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The roles of viruses in brain tumor initiation and oncomodulation

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Abstract

While some avian retroviruses have been shown to induce gliomas in animal models, human herpesviruses, specifically, the most extensively studied cytomegalovirus, and the much less studied roseolovirus HHV-6, and Herpes simplex viruses 1 and 2, currently attract more and more attention as possible contributing or initiating factors in the development of human brain tumors. The aim of this review is to summarize and highlight the most provoking findings indicating a

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potential causative link between brain tumors, specifically malignant gliomas, and viruses in the context of the concepts of viral oncomodulation and the tumor stem cell origin.

Keywords

Gliomas; Brain tumors; Viruses; Herpesviruses; Retroviruses; Oncomodulation; Progenitors; Stem cells

Introduction

Malignant gliomas are histologically heterogeneous and invasive brain tumors that are associated with a disproportionally high mortality rate [1]. With no specific pathogenetic mechanisms identified by now for the majority of gliomas except for the exposure to the ionizing radiation and gene polymorphisms that affect detoxification, DNA repair and cell cycle regulation, the attention of researchers has recently been drawn to the possible infectious etiology of brain tumors. In this review we discuss the role of retroviruses in animal models of glioma and the possible impact of some human herpes viruses on the initiation and formation of brain tumors. While nowadays the role of stem cells as the major players in tumorigenes is widely discussed, we put together the relatively scarce data on the interactions of herpes viruses with local neural stem/progenitor cells as well as non-transformed astrocytes and glioma cells. Such interactions may potentially cause on-cotransformation, or influence various intracellular signaling pathways that will predispose cells to oncogenic changes, or further drive the formation or aggravation of the existing malignant phenotype with negative implications for the therapy of gliomas.

Retroviruses in animal models of brain tumors

Since the end of 1960s Rous sarcoma virus (RSV) and its closely related avian sarcoma leukosis virus (ASLV) were used in experimental animal models for induction of brain tumors [2–9] with morphological similarity to human gliomas [9, 10]. Both RSV and ASLV belong to the group of retroviruses, type C. While RSV and ASLV induce neurogenic tumors in many species, the naturally occurring fowl glioma has also been shown to be caused by the specific strain of a subgroup A of ASLV [11–13]. This strain could induce gliomas after injection in ovo, although the virus had the broad tissue tropism similar to other ASLV [14–17]. It had previously been reported that both cell cultures derived from chemically induced gliomas in Sprague-Dawley rats [18] and hydrocortisone-hypersensitive variant of rat glioma C6 cells line [19] also produced the so-called C-type viral particles, the morphologically similar group of enveloped RNA virus particles with an electron dense central nucleoid that is associated with certain cancers, such as sarcomas and leukemias. The particles were produced only in response to the treatment of cells with glucocorticoids. The latter are known to enhance the production of B type mouse mammary tumor virus (MMTV), and to exert immunosuppressive effects in vivo. The particles demonstrated reverse-transcriptase activity, yet poor transforming efficiency [19]. Steroids are regularly used to reduce cerebral edema in glioma. They might activate the production of retroviral-like particles in human glioma cells, but additional studies are required to determine if this was the case.

Sequences bearing homology to retroviral elements are inherent constituents of the human genome. They include *endogenous retroviruses* (often defective and non-infectious), LTR-, and poly-A (non-LTR) *retrotransposons*, which can amplify themselves, *retroposons* (*retrotranscripts*), the repetitive DNA fragments, which in contrast to retrotransposons do not encode Reverse Transcriptase, and other so-called *retroelements* [20]. Retroelements are

known primarily as mobile DNA species integrated at various positions in the genomes of their host species. Many of them, such as for example, human LINE-1 (L1) retroelements, are considered to be essential for the regulation of mammalian gene expression [21, 22] and embryonic development [23, 24]. Of special interest are the findings that human L1 retroelementss are abundant in the brain as compared to other tissues, undergo transpositions in cultured human neural stem cells [25], and are controlled by the same factors that are involved in neuronal development [26]. Importantly, retroelements might be involved in mutagenesis and cancer initiation [27, 28]. As an example, the random amplified polymorphic DNA (RAPD) analysis of tissue obtained from the highly malignant human glioblastoma multiforme in comparison with genomic DNA from the normal human tissues revealed the loss of a 443 bp long DNA fragment that had 91% homology with fragments of three retroposons belonging to the human endogenous retrovirus HERV-K, which resembles MMTV. Interestingly, the altered fragment spanned a GC rich region, the polypurine tract, the steroid hormone responsive element and the enhancer core of these retroposon sequences [29]. In addition, several stretches of this altered sequence were also present in inverted repeats of human XRCC1 gene, which is involved in the efficient repair of DNA single-strand breaks, and of the BRCA2 tumor suppressor gene, which, in turn, plays an important role in the error-free repair of DNA double-strand breaks. Therefore, the regions of tumor suppressor genes harboring retroviral elements may be subjected to mutations, rearrangements, increased frequency of recombination, and other events resulting in genomic instability and neoplasia.

