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REVIEW ARTICLE

Cancer stem cells and malignant gliomas. From pathophysiology to targeted molecular therapy

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Summary

High grade gliomas, the most frequent and most malignant brain cancers, grow rapidly and infiltrate the cerebrospinal axis causing deficits in cognition, mobility, balance or speech and are typically resistant to radiation and chemotherapy. Despite recent progress, WHO grade III and IV gliomas still represent a great challenge in oncology, with overall poor outcomes and inevitable lethality. While radiotherapy and temozolomide are considered the standard first-line approach for therapy of newly diagnosed malignant gliomas, the treatment protocols for recurrent tumors remain ill-defined. Increasing evidence suggests that tumors of the central nervous system are derived from proliferatively active neural stem cells residing in defined neuropoietic niches of the adult brain. These cancer stem cells, also identified in other tumors, provide a reservoir of cells with self-renewal capabilities, can maintain the tumor by generating differentiated non-stem tumor cells and are responsible for recurrences after ablative neurosurgical therapy and chemoradiotherapy.

The only way to successfully control recurrent malignant gliomas and even hope for a cure in the future is by combining standard chemotherapy with immunotherapy. Despite the apparent improvements of current treatments, it should be realized that the characteristic brain tumor niche may provide recurrent gliomas an "escape mechanism" from anticancer treatments. Thus, the use of targeted molecular therapy drugs may effectively inhibit or at least slow down cancer stem cell proliferation and stop the brain microenvironment from allowing furtive invasion and proliferation of highly aggressive malignant gliomas.

Key words: cancer stem cells, high grade gliomas, modern therapeutic approach, pathophysiology

Epidemiology and diagnosis

The human brain is the highest organized and most complex organ in the body, with unique features such as the extensive three-dimensional structure with gray and white matter and high density of blood vessels that make it a well-perfused organ; and this despite the blood-brain barrier that both selectively regulates the penetration of substances into the brain parenchyma and limits the invasion potential of brain cancers to the cerebrospinal axis. Malignant brain tumors are generally highly proliferative and represent the leading cause of cancer-related death in children and the 4th leading cause in adults [1].

Brain cancers are today classified by the WHO according to the normal cell type in the brain that the tumor resembles most. In this way, pathologists identify both glial cell tumors (i.e. astrocytomas, diagnosed oligodendrogliomas or ependymomas) and neural tumors (i.e. medulloblastoma) [2]. The prognosis for patients diagnosed with a WHO grade III glioma (anaplastic astrocytoma, anaplastic oligoastrocytoma and anaplastic oligodendroglioma) and grade IV glioma (glioblastoma multiforme) remains extremely grave, with a median survival for those diagnosed with glioblastoma from 8 to 15 months, but a slightly better prognosis for grade III glioma with a median survival of 12 to 24 months. The prognosis of recurrent malignant gliomas is even worse with a median survival of 3 to 9 months, despite state-of-the-art therapy [3,4].

Clinical symptoms of gliomas include most often persistent non-migraine headaches that occur while

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sleeping and accompanied by vomiting or confusion [5], gastrointestinal disorders such as nausea or vomiting especially in children, or seizures depending on the location- partial or generalized [6]. Patients also experience mental changes, memory loss, impaired concentration, gradual loss of movement or sensation in an arm or leg, visual disturbances, dyslexia, bradycardia or meningeal infections [7,8]. All the clinical symptoms are then confirmed by laboratory investigations and magnetic resonance imaging (MRI) is currently considered the standard modality of choice for the evaluation of brain pathology. Most MRIs employ a field of 1.5 Tesla, although high-field MRI systems operating at 3 Tesla are also available, with the use of gadolinium-based chelates for contrast-enhanced MRI. Lesion enhancement is based on either a disruption of the blood-brain barrier or an increased or pathological angiogenesis of the underlying tissue, but differential diagnosis is also possible with the help of other elements, such as the linear enhancement along the dura mater on contrast T1-weighted resonance image, also known as the dural tail sign [9,10].

The treatment will begin with maximal surgical resection, the extent of which is improved by numerous methods such as stereotactic navigation, intraoperative ultrasound or intraoperative MRI, limited though by the fact that the images they generate are physically separated from the operative field and requiring the surgeon to correlate imaging data with what is visually observed through the operating microscope. Diagnosis and the treatment of choice will then be decided only after the pathology examination of the tumor, relying ever more on functional genomics and proteomics than on classic morphopathology [11].

