression profile resembles that of rod precursor cells at week 15 of human retinal development [22]. Group 4 medulloblastomas also arise from GNPCs; however, they have expression profiles that are similar to the ones found in cerebellar glutamatergic granule neurons at late fetal developmental stages [22].

WNT-driven medulloblastomas have the best prognosis among all medulloblastomas, with a 95% 5-year survival rate. Unfortunately, it is the least common of the four medulloblastoma subtypes [16,18]. WNT-driven medulloblastomas very often carry mutations in the  $\beta$ -catenin encoding gene, *CTNNB1*, that promote the stabilization and nuclear localization of this protein [16,18]. In addition to mutations in *CTNNB1*, heterozygous somatic *TP53* mutations can also be present [16]. SHH medulloblastomas have an intermediate prognosis, with 5-year survival rates of 60–80%. Nearly all tumors harboring desmoplastic or nodular histology are restricted to this subgroup [16]. The SHH medulloblastoma can be divided in two distinct patient populations, infants and adults of which the tumors are generally *TP53*-wildtype as compared to patients aged 4–18 years old, with a *TP53*-mutant SHH medulloblastoma [5]. Roughly 20–25% of the SHH medulloblastomas have a mutated *TP53* gene,

of which half originates from a germline mutation [5]. A report by Bhatia et al. shows that the accumulation of fatty acids due to exaggerated de novo lipid synthesis is a typical hallmark of SHH medulloblastomas [23]. This characteristic appears when excessive SHH signaling leads to inactivation of the tumor suppressor retinoblastoma (Rb), which in turn leads to the activation of the transcription factor E2F1 and of the metabolic regulator PPAR $\gamma$  [23]. Therefore, antagonizing PPAR $\gamma$  might be a good therapeutic approach in SHH-driven medulloblastomas or, generally, in tumors that display inactivation of Rb [23]. Tumors classified as subgroup 3 medulloblastomas frequently display large cell or anaplastic histology, are more common in men, are almost always restricted to pediatric patients and have the worst predicted outcome [16,18]. The majority of group 3 medulloblastomas also contain deregulated expression of the *MYC* gene [16,18]. Finally, group 4 medulloblastomas are the most frequent molecular subtype of medulloblastoma. This subgroup is much more common in men than in women and adults suffering from it have a worse prognosis compared to children [16,18]. The presence of the isochromosome 17q is characteristic of group 4 medulloblastomas, as well as the loss of one copy of the X chromosome in female patients [16,18]. Nevertheless, many medulloblastomas do not display any apparent genetic mutations. Therefore, it has been proposed that epigenetic alterations could be an important factor in medulloblastoma tumorigenesis [3,9,16,24].

### Cytomegalovirus infection in humans

Human cytomegalovirus (HCMV) is a  $\beta$ -herpesvirus specifically infecting humans. The seroprevalence of this virus varies greatly and ranges from 30% to 70% in developed countries and is increasing with age. Meanwhile, the seroprevalence in particular population groups such as poor socioeconomic groups or in developing countries can be as high as 90% of the population [25]. In most affected individuals, the virus endures a lifelong latency, but in immunocompromised patients the virus can reactivate and lead to productive replication and disease [25]. Some typical situations of immune deficiency are found in HIV patients, in patients with inflammatory bowel disease under treatment with TNF $\alpha$  inhibitors, immediately after solid organ or stem cell transplantation, etc. The recipients of transplantations are at a relatively high risk of developing HCMV-related disease, especially in the cases where the organ recipient is serologically negative and the donor is serologically positive [25].