Herpesviruses and oncomodulation

Herpesviruses are a large family of DNA viruses that can cause latent or lytic infections. The classification of human herpesviruses is shown in Table 1. Epstein-Barr virus (EBV) and Kaposi's sarcoma-associated herpes virus (KSHV) are proven to play an important role in the development of various cancers (EBV—in Burkitt's and Hodgkin'n lymphomas, nasopharyngeal carcinoma, KSHV—in Kaposi's sarcoma and primary effusion lymphoma), notably—often in immunocompromised patients. Other herpesviruses have also been suspected to be linked with various tumors, brain tumors being studied most intensely, even though the direct role of most of herpesviruses in tumori-genesis has not been proven yet.

With this regard, the concept of "oncomodulation" has emerged [30, 31]. Oncomodulation is defined as the ability of viral proteins and non-coding RNAs to promote oncogenic processes without direct oncotransformation but through disturbances in various intracellular signaling pathways. They may include interference with the activity of tumor suppressor genes, enhancement of cell proliferation, motility and invasiveness, inhibition of apoptosis and cellular senescence, shift from the precise to error-prone DNA damage repair pathways, immune evasion, selection of the malignant phenotype, epigenetic changes, which in turn, may also regulate virus latency and reactivation [32], and aberrant angiogenesis. As the growing number of evidences suggests that tumors originate from local stem/progenitor cells, deregulation of cell differentiation can also be viewed as the sign of tumor-promoting activity.

We will review the human cytomegalovirus (HCMV), by now one of relatively better studied herpesviruses, which spectrum of activities may be considered as a prototype for oncomodulation, and compare its pro-oncogenic properties with those of human herpes simplex virus 1 and 2 (HSV) and herpes lymphotropic virus (HHV-6) (Table 2).

Pro-oncogenic properties of HCMV

Human cytomegalovirus (HCMV) is a widespread human virus that has been mainly known to cause disease in immunocompromised patients [33, 34]. The virus is believed to persist

mainly in myeloid cells but may be reactivated and infect different tissues in immunocompromised or cancer patients due to cancer-related immunosupression and chemo- and radiation therapy, inflammation and stress [32, 35–41]. By now HCMV has been the most intensely studied virus for its possible link with various tumors, including brain tumors. The HCMV genome encodes more than 200 proteins, and their expression occurs in three sequential stages after infection: immediate early (IE), early (E), and late (L). These proteins have multiple biological activities that interfere with physiological functions in infected cells [42].

HCMV presence in human brain tumors

A possible relationship between HCMV and cancers had been prompted in the early 1970s by the finding of increased anti-HCMV antibody titers in patients with cervical carcinoma [43]. Recently by employing highly sensitive techniques, HCMV has been found in tumor cells of more than 90% of patients with breast cancer, colon cancer, cervix cancer, prostate carcinoma, and EBV-negative Hodgkin's lymphoma [30, 32, 44, 45]. The presence of HCMV genomic sequences as well as its proteins expression has also been detected in malignant gliomas of various grades [46–49]. In nearly 80% of patients with brain tumors HCMV DNA was also detected in the peripheral blood suggesting either systemic reactivation or viral shedding from tumor cells to the periphery [50, 51]. Moreover, those patients, who had a low viral load, lived twice as long compared to patients with high levels of infection [52]. The non-structural HCMV 72 kDa immediate early (IE) 1 protein (IE72), also known as UL123, is one of the first HCMV antigens expressed in an infected cell. IE72 could be detected in about 16–90%, and pp65 protein—in about 50% of the cases in brain tumors [52, 53]. Both proteins could be detected by immunohistochemical methods. It has been reported that vaccination with autologous dendritic cells as adjunctive therapy in malignant gliomas once resulted in an extremely robust anti-HCMV-specific CD8+ T-cell response to pp65 [54]. It is noteworthy that non-cancer cells even in the vicinity of tumors appear to be HCMV negative.