Molecular pathology of malignant gliomas

The use of clinical and pathologic factors to characterize high grade gliomas has been a challenging endeavor due to the diversity of these tumors, even among those of the same grade and histologic type. The transition between assessing gene expression on a gene-by-gene basis using techniques such as Northern blot and the simultaneous whole genome evaluation has represented a revolution in tumor biology. The accurate identification and thorough characterization of high grade gliomas are essential to enhance our understanding of their malignant behavior, and the correct differentiation between *de novo* and secondary high grade gliomas is essential in order to help develop novel therapies that may aim at cure.

The first distinction between the two brain cancer types was first reported by the German pathologist Hans Joachim Scherer [12], while working as a political refugee in Anvers. WHO listed glioblastoma multiforme as a poorly differentiated and embryonal tumor up to the ’80s when immunohistochemistry proved it to be an astrocytic neoplasm, but evidence that the two subtypes represent distinct entities that affect patients at different ages, show different RNA and protein expression profiles, develop through different genetic pathways and are different regarding the response to therapy has been published only in the past 10 years. Present-day studies stratify grade II and III glioma patients according to their 1p/19q codeletion status and grade IV gliomas according to their O-6-methylguanine-DNA methyltransferase (MGMT) status, with very important clinical applications for glioblastoma in relation to their response to temozolomide according to Hegi et al. [13]. MGMT is a DNA repair enzyme that removes alkylating lesions induced by cytotoxic drugs and whose silencing through methylation of its promoter is correlated with increased sensitivity to alkylating agents. MGMT methylation occurs in almost 50% of glioblastomas and its clinical value has been proven both in patients treated with nitrosourea and temozolomide plus radiation therapy [14,15].

Other key genetic aspects of gliomas are the isocitrate dehydrogenase (IDH)1/ IDH 2 mutations, whose enzymatic activity was determined in cultured glioma cells that were transfected with these genes, largely due to the research led by Vogelstein and Velculescu [16]. IDH 1 serves as a major source of cytosolic nicotinamide dinucleotide phosphate (NADPH) production, necessary for the regeneration of reduced glutathione which acts as the main antioxidant in mammalian cells. Thus, as the only known source of peroxisomal NADPH, the IDH proteins are key elements in the cellular control of oxidative damage and may be used as diagnostic or predictive markers between difficult cases of *de novo* and secondary grade IV gliomas [17]. Also, it has been proven that secondary gliomas arise from lower-grade precursors with p53 mutations, while *de novo* gliomas are thought to harbor epidermal growth factor receptor (EGFR) amplification and develop rapidly, arising from neural stem cell precursors or cancer stem cells [18,19].

Current standard of care

The current standard of care for glioblastoma multiforme is radiotherapy plus concomitant and adjuvant temozolomide [20]. Radiotherapy consists of irradiation at a dose of 2 Gy per fraction given once a day for 5 days

every week over a period of 6 weeks, for a total dose of 60 Gy. Computer tomography-based planning delivers ionizing irradiation to the gross tumor volume with a 2-3 cm margin for the clinical target volume. Temozolomide is administered concomitantly with radiotherapy at a dose of 75 mg/m^2/day, 7 days a week for a maximum of 49 days. Afterwards, 6 cycles of adjuvant temozolomide are administered after a 30-day break, 5 days a week for the next month. Temozolomide is an oral imidazotetrazinone methylating agent, rapidly absorbed with excellent bioavailability, and undergoes spontaneous hydrolysis at physiological pH into 5-(3-methyl triazen-1-yl) imidazole-4-carboxamide (MTIC), its active metabolite. MTIC is afterwards rapidly degraded into methyldiazonium and 5-aminoimidazole-4-carboxamide and then finally excreted by the kidney [21].

Standard radiotherapy of 60 Gy is not good enough in controlling high grade gliomas and further dose intensification to the centrally enhancing region may help improve the prognosis for such patients. Conformal techniques, such as intensity modulated radiation therapy (IMRT), permit both improvement in dose conformality and steeper dose gradients outside the target volume, having been shown to deliver conformal doses to the target while sparing the healthy brain tissue [22]. High-tech radiation therapies for malignant gliomas also include brachytherapy [23], or stereotactic radiosurgery [24], even though accessible only for patients treated at highly specialized medical institutions in the US or Europe.