### Cytomegalovirus-associated oncogenesis

Different infectious agents have been described to play a role in central nervous system (CNS) cancers, as reviewed by Alibek et al. [26]. One of these infectious agents is HCMV. HCMV has been widely described to be present in different cancer types as an oncomodulator rather than as a tumor initiating virus [6–8], e.g. by promoting a pro-inflammatory environment. A part of the pro-inflammatory state that is promoted by HCMV occurs via the up-regulation of the enzyme cyclooxygenase-2 (COX-2), which favors inflammation by inducing the synthesis of inflammatory mediators such as PGE $_2$ . COX-2 has been found to be up-regulated by the HCMV-encoded protein US28, via induction of the NF $\kappa$ B signaling pathway [27]. The relevance of COX-2 in tumor progression is highlighted by the fact that the use of its selective inhibitor celecoxib delays tumor formation [27], which has also been shown in medulloblastoma cell culture and mouse models [28]. Moreover, the promotion of an inflammatory environment has been observed in human medulloblastomas [29]. A pro-inflammatory tumor microenvironment can add to medulloblastoma progression, with

tumor-associated macrophages contributing to tumor cell growth, especially in the SHH subgroup [30].

COX-2 can be up-regulated in medulloblastoma and one of its derived products, PGE<sub>2</sub>, in turn, stimulates medulloblastoma cell proliferation [31]. The relevance of COX-2 in medulloblastoma growth *in vivo* is highlighted by the finding that its selective inhibition with celecoxib causes an increase in apoptosis and an inhibition of tumor growth [31]. In addition to favoring an inflammatory environment that sometimes promotes carcinogenesis, activation of COX-2 also stimulates tumor progression by inducing vascular endothelial growth factor (VEGF) and cyclin D1 expression [27]. The relevance of COX-2 in promoting tumorigenesis is supported by the notion that celecoxib-mediated inhibition of COX-2 cooperates with all-*trans* retinoic acid to induce cell differentiation *in vitro*, which makes COX-2 an attractive anti-tumor prospect [32].

Others show that HCMV-encoded protein US28 promotes proliferation of the infected cells by activation of the IL-6-STAT3 axis resulting in up-regulation of VEGF and interleukin-6 (IL-6) [33]. Consistent with previous findings, the induction in IL-6 expression comes as a result of an increased NFκB signaling [27,33]. Increased IL-6 levels lead to a stimulation of STAT3 phosphorylation both in the HCMV-infected cells as well as in the neighboring cells, meaning that US28-dependent activation of STAT3 can take place both in an autocrine and in a paracrine manner [33]. Thus, STAT3 activation results in US28-induced cell proliferation. Because one of the STAT3 targets is IL-6, induction of STAT3 creates a US28-initiated positive feedback loop leading to a persistent activation of STAT3-dependent cell proliferation [33]. A summary of the oncomodulatory roles of HCMV in medulloblastoma is schematically represented in Fig. 1.

HCMV has been found in 99% of cases of brain metastases of breast and colorectal cancers, with the patients harboring low-grade HCMV infection tending to have longer overall survival rates as compared to high-grade HCMV infection [34]. This suggests that HCMV has a biological role in the initiation of metastasis of carcinomas [34]. The involvement of HCMV in different CNS tumors and the possible advantage of targeting this virus to treat various types of human cancer is summarized in Ref. [3]. HCMV-encoded protein US28 expression has been shown to correlate with poor survival in glioblastoma patients, suggesting that targeting HCMV seems to be a promising strategy [3,33]. Further studies are required to determine whether other HCMV proteins or transcripts play roles in medulloblastoma oncogenesis. In this context, HCMV transcriptome and proteome analyses in medulloblastoma might be helpful.

In line with targeting HCMV as a potential treatment for various human tumors, shifting the immune system to suppress HCMV is currently being investigated as a potential therapy for HCMV-related cancers. With this goal in mind, different vaccines (viral,

non-viral and DNA vaccines) are at present being tested, as reviewed in Ref. [35].