HCMV and neural precursors

The adult human brain maintains a population of progenitor cells in the subventricular zone (SVZ), the largest germinal center in the brain and source of local stem/progenitor cells within the walls of the lateral ventricle [55]. Most gliomas have been shown to contact the walls of the lateral ventricle [52]. Cells in the SVZ and ventricular zone appear to be the primary targets for the HCMV in connection with congenital HCMV infection [56–58]. Analogously to the observations that it interferes with differentiation of myeloid cells into the macrophages and dendritic cells, HCMV has been reported to inhibit both neuronal [59] and astrocyte differentiation as indicated by downregulation of glial fibrillary acidic protein [57, 60, 61]. In transgenic mice expressing gene-reporters driven by the HCMV IE enhancer/promoter its activity was strongly induced in reactive astrocytes in response to a neocortical stab lesion [58]. Neural progenitors and primary cultures of differentiated human astrocytes appear to be the most permissive for HCMV infection [59, 62], and support productive replication of HCMV [62–64]. However, susceptibility to HCMV infection declines following differentiation of neural precursors into neurons [64, 65], and in immortalized astrocytic cell lines susceptibility to HCMV varies from complete resistance to partial expression of viral genes [59, 66]. The cell and tissue specificity of HCMV depends on the presence and activity of SP1 cell transcription factor. SP1 together with HCMV 86-kDa IE2 protein (IE86) forms a complex that binds to an inverted-repeat element of HCMV UL54 (polymerase) promoter [67], thus activating replication of the virus.

Platelet derived growth factor (PDGF) and its receptors (PDGFR) are essential to the self-renewal of neural stem cells. In vitro studies demonstrated that PDGF signaling results in

inhibition of their differentiation into neurons, astrocytes and oligodendrocytes, and has a growth promoting effect in the neural progenitor cell population [68]. Many human gliomas express markers of glial progenitors, in particular, PDGFR alpha, which expression as well as phosphorylation correlates with malignant histology in pediatric gliomas [69]. In turn, PDGF ligands are powerful mitogens for both glioma cells and adult glial progenitors [70]. Infusion, or retroviral-mediated delivery of PDGF B ligand into the lateral ventricles resulted in massive expansion of both infected and uninfected glial progenitors with the characteristic for gliomas cellular atypia and pleyomorphism [52]. Interestingly PDGFR alpha is activated by HCMV and absolutely required for HCMV internalization, activation of downstream signaling and production of infectious virus [71]. However it was reported that in smooth muscle cells HCMV downregulates expression of PDGFR alpha and beta [72]. It is not clear whether HCMV binding to PDGF receptor may mimic the action of PDGF ligands, or if HCMV exploits this opportunity to maintain its replication. Nevertheless, efficient HCMV infection, or even expression of some of its proteins even out of the whole virus context significantly alters multiple pathways related to cell cycle, apoptosis, DNA repair, cell invasion, angiogenesis and host immune response (see “HCMV and cell cycle” Section).

