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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.

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 β-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_2, Prostaglandin E2; 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 β-catenin encoding gene, *CTNNB*, 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 PPARγ [23]. Therefore, antagonizing PPARγ 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 β-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 TNFα 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 NFκB 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