### Cytomegalovirus as a target for medulloblastoma therapy?

In line with the role of HCMV in medulloblastoma oncogenesis, in the past few years some studies where HCMV or its specific components are targeted have yielded promising results for the treatment of cancer. In Ref. [36], Xue et al. have analyzed the applicability of T-cell therapy against cancer, using leukemia as the cancer model and the HCMV-encoded protein pp65 as the target antigen. They activated T cells with anti-CD3 antibodies and, afterwards, transfected them with a retroviral vector encoding for a pp65-targeting TCR [36]. Thereby, they achieved the activation of both CD4<sup>+</sup> and CD8<sup>+</sup> T cells and associated cytokine synthesis upon stimulation with the epitope. After testing the avidity of both sets of T cells, overexpression of CD8 co-receptor is needed in CD4<sup>+</sup> cells to efficiently recognize the target peptide at low concentrations [36]. Moreover, CD4<sup>+</sup> T cells present a robust production of TNFα, IL-4 and IL-5, as compared to background levels expressed by CD8<sup>+</sup> T cells, with this effect not being changed after overexpression of the CD8 co-receptor [36]. To test if these effects had an influence in tumor development, they used NOD/SCID mice subcutaneously challenged with human leukemia K562 cells expressing HLA-A2 and pp65. In these mouse models, CD4<sup>+</sup> cells expressing the CD8 co-receptor and a TCR against a pp65 epitope efficiently eradicate the tumor [36]. This study shows that targeting HCMV-encoded proteins can be a tool for treating tumors. However, as we mentioned before, the *in vivo* experiments are carried out in mice challenged with leukemia cells, and it needs to be tested in the future if the reported effect is also observed when treating medulloblastoma.

Except for medulloblastoma, the applicability of using immunotherapy against HCMV for the treatment of other neurological tumors has been demonstrated, including glioblastoma [37–39]. These studies have demonstrated that *ex vivo* matured dendritic cells (DCs) were efficiently generated from peripheral blood mononuclear cells of glioblastoma patients. Transfection of these DCs with the pp65 RNA efficiently stimulates the expansion of HCMV-specific autologous (cytotoxic) CD4<sup>+</sup> and CD8<sup>+</sup> T cells [37,38]. Treatment of glioblastoma patients with pp65-pulsed DCs prolongs progression-free survival and overall survival, which is enhanced when combined with dose-intensified temozolomide (DI-TMZ) treatment [40].

Another example of the potential of targeting HCMV to control tumor growth is a study carried out by Baryawno et al. [9]. They report that the use of the antiviral agent ganciclovir leads to a reduced clonogenic capacity of medulloblastoma cell lines *in vitro*. The use of the COX-2 inhibitor celecoxib also reduces this

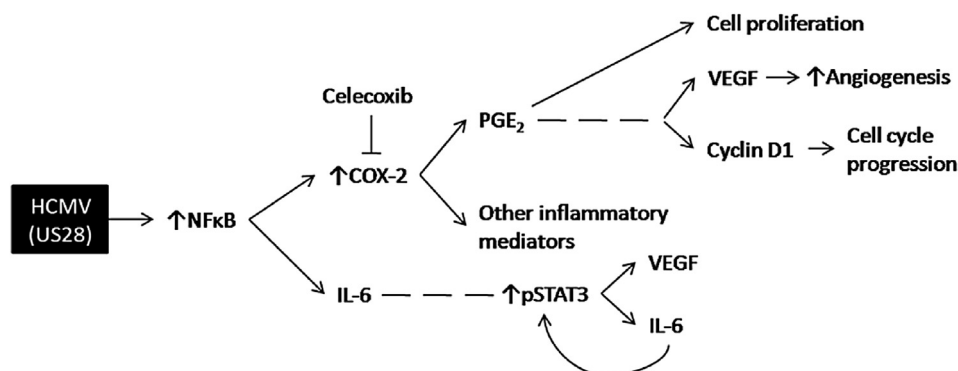


Fig. 1. Schematic representation of the oncomodulatory role of HCMV in medulloblastoma.

**Table 1**

Summary of the techniques and viral components used in different papers to detect HCMV presence in medulloblastoma.