HCMV and cell cycle

Stem cells in vivo represent quiescent (G0) cell pool that intermittently gives rise to tissue-specific progenitors with robust proliferative potential, the so-called transiently amplifying (TA) cells, that, in turn, eventually become terminally differentiated [73]. The retinoblastoma tumor suppressor protein (pRb) is responsible for transcriptional repression of cyclin A, a positive regulatory component of kinases required for the progression through S phase and for the transition between the G2 and M phases of the cell division cycle [74]. IE72, IE76, pp71, and UL97 HCMV proteins are able to interact, phosphorylate and inactivate proteins of Rb family (Rbs) that includes pRb, p107 and p130. In addition, binding of pp71 to Rbs induces DNA synthesis in quiescent G0 cells [75, 76]. These changes may prompt resting in G0 phase local progenitors to generate the pool of TA with their following massive expansion. The levels of the protooncogenes c-myc, c-fos and c-jun, as well as of cyclin E and Cdks are rapidly upregulated following infection of cells by HCMV [77], and the $p21^{waf1}$ protein, which arrests cells in the G1 phase, becomes degraded [78]. HCMV chemokine receptor US28 also enhances cell proliferation [79, 80]. However, HCMV may block cell cycle progression as well [30, 32]. The controversy of the existing data could probably be explained by the status of p53 protein in the cell lines used for experiments. Specifically, in some glioma cell lines, p53 is mutated and therefore acts oppositely to its wild type counterpart by failing to transactivate its usual target genes with anti-oncogenic activities, but instead de-repressing or transactivating a plethora of protooncogenes [81, 82]. In addition, mutated p53 activates some viral promoters, in particular, the human cytomegalovirus major immediate-early promoter-enhancer, the long terminal repeat promoters of Rous sarcoma virus, and human T-cell lymphotropic virus type I [83]. In normal permissive cells, HCMV-encoded regulatory proteins induce cell cycle arrest in both the G1/S and G2/M check-points [84, 85] and prevent cellular DNA replication while enabling replication of viral DNA [86, 87]. In HCMV-infected cells, cyclins A and D1 are inhibited, and IE86 may induce cell cycle arrest by activating an ataxia telangiectasia mutated gene–dependent phosphorylation of p53 at Ser15. These events result in p53 accumulation and activation, leading to a p53-and p21-dependent inhibition of cell cycle progression [88], but only in cells with intact p53. In normal fibroblasts expressing wild-type p53, HCMV IE1-72 protein cannot drive cells out of quiescence, whereas IE1-72 can induce S phase and delay cell cycle exit in p53-deficient cells [30]. Other virus regulatory proteins, for example the pUL69, contribute to HCMV-induced cell cycle arrest [86]. In T89G glioblastoma cells with disrupted p53 signaling, persistent HCMV infection

did not induce cell cycle arrest and virus antigen-positive cells continued to divide [51]. In turn, p53, may be downregulated by IE72, or inactivated by mtrII protein encoded within the morphological transforming region II (mtrII) of HCMV strain Towne [89]. Another tumor suppressor gene thrombospondin-1 (TSP-1) is down-regulated by IE72. TSP-1 is involved in the inhibition of cell growth, adhesion and motility, and is upregulated by Rbs [52, 61]. Again these results were obtained with U373 malignant glioma cell line, which harbors the p53 mutant (R273H), and it is not clear whether down-regulation of aberrant p53 has pro- or anti-tumor consequences. The putative effects of HCMV on the cell cycle are summarized in Fig. 1.

HCMV and cellular senescence

HCMV induces constitutive expression and activation of human telomerase reverse transcriptase (hTERT) both in several malignant glioma cell lines and in normal fibroblasts. HCMV-mediated transactivation of the *hTERT* gene is also dependent on the presence of Sp1-binding sites in the hTERT promoter and accompanied by increases in Sp1 binding, acetylation of histone H3, and a reduction in histone deacetylases (HDAC-1 and -2) binding at the hTERT promoter, which is consistent with local chromatin remodeling at the sites of active transcription [42]. Telomerase is commonly activated in cancer cells of both viral and nonviral origin, and hTERT activation is sufficient to immortalize normal diploid cells [31]. In addition, hTERT promotes cancer cell growth and shifts the balance toward DNA repair instead of apoptosis, thus potentially rendering tumors chemo- and radioresistant. Ectopic expression of only IE72, out of the roughly 200 different HCMV gene products, was sufficient to reproduce the viral effects on hTERT promoter activation [42]. IE72 is a promiscuous transcriptional activator of numerous viral and host cell genes. It interacts with several common cellular transcription factors including CTF1, E2Fs, and Sp1 and targets histone deacetylases (HDACs) to promote histone acetylation [90].

HCMV and DNA damage

HCMV has been demonstrated to induce chromosomal damage [91, 92], by both randomly distributed chromatid breaks at low frequencies, and site-specific chromosome 1 double-strand breaks (DSB) at positions 1q42 and 1q21 [93]. The chromosomal breaks were predominantly chromatid breaks rather than chromosome breaks, which is explained by the experimental settings when a large proportion of cells were in S or G2/M phases of the cell cycle. Eukaryotic cells repair DSB primarily by two mechanisms: homologous recombination (HR) and nonhomologous end-joining (NHEJ). HR uses a DNA molecule with significant length of sequence homology (undamaged sister chromatid or homologous chromosome as a DNA template) to prime the repair DNA synthesis. In contrast, NHEJ, and relatively less studied microhomology-mediated end joining (MMEJ) are both the error-prone joining of DNA ends without the requirement for sequence homology. NHEJ plays an especially important role in DSB repair during the G1 phase of the cell cycle when no sister chromatid is available. Since HCMV may block cell cycle progression in G1 phase, the prevalence of NHEJ may result in mutations and translocations therefore increasing genetic instability. The possible targets residing near 1q42 include the ADPRT locus involved in DNA repair and replication [94], whose deletion has been connected to the development of glioblastoma [95], and breast cancer tumor suppressor gene, which is located at 1q21–31 [96]. HCMV virion binding and/or entry was necessary and sufficient to induce chromosomal damage even in the absence of de novo viral gene expression. Therefore, neural progenitors could be infected with HCMV, incur chromosomal damage and pass this damage on to daughter cells that might become origins of the tumors.