Vessel co-option is important as an initial step in the development of brain tumors and glioma cells migrate along the existing blood vessels to maintain their survival, which will eventually allow cancer cells to migrate away from the initial tumor mass and infiltrate adjacent white matter tracts and cortical areas. As every single cancer cell may infiltrate the normal brain parenchyma and thereby escape therapeutic interventions like neurosurgery, radiation therapy or chemotherapy, the extensive neoangiogenesis will allow cells to acquire enough nutrients and oxygen and maintain their survival. For these reasons, antiangiogenic therapeutic regimens promise a novel approach to therapy-resistant tumors [25]. As gliomas express very high levels of VEGF *in situ* and inhibition of VEGF signaling slows down their growth in xenograft models in immunodeficient mice, bevacizumab (Avastin) given in combination with cytotoxic agents may seem like a promising solution. This comes despite initial reluctance to evaluate bevacizumab in patients with WHO grade III and IV brain cancers taking into consideration the possibility of inducing intracerebral hemorrhage, a hypothesis proven otherwise by clinical trials that used Avastin in combination with irinotecan [26,27].

Brain oncogenesis

Recent data suggest that glioblastoma multiforme contains a subpopulation of cancer cells with stem-like characteristics, including self-renewal and multidrug resistance [28]. The adult human brain harbors astrocyte-like neural stem cells within the subventricular zone, near the ependyma of the brain ventricles. This area is a mitotically active cell layer during the adult life that acts as a source of stem cells, retaining the ability to produce both neurons and glial cells in response to injury and signalling factors. In rats, 6-hydroxydopamine lesions and infusion of transforming growth factor α (TGFα) stimulates massive proliferation, directed migration and neuron differentiation, just as *in vivo* administration of epidermal growth factor (EGF) and fibroblast growth factor induce migration of subventricular zone cells away from the lateral ventricle walls into the adjacent parenchyma [29]. Animal models also showed that induced brain neoplasia by *in utero* exposure to ethylnitrosourea almost always appear in periventricular regions. These cells correspond to bipolar progenitor cells that may differentiate both into neurons and glial cells, expressing both glial fibrillary acidic protein (GFAP) and nestin [30]. Also, as normal stem cells from periventricular tissues can be recruited to migrate into tumor sites after having received signals from other cells and subsequently either support or fight back cancer cells, one may support the idea that transformation events in progenitor cells are involved in brain oncogenesis.

The hypothesis that subependymal plate or subventricular zone contain embryonal niches where neuroprogenitor cells reside is completed by the idea of spontaneous transformation. Spontaneous transformation in human cells is rare because of the two control points that regulate the lifespan of cells: senescence and crisis phase. Shiras et al. provide evidence, showing that normal progenitor cells may undergo p28 senescence and then enter a crisis phase with only a few cells escaping and undergoing immortalization and spontaneous malignant transformation [31]. The authors used a model composed of a long term *in vitro* culture of human neuroglial cells and an established cell line, both derived from the same adult diagnosed with glioblastoma multiforme. They depicted the spontaneous human non tumorigenic CD133+ stem cells to highly aggressive CD133+ cancer stem cells after activation of Notch and their transcriptional regulators of the Hes family leading to genomic instability.

The stem cell niche is a very complex structure composed of neuroglial progenitors that home to the niche and can be subverted to proliferate or go into quiescence state, adult neurons that secrete factors and guid-

ance molecules that contribute to cell mobility through the cerebrospinal fluid or microglia, and communicate with other cells using different chemokine axis. Also, the periventricular microenvironment is composed of astrocytes that provide neurotrophic factors, oligodendrocytes that form the main component of white matter tracts- a preferred conduit of invasion in high grade gliomas-and, last but certainly not least, blood capillaries [32].

Multiple growth factors are involved in gliomas, with frequent autocrine or paracrine loops and the expression of these molecules increases as the grade increases. The expression of growth factors and their receptors such as EGF, platelet derived growth factor (PDGF), TGFα or basic fibroblast growth factor (bFGF) is not normally encountered in the normal brain tissue or only weakly and in a very small number of cells. Oligodendrogliomas show very little expression of such markers compared with malignant oligodendrogliomas where some expression is seen, but still far less than in anaplastic astrocytomas or glioblastoma multiforme. The results are confirmed by pilocytic astrocytomas, that also show little expression of growth factors with the exception of TGFα, in comparison with grade III or IV gliomas [33]. Non tumor cells, such as endothelial cells or reactive astrocytes or microglia, can therefore act through paracrine mechanisms to stimulate the tumor cells and influence the migratory and invasive behavior of the newly formed glioma.