Reference→	[9]	[10]	[11]	[12]	[13]
HCMV Detected	yes	yes	no	no	no
Used detection Method	IHC, IF, ISH, flow cytometry, PCR, FISH	IHC	IHC	IHC	IHC, PCR
HCMV analyzed Proteins	IE, late proteins, pp65	pp65	pp65, early antigen and IE	IE1/2, late antigen	IE, early antigen
HCMV analyzed genetic material	IE, pp150, gB DNA; IE, gB RNA	n.d.	n.d.	n.d.	HCMV DNA
Type of analyzed Sample	FFPE, frozen tissue samples, MB cell lines	FFPE	FFPE, MB cell lines	FFPE	FFPE
<i>In vitro</i> antiviral Treatment	Ganciclovir ± celecoxib reduced clonogenic capacity.	n.d.	n.d.	n.d.	n.d.
<i>In vivo</i> antiviral Treatment	Valganciclovir ± celecoxib reduced tumor growth.	n.d.	n.d.	n.d.	n.d.

FISH: Fluorescence *in situ* hybridization, FFPE: formalin fixed paraffin embedded clinical specimens, gB: glycoprotein B, HCMV: Human Cytomegalovirus, IE: immediate early, IF: immunofluorescence, IHC: immunohistochemistry, MB: medulloblastoma, n.d.: not determined, PCR: Polymerase Chain Reaction.

clonogenic capacity by preventing HCMV replication through a decrease in PGE<sub>2</sub> levels [9]. This is consistent with the finding that celecoxib decreases the phosphorylation state of STAT3 [28,41], leading to reduced stem-like cell abilities of medulloblastoma cancer stem cells and higher sensitivity to ionizing radiation [28]. Baryawno et al., observed that valganciclovir and celecoxib synergistically reduced tumor growth of HCMV-infected tumor cells [9]. This study, therefore, may suggest that targeting HCMV is a promising therapeutic approach for medulloblastoma.

### Controversies about the presence of cytomegalovirus in medulloblastoma

The presence of HCMV in medulloblastoma has given rise to an intense debate in the literature over the past years. Several groups have reported the presence of HCMV in human medulloblastoma tissue, in medulloblastoma cell lines and in medulloblastoma xenografts [9,10]. Baryawno et al. have observed that the medulloblastoma cells positive for HCMV, as measured by immunohistochemistry, coincide with those with an induction of COX-2 expression, in line with the pro-inflammatory role of HCMV [9]. Moreover, in another study, the expression of the HCMV late protein pp65 was detected in a high percentage of medulloblastoma cells [10]. However, other groups have not been able to detect HCMV in medulloblastoma [11–13]. A similar controversy arose around the involvement of HCMV in glioblastoma and it was finally settled when a consensus was reached in 2011, as reported by Dziurzynski et al. [42], agreeing that there is enough evidence to support an oncomodulatory role for HCMV in certain malignant gliomas. In spite of this consensus, however, ongoing publications keep challenging the presence of HCMV in glioblastomas [43–45].

A variety of detection methods have been used in these and other studies for the detection of HCMV in tumors, including polymerase chain reaction (PCR) and immunohistochemistry. Also, different viral components have been used as a marker for the presence of HCMV. The variety of materials, methods and markers used in this context (summarized in Table 1) can at least partly explain the discrepancies in the detection of the virus within the tumors even though there is a positive HCMV serology in the affected individuals. Libard et al. report that the distribution of HCMV within the tumor might be patchy and uneven, and this could also explain the differences among the studies [10]. In addition, there is no gold-standard positive and negative control to determine true positives. These problems should be solved in the future to undoubtedly confirm the involvement of HCMV in the development of medulloblastoma and use this knowledge to be able to develop new and effective therapies for the affected patients.

### Conclusion

In this review we have briefly discussed the controversy that is present nowadays in the literature regarding the presence or absence of HCMV in medulloblastoma and the role it may play in

the development of this cancer type. Some *in vivo* and *in vitro* studies have shown promising results in the treatment of medulloblastoma by targeting HCMV, whereas other groups have not been able to detect HCMV in medulloblastoma. Further research is required to elucidate the potential role of HCMV in medulloblastoma carcinogenesis and to establish the virus as a (immuno) therapeutic target to improve patient outcome.

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### Conflict of interest

The authors declare no competing interests.

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