HCMV and mutagenesis

It has been reported that HCMV IE72 and IE86 proteins are mutagenic and can cooperate with the adenovirus E1A protein to transform primary baby rat kidney (BRK) cells [97]. In addition, stable cell lines transformed by HCMV were shown to harbor an activating mutation in both alleles in H-Ras, the proto-oncogene, related to the development of certain types of cancers [98]. Since HCMV proteins and DNA were not present in cell lines derived from the transformed BRK foci, it is not clear whether the mutations in H-Ras result from direct mutagenic activity, or HCMV acted as a selector for the mutant phenotypes.

It is noteworthy that persistent HCMV infection of a number of tumor cell lines including glioblastomas appears to be dependent on selection of the novel slowly growing virus strains with mutations/deletions in the coding sequences of viral regulatory proteins [99–101]. The subculturing of virus-containing tumor tissues, as well as HCMV-transformed human embryo cells results in the loss of HCMV [84, 85, 102]. It appears that the consistent presence of HCMV in tumors in vivo may also be dependent on the tumor microenvironment, in particular, hypoxia that is characteristic for all solid tumors including gliomas, and has been reported to influence replication of some viruses [103–111].

Other pro-oncogenic properties of HCMV

Other activities of HCMV include inhibition of cancer cell apoptosis and immunogenecity, enhancement of cell migration, invasion, adhesion to the endothelium, and angiogenesis (reviewed in [30, 32, 52]. Those properties of HCMV also appear to have variable effects in normal cells and in cancer cells. HCMV infection stimulates invasiveness of gliomas [51, 79, 80, 112]. Human glioblastoma cells expressing US28, a chemokine receptor of HCMV, exhibited increased malignancy after injection in nude mice. In contrast, US28 induced apoptosis in nontumorigenic human cells [80]. It appears that expression of HCMV products even out of the context of the whole virus can induce significant changes in the cellular signaling network.

In conclusion, HCMV presence in the tumors may induce the shift toward more malignant phenotype. Therefore, HCMV may represent a therapeutic target, and in experimental models it has been shown that general antiviral therapeutic strategies or inhibition of HCMV IE genes expression has counteracted and reverted HCMV-induced malignant changes and chemoresistance [31, 52].

HHV-6

HHV-6 (Roseolovirus, herpes lymphotropic virus) was first isolated in 1986 from AIDS patients and patients with other lymphoproliferative disorders [113]. HHV-6 uses CD46 cell surface molecule, which is expressed in all nucleated cells, as its cellular entry receptor [114]. Such broad tropism combined with immunological and molecular evidence of HHV-6 infection in individuals raised the question of the pathogenicity of this virus in some diseases [113, 115]. HHV-6 has been linked with several CNS diseases including enecephalitis in non-immuno-compromised patients as well as digestive problems in immunosupressed patients, severe maternal-fetal infections, but most important—with hematological malignancies [116–118]. Below we briefly review some features of HHV-6 that associate it with brain tumors.

HHV-6 presence in human brain tumors

A number of reports described the finding of HHV-6 sequences and proteins in adult and pediatric brain tumors by various techniques including PCR, in situ hybridization, and immunohistochemistry [119–125]. Other studies demonstrated HHV-6 DNA sequences in non-pathological brain tissues as well, though at lower levels [117]. It is not clear whether

detection of HHV-6 can be explained by primary infection or reactivation due to the tumor-induced dysfunctions of immune surveillance mechanisms and enhanced glial cell proliferation [120].