Molecular signalling pathways

Epigenetic alterations and molecular signalling pathways allow the cancer cell to adapt to chances in its microenvironment and sometimes DNA-methylation, histone-modification patterns or gene silencing have unexpected consequences with regard to gene expression, such as the growth promotion or growth inhibition of the tumor. Since cancers are considered to appear because of abnormal modulations of the normal physiology of the human body, similarities between normal and cancer stem cells demonstrate that the pathways that control the growth and development of a tissue are severely perturbed in malignancies, leading to invasion and metastasis. Similar genes are involved in regulating the self-renewal of these cells, such as Jagged-Notch or Wnt-Frizzled pathways.

Activated Notch signalling is capable of affecting both tumorigenesis and normal stem cell development, being also necessary for maintaining a pool of undifferentiated stem cells in the periventricular zone. Notch functions include cell fate decisions through glial and neuronal development and thus the deletion of Notch1 results in a decrease of neural stem cells. In the oligodendrocyte lineage Notch activation has been shown to suppress terminal oligodendrocyte differentiation and also in the case of rat retina, Notch signaling can promote the specification of Müller glia. It is also the case of radial glia in the telencephalon from cortical stem cells and astrocytes in the adult brain from hippocampal multipotent progenitors [34]. Notch signalling is activated by binding to its ligands Delta and Jagged family members, which later on results in cleavage of the Notch extracellular domain by an ADAM-family metalloprotease called TACE (Tumor Necrosis Factor Alpha Converting Enzyme). This process is followed by cleavage of the intracellular domain from the membrane by γ-secretase, which later on translocates into the nucleus and activates the transcription of downstream target pluripotency genes [35].

The Sonic Hedgehog (SHH) pathway inhibitors may slow down the growth of medulloblastomas, but gliomas in mice and inhibition of the Notch pathway by using γ-secretase inhibitors will neither block cancer stem cells self-renewal nor decrease the tumor invasion potential. Originally identified as a mediator of segmental polarity in the fly, the SHH pathway is essential in mammalian embryology. The three orthologues of the Hedgehog gene- SHH, Indian (IHH) and Desert (DHH)- establish key morphogenic gradients for axial patterning of the embryo. Aberrant activation of SHH signaling was initially associated with the basal cell nevus syndrome, also known as Gorlin syndrome, which carries germline mutations in one allele of the Patched (Ptch) gene. Ptch encodes Ptch-1 protein, a 12-transmembrane protein with homology to resistance, division and drug-transport family. Ptch also acts catalytically to inhibit the 7-transmembrane protein Smoothened (SMO), rendering the pathway inactive in the absence of SHH ligand [36]. Also, in cells carrying a mutated Ptch1 allele, SMO signalling is inadequately repressed and leads to unrestrained activation of Gli-1, a transcription factor and putative oncogene capable of inducing cancer development in both the adult brain and in the skin [37].

Another important pathway is the Wnt/β-catenin one, that initiates a signaling cascade critical in both the normal development and oncogenesis, the hallmark of this pathway being the activation of the transcriptional role of the multifunctional protein β-catenin. Wnt signalling inactivates GSK-3β and prevents β-catenin phosphorylation leading to its accumulation in the cytoplasm and subsequent translocation to the nucleus. Transcription factors in the Wnt pathway regulate the expression of genes responsible for self-renewal, differentiation

and proliferative potential in both normal and cancer cells. Nanog is believed, to be a major factor for the self-renewal of glioma cancer stem cells and is activated by Oct4/Sox2, but suppressed by the Wnt pathway [38].

Interplay between SHH, Wnt and Notch signals creates a very complex morphogenic field that governs the initial development of stem cells in the brain and dysregulation of these signals is characteristic of high grade gliomas. Thus, inhibition of cancer stem cells may be mediated by molecules that block the specific signalling pathways and not by conventional chemo-radiotherapy, proven to target mainly the transit amplifying cancer cells.

Cancer stem cells and resistance to conventional therapy

As therapy-resistant high grade gliomas constitute one of the most common cause of cancer deaths, there is an urgent need for development of alternative targeted therapies. The most compelling evidence of the existence of brain cancer stem cells is derived from the glioblastoma multiforme recurrence model, where a WHO grade III glioma receives radiation therapy and temozolomide treatment, but a second glioma will appear after only several months. It is possible that cancer arises in a cell at any stage of differentiation, from the most primitive stem cells to the most differentiated tissue-specific cell. Early events are most likely to occur in normal stem cells, as only these cells live long enough to accumulate the several genetic changes required for an invasive cancer to develop. Once one or more initiating genetic changes have occurred in the progenitor, all the downstream cells will contain this change, in which case it is possible that one of the daughter cells acquire not only the properties of a stem cell, but also the additional genetic changes that allow the cancer to progress to the next step and invade the surrounding tissues.