HHV-6 and neural precursors

HHV-6 has been shown to infect human mature oligodendrocytes and astrocytes in vitro and in vivo [126, 127]. Two viral variants (HHV-6A and HHV-6B) may elicit different infection patterns: HHV-6A results in productive lytic infection while HHV-6B is associated with a non-productive (apparently latent) infection. [127]. It appears that HHV-6 can infect glial precursors as well and shift their differentiation toward oligodendrocytes [128]. Various medulloblastoma cell lines as well as clinical specimens obtained from brain tumors also express CD46 [129].

Apoptosis and cell cycle

It has been reported that HHV-6 infection of human oligodendrocytes and their immediate precursors induce apoptosis via caspase-independent pathways [130]. However, it is not clear which viral variant was used in the experiments. The opposite results were obtained with glial precursors, which infection with both HHV-6A and HHV-6B resulted in alterations in cell morphology and impairment of cell replication but not cell death. Infected cells demonstrated cell cycle arrest in G1/S phase, downregulation of the glial progenitor cell marker A2B5 and a corresponding increase in the oligodendrocyte differentiation marker [128]. It is not clear whether the HHV-6-induced cell cycle arrest is irreversible. One of the unique features of HHV-6 is its ability to stably integrate into the telomeres of chromosomes during latency and vertically transmit through the germ-line [131–134]. Reactivation of the integrated HHV-6 genome can be achieved in the presence of histone deacetylase inhibitor [132]. It was suggested that HHV-6 genome may serve as an initial template for telomere elongation [114], and therefore counteract apoptosis and enhance cell proliferation during the latency.

Tumor-initiating properties

HHV-6 DNA and specifically its ORF-1 gene can transform human epidermal keratinocytes and NIH 3T3 cells in vitro. Moreover, cells expressing ORF-1 protein produce fibrosarcomas when injected into nude mice. The ORF-1 protein binds and inactivates p53, and another HHV-6 gene product U95 binds to nuclear factor-kappa B (NF-kB), which deregulation has been postulated to contribute to cancer [118, 135].

HHV-6 and immunomodulation

Like other herpesviruses HHV-6 expresses a number of proteins that counteract host's immune system and allow HHV-6 to escape immune surveillance, especially during the latency [114, 136]. HHV-6 upregulates interleukin-10, inhibits IFN-gamma, and in general the immune disturbances induced by HHV-6 appears to be a shift from a Th-1 to a Th-2 type cytokine profile [137]. HHV-6 reactivation is usually accompanied by reactivation of other herpesviruses, such as HCMV and EBV [138–142], as well as in HIV-infected individuals (HHV-6 has been proposed as a potential co-factor in AIDS progression) [114, 143], and in cancer patients [144].

HSV-1 AND -2

Herpes simplex viruses cause a lytic infection in epithelial cells. HSV-1 can be transmitted through skin contact during outbreaks. HSV-2 is a primarily sexually transmitted human infection. Both HSV- 1 and HSV-2 can persist in the nerve cells in a latent state, in which the viral genome persists in a nonintegrated form without causing disease in an immune-

competent host [145]. Since 1960s HSV-1 and HSV-2 were intensely studied for their possible association with cancers, specifically—head and neck and cervical cancers [146, 147]. Of interest is the recent discovery of HSV-1 and -2 DNA in malignant and benign thyroid tumors. During tumor progression, thyroid cells acquire increased susceptibility to HSV due to activation of mitogenic signaling in cancer cells and increased expression of nectin-1, the receptor that is necessary for HSV-1 cellular entry [148].

Virtually all neurons, ependymal cells, choroid plexus epithelial cells, meningothelial cells, vascular endothelial cells, as well as many oligodendrocytes, astrocytes, and vascular smooth muscle cells express nectin-1 [149–152], However, reports on the presence of HSV-1 DNA in brain tumors are contradictory [123, 153, 154]. This may be explained both by the differences in the sensitivity of the used techniques and by the presence of only the fragments of the viral DNA. It was reported earlier by several laboratories that in a small fraction of permissive cells a portion of the viral genome is either damaged or missing [155–158], and only a fragment of HSV-2 DNA may be enough to induce tumorigenic transformation [159–162].