Cancer stem cells were first isolated in acute myeloid leukaemia as $CD34^+$ $CD38^-$ cells, and after just a few years, from solid tumors, including hepatocellular carcinoma and brain cancer [28,39]. Brain cancer stem cells were also isolated using a variety of methods, including isolation of the "side population" based on the exclusion of different dyes, on their ability to form tumor spheres under serum-free non-attachment conditions and on the basis of CD90, CD133, Nanog, ALDH1, Sox 2 and Oct 3/4 surface markers expression [40].

Current therapies are not yet curative as cancer stem cells may escape through both increased efflux of chemotherapeutic agents due to the ABCB1 (MDR, P-gp) and ABCG2 cell membrane proteins, and through increased DNA repair. Several proteins of the ABC transporter superfamily are overexpressed by stem cells and make up the so-called "side population", having the capability for accelerated efflux from the cells of fluorescent dyes Hoechst 33342 and Rhodamine 123, transported by the very same ABC family proteins [41].

Radiotherapy plays and important role in the management of gliomas, but the radioresistance of tumor cells limits the benefit of ionizing radiation. The developed resistance is related to global changes in the expression of proteins interfering with various intracellular pathways. Such is the case of overexpressed pre-mRNA-processing factor 19 (PRPF19) and programmed cell death 6-interacting protein (PDCD6IP) that reduce the levels of apoptosis in cells exposed to stress or DNA damaging factors [42].

Because it is much easier to kill downstream cells than cancer stem cells, it can be explained why the vast majority of brain cancers responds for relatively short periods to drugs or radiation therapy, until the stem cell pool recovers and resumes its inexorable growth.

Targeted molecular therapy

It is well known that cancer stem cells are immortal due to the telomerase enzyme hTERT. Telomerase is present in all brain malignant tumors and has a very high activity. One small molecule shown to inhibit hTERT *in vitro* and *in vivo* is RHPS4, shown to stabilize the 4-stranded G-quadruplex structure formed by the tracts of G-rich single-stranded DNA at the telomeres. Another promising agent with similar effects is the phosphoramidate oligonucleotide GRN163L, targeting the telomerase active site and inhibiting the binding to telomeres in $CD133^+$ cells [43,44]. Phosphate and tension homolog (PTEN) is a lipid phosphatase known to play a vital role in the proliferation, motility, survival and metabolism of cells and interacts with many signalling pathways, including p53, Akt/PI3K and mTOR. In central nervous system neoplasia loss of PTEN occurs and re-expression in various cell lines results in apoptosis. Re-expression is achieved by inhibition of PI3K with wortmannin and LY294002, but these compounds have broad specificity and have not been employed in the clinical setting.

The Wnt/β-catenin pathway controls self-renewal and proliferation of cancer stem cells, the members of the Wnt being generally secreted by other cells of the niche and bind to the 7 transmembrane receptor Frizzled. Targeted molecular therapy is difficult to perform because of the high complexity of the pathway. Wnt an-

tibodies proven to induce apoptosis are currently being developed in non-small cell lung carcinoma, melanoma and mesothelioma [45], but no results have been published for gliomas.

Hedgehog signalling is a highly conserved developmental pathway and orchestrates body patterning, contributing to stem cell maintenance. The best known hedgehog inhibitor is cyclopamine, that targets SMO and is shown to downregulate drug transporter expression in therapy-resistant gliomas, enhancing chemotherapy effectiveness [46]. An even better pharmacokinetic profile has been shown by GDC-0449, a SMO antagonist currently in phase II clinical trials for ovarian and colorectal carcinoma, as well as basal cell carcinoma. This molecule has also shown outstanding results in the treatment of medulloblastoma [47].

Another important pathway in the stem cell conundrum is Notch signalling, that regulates cell fate determination. Notch proteins are heterodimeric receptors that interact with the surface ligands Delta, Delta-like and Jagged from an adjacent cell. This binding will release the intracellular Notch domain through proteolysis by ADAMs and γ-secretase/presenilin. The effects will be either oncogenic or tumor-suppressing. The best Notch inhibitors are the gamma secretase molecules, which prevent the release of the intracellular Notch domain by inhibiting its cleavage. Such substances, like DAPT or MK0752, are currently under phase I clinical trial investigation for $CD34^{+}CD38^{-}$ cancer stem cells in acute lymphoblastic leukaemia and $CD133^{+}$ cancer stem cells in central nervous system malignancies [48].

Newcomb et al. reported that peripheral vaccination of mice with modified autologous tumor cells that secrete granulocyte-macrophage colony stimulating factor (GM-CSF) combined with ionizing radiation to the whole brain cured up to half of the laboratory animals using a syngeneic, intracranial model of murine glioblastoma multiforme [49,50]. The same research group explored strategies to merge standard radiotherapy with immunotherapy by testing an alternative immunotherapeutic approach using an antibody-directed to the co-stimulatory molecule CD137. This molecule, a member of the tumor necrosis factor receptor family shown to augment CD4+ and CD8+ T cell responses, may act as a target in brain cancer therapy after using a low therapeutic dose of ionizing irradiation due to the induction of local tumor cell death and by providing signals to enhance the presentation of tumor-derived antigens to antitumor T cells.

Cancer immunotherapy may also rely on the use of dendritic cells for antigen presentation in peripheral lymph nodes, where CD8+ T lymphocytes initiate a cytolytic anticancer reaction. In gliomas such a response does not develop due to the specific microenvironment, strongly characterized by the presence of diverse immunosuppressive factors that allow the tumor cell to escape immune surveillance. Using a mouse model of malignant glioma obtained by brain injection of GL261 cells, Pellegatta et al. studied the effects of intratumoral injection of pulsed dendritic cells with tumor lysate in established high grade gliomas [51]. The dendritic cells did not migrate to cervical lymph nodes and increased survival significantly when combined with peripheral vaccination.

Another way to target cancer stem cells in brain

Table 1. International clinical trials on targeted molecular therapy for malignant gliomas

Drug	*Phase*	*Number of patients*	*Institution*	*Details*
Cilengitide	I/II	112	NABTT, USA	Underway
Temsirolimus	I	46	NCCTG, USA	Underway
Cetuximab	I/II	46	Universitätsklinikum Heidelberg, Heidelberg, Germany	Without temozolomide
Vatalanib	I/II	180	EORTC, Europe	Currently stopped
Vorinostat	II	66	Mayo Clinic, Rochester, USA	NCCTG trial
Cilengitide	I/II	52	Centre Hospitalier Vaudois, Lausanne, Switzerland	With temozolomide and radiotherapy
CpG oligonucleotides	II	31	Institute Gustave Roussy, Paris, France	Underway
Lenalidomide	I/II	60	Dana Farber Cancer Center/Harvard Medical School, USA	With temozolomide and radiotherapy
Valproic acid	II	41	National Cancer Institute/National Institutes of Health, Bethesda, USA	Histone deacetylase inhibitor. Underway
Carmustine wafer	II	72	Sidney Kimmel Cancer Center/Johns Hopkins University, Baltimore, USA	Underway

NABTT: New Approach to Brain Tumor Therapy CNS Consortium, NCCTG: North Central Cancer Treatment Group, EORTC: European Organisation for Research and Treatment of Cancer

tumors is by combining radiation with the oncolytic activity of Parvovirus H1 (H-1PV). Geletneky et al. demonstrated the susceptibility of previously irradiated glioma cells to H-1PV-induced oncolysis and support the ongoing development of a clinical trial of oncolytic virus therapy in patients with recurrent glioblastoma multiforme [52]. These results are supported by Myers et al. in a toxicology study of intracerebral administration of a measles virus derivative producing carcinoembryonic antigen in Rhesus macaques [53]. This toxicology study supports a phase I trial of intratumoral and resection cavity administration of oncolytic viruses in recurrent glioma patients. As oncolytic virus strains have emerged as novel antitumor agents with significant efficacy against gliomas along with the other experimental treatment options, the development of non-invasive treatment strategies are highly necessary for this lethal incurable disease (Table 1).

Conclusion

Gliomas constitute a complex disease caused by genomic and epigenetic aberrations that affect a defined set of cellular properties. Although the brain cancer stem cell model is only at its early stage of development, this hypothesis is crucial for the understanding of gliomagenesis, as well as for assessing successes and failures of future early treatment using targeted molecular agents.

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