Both HSV-1 and-2 induce apoptosis in infected cells at the early stage of infection. However, it is well established that apoptosis in HSV-infected cell is blocked at later stages, especially during the latency, via cooperation of multiple viral gene products and cellular factors [163–166]. Interestingly the cells demonstrated different levels of sensitivity to HSV-1-induced apoptosis. For example, human cancer cells display an exquisite sensitivity to HSV-1-induced apoptosis [164]. However, apoptosis is significantly delayed during the infection of astrocytes [167]. It appears that primary cells are generally resistant to HSV-1-dependent apoptosis [164]. The anti-apoptotic activity of HSV, which is linked to the so-called Latency Associated Transcript, may explain the above described findings of HSV DNA in thyroid tumors as well as the ability of the fragments of viral DNA to induce oncogenic transformation. One may speculate that, for example, in case of genotoxic stress latent HSV infections may shift the balance from apoptosis towards error-prone DNA repair, which is associated with genomic instability and cancer.

In addition, HSV-1 vectors genetically engineered for cancer gene therapy (both replication-competent and deletion mutants) were found to upregulate the promoters of human telomerase reverse transcriptase as well as other cancer-linked promoters (tyrosinase and probasin) in both tumor and non-tumor cells, and such activity was attributed to VP16, ICP4 and especially ICP0 viral gene products [168].

As mentioned above, herpes infections and herpes-associated cancers appear to be linked with immunodeficiency. Dissemination of herpes zoster [169–177] as well as reactivation of HSV-1 [178–184] have been reported in cancer patients who were subjected to chemo- and radiotherapy. However, the mechanisms of reactivation remain unknown. There are a number of clinical reports on the cases of HSV-1 encephalitis in patients with gliomas who received radiotherapy [185–187]. In tumor cells and skin fibroblasts, HSV-1 can be reactivated by both ultraviolet [188–190] and ionizing radiation [191, 192]. In turn, HSV-1 may render infected cells more radiosensitive through the expression of the immediate-early protein ICP0, which downregulates DNA-dependent protein kinase and delays repair of DNA double-strand breaks [193]. Rat glioma C6-derived cell line may become more susceptible to HSV-1 upon the treatment with glucocorticoids [194–197]. HSV-2 can be reactivated from those C6-BU-1 cells by superinfection with murine cytomegalovirus (MCMV), but not with UV-irradiated MCMV or human cytomegalovirus.

Interestingly, HCMV may also be reactivated during space flights [198, 199], which is explained by stress, but also may be related to the low dose ionizing radiation. Other

similarities between HSV-1 and HCMV include: (i) upregulation of hTERT [168]; (ii) transactivation of HSV-1 UL9 by mutant p53 [83]; (iii) interplay of both HCMV and HSV-1 with gamma interferon and tumor necrosis factor alpha in the process of reactivation from the latency [32, 190, 200, 201]; (iv) dependence of HCMV, HHV-6 and HSV-1 replication on the inhibition of histone de-acetylation [90, 202, 203] (for example, HCMV cannot replicate in human teratocarcinoma cells because they express histone deacetylase-3 [202]); (v) contribution to both pro- and anti-apoptotic processes [204]: in mouse peritoneal macrophages [205] and neurons [206] productive HSV-1 and HSV-2 infection results in virus multiplication and cell death, whereas in cervical cancer cell lines HSV-2 boosts DNA synthesis in G1 and S phases of cell cycle [207]; (vi) inhibition of immune response via downregulation of MHC class 1 in infected glioma cell line [208]. HSV-2-transformed murine tumors cell lines may inhibit immune response through expression of TGF-beta [209].

Other herpesviruses

A cohort of epidemiological studies reported a correlation between the presence of antibodies against various herpesviruses and onsets and survival rates in cervical and head and neck cancers [210–222], and inverse correlation between the anti-HHV-3 immunoglobulins and the onset of gliomas [223, 224].

EBV was detected in a significant number of samples obtained from patients with pilocytic astrocytoma, a non-malignant glioma [123]. However, EBV, which is known for its link with primary brain lymphomas [225, 226], has not been associated with malignant gliomas before.

Conclusions

While herpesviruses are widespread among the human population, pre-existing conditions, such as mutations of tumor suppressor proteins, fluctuations in microRNA profiles, or other biomarkers may explain why some infected individuals are at higher risk to develop brain tumors as well as other cancers. The ability of herpesviruses and possibly other viruses to contribute to tumorigenesis may vary and is apparently dependent on the heterogeneity of cell populations within normal tissues. The experimental paradigms of pathogenesis of brain tumors that include the use of glial stem/progenitors appear to be the most interesting in revealing the oncogenic potential of latent viruses, most of all, herpesviruses, which remain “the usual suspects” and are kept in the spotlight of modern cancer research. The availability of well-characterized cell lines obtained from human gliomas [227, 228] with the properties of cancer stem cells (expression of stem cell markers, multipotency and ability to initiate brain tumors after being transplanted to immunocompromised animals) allows researchers to explore the interactions between the viruses and cancer stem cells with regard to the possible impacts on the clinical outcome and efficiency of currently used therapeutic approaches. Finally, targeting herpesviruses cellular entry receptors on tumor cells may one day become a part of the complex anti-tumor therapy.

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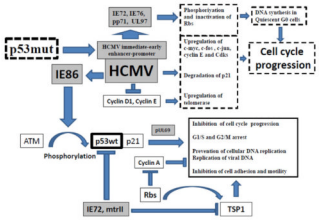

Fig. 1.
HCMV and cell cycle: *shadowed boxes* depict HCMV transcriptional elements and proteins

Table 1

Classification of human herpesviruses [229]

Virus	Type	Subfamily	Diseases
Herpes simplex virus-1 (HSV-1)	HHV-1	α (alpha)	Oral and/or genital herpes, herpes encephalitis in patients with gliomas, herpes infections in immunocompromised patients
Herpes simplex virus-2 (HSV-2)	HHV-2	α	Oral and/or genital herpes (predominantly genital), other herpes simplex infections
Varicella zoster virus (VZV)	HHV-3	α	Chickenpox and shingles, infections in immunocompromised patients
Epstein-Barr virus (EBV), lymphocryptovirus	HHV-4	γ (gamma)	Infectious mononucleosis, Burkitt's lymphoma, CNS lymphoma in AIDS patients, post-transplant lymphoproliferative syndrome (PTLD), nasopharyngeal carcinoma, HIV-associated hairy leukoplakia
Cytomegalovirus (CMV)	HHV-5	β (beta)	Infectious mononucleosis-like syndrome, retinitis, infections in immunocompromised patients
Roseolovirus, Herpes lymphotropic virus	HHV-6	β	Sixth disease (roseola infantum or exanthem subitum)
Roseolovirus	HHV-7	β	Analogously to HHV-6 Sixth disease (roseola infantum or exanthem subitum)
Kaposi's sarcoma-associated herpesvirus (KSHV), a type of rhadinovirus	HHV-8	γ	Kaposi's sarcoma, primary effusion lymphoma, some types of multicentricCastleman's disease

Table 2

Selected pro-oncogenic properties of HCMV, HSV and HHV-6

	HCMV	HHV-6	HSV-1 and -2
Detection in the tumors	Brain tumors, breast cancer, colon cancer, cervix cancer, prostate carcinoma, EBV-negative Hodgkin's lymphoma	Brain tumors, lymphomas and leukemias, cervical cancer	Malignant and benign thyroid tumors
Cellular entry receptor	PDGFR alpha	CD46	Nectin-1 and-2, HSV entry mediator A
Distribution of cellular entry receptors	Various cell types including astrocytes and neural stem/ progenitor cells,	Various cell types including astrocytes and neural stem/ progenitor cells	Various cell types including neurons, ependymal cells, oligodendrocytes, astrocytes. Neural stem/ progenitor cells (?)
Expression of the cellular entry receptors in gliomas	Yes	Yes	Yes[a]
Influence on cell cycle progression	Differs between the transformed and primary cells, probably depends on P53 status	(?)	(?)
Pro- and anti-apoptotic activity	Anti-apoptotic effect. Pro-apoptotic effect related to blocking cell cycle progression (?)	(?)	Differs between the cancer cells and normal cells. Pro- apoptotic in the lytic, and anti-apoptotic in the latent phase
Cellular senescence	Upregulation of telomerase	Integration into telomeres. Elongation of telomeres (?)	Upregulation of telomerase
Cellular differentiation	Inhibition of cell differentiation, reactivation in differentiated cells (?)	(?)	(?)
Transactivation in the absence of wild type p53	Yes	(?)	Yes
DNA-damage	Yes	(?)	(?)
Mutagenesis of cellular genomic DNA	Yes (?)	(?)	(?)
Dependence on histone deacetilase inhibition	Yes	Yes	Yes
Immunomodulation	Yes	Yes	Yes
Cell migration, invasion, angiogenesis	Enhancement	(?)	(?)

[a] Author's data (unpublished)