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REVIEW

Therapeutic potency of oncolytic virotherapy–induced cancer stem cells targeting in brain tumors, current status, and perspectives

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Abstract

Brain tumors are the most common form of solid tumors in children and is presently a serious therapeutic challenge worldwide. Traditional treatment with chemotherapy and radiotherapy was shown to be unsuccessful in targeting brain tumor cancer stem cells (CSCs), leading to recurrent, treatment-resistant secondary malignancies. Oncolytic virotherapy (OV) is an effective antitumor therapeutic strategy which offers a novel, targeted approach for eradicating pediatric brain tumor CSCs by utilizing mechanisms of cell killing that differ from conventional therapies. A number of studies and some clinical trials have therefore investigated the effects of combined therapy of radiations or chemotherapies with oncolytic viruses which provide new insights regarding the effectiveness and improvement of treatment responses for brain cancer patients. This review summarizes the current knowledge of the therapeutic potency of OVs-induced CSCs targeting in the treatment of brain tumors for a better understanding and hence a better management of this disease.

KEYWORDS
brain tumor, cancer stem cell (CSC), oncolytic virotherapy (OV)

1 | INTRODUCTION

Cancer stem cells (CSCs) or cancer-initiating cells are known as a subpopulation of cancer cells with several special features including self-renewal capacity, nonstop proliferation potential, tumor growth, metastasis, homing, cancer recurrence potential, and capacity to seed new tumors when implanted in an appropriate host.[1,2] Furthermore, CSCs possess prominent organizing capacities, meaning that they signal neighboring cells to prepare essential nutrients as well as participating in the elusion from the immune system, providing a suitable environment for tumor growth and metastasis.[3]

Different concepts in cancer research including self-renewal, heterogeneity, relapse after treatment, and resistance to conventional chemotherapies are associated with CSCs characteristics.[4,5] It has been shown that extensive expression of drug efflux pumps on the CSCs surface contributes to the chemoresistance of these cells.[6] The resistance of CSCs to the most aggressive radiation and chemotherapies can be partially explained by the fact that CSCs are predominantly in the inactive G0 phase, and are thus not prone to destruction by chemotherapy and radiotherapy that usually target actively dividing cells.[7,8] Therefore, several recent studies have focused on targeting CSCs as a novel therapeutic approach in cancer treatment.

Oncolytic virus-(OV) based cancer therapy has been widely recognized as a novel treatment of various cancers.[9] In general, OVs are described as either genetically modified or naturally occurring viruses which are able to penetrate, replicate, and kill cancer cells without harming healthy tissues.[10] OVs kill cancer cells via direct oncolysis, stimulating antitumor immune responses, triggering the collapse of tumor vasculature, etc.[11,12] In comparison with conventional cancer therapies, not only do OVs target cancer cells with high specificity, leading to tumor regression, they also can survive after lysing cancer cells and infect bordering cells.[9,13]

Malignant brain tumors, particularly anaplastic astrocytoma and glioblastoma multiforme are aggressive neoplasms with high mortality and morbidity among both adults and children.[14,15] In spite of the development of numerous therapeutic approaches, the incidence of malignant brain tumors has enhanced mainly due to the existence of brain tumor stem cells (BTSCs).[16] OVs have emerged as an efficient strategy for glioma therapy.[17] In several clinical trials, it has been demonstrated that OVs are capable of destroying BTSCs, meeting safety standards as well as showing no significant toxicity.[18] The aim of this review is to summarize the therapeutic potency of OV-induced CSCs targeting in the treatment of brain tumors.

2 | OV-INDUCED CANCER CELL TARGETING

Targeting cancer cells with high specificity without harming normal cells is an old challenge in cancer therapy.[19] OVs provide a new method for specifically targeting cancer cells due to natural properties of the viruses. In line with this, it has been validated that several human viruses have a natural tropism for particular tissues. Thus, these viruses are ideal candidates for targeting specific cancers. For instance, HIV naturally infects T lymphocytes, which can be utilized for the treatment of the T cell−specific lymphoblastic leukemias.[20] Furthermore, some cancer cell −specific receptors and recognition molecules can be expressed on viruses, enhancing OV-mediated cancer cell targeting. Consistently, Schneider et al[21] showed that genetically modified measles virus which expresses hemagglutinin on its surface is capable of entering cells expressing specific receptors including epidermal growth factor or the insulin-like growth factor 1, leading to extensive syncytium formation and cell death. Moreover, cancer cell properties including increased DNA replication and abnormalities in various cell-cycle checkpoints provide an ideal environment for virus replication.[22] Thus, viruses can be genetically modified in a way that allows them to be replicated in cancerous but not healthy cells. For example, T-Vec is a double-mutated HSV-1 with deletions in the γ34.5 and α47 genes.[23] It has been shown that deletion of γ34.5 prevents the virus from replicating in normal cells, while γ34.5-deficient HSV-1 can still replicate in cancer cells.[24] Furthermore, cancer cells have a tendency to resist apoptosis and translational suppression, two characteristics which are known as favorable tools for the growth of several types of viruses. Moreover, cancer cells overexpress some specific virus receptors leading to higher uptake of viruses in comparison with normal cells. For instance, cancer cells overexpress coxsackievirus adenovirus receptor, laminin, CD155, and CD46 which allows for higher uptake of adenovirus,[25] sindbis virus,[26] polio virus[27], and measles virus,[28] respectively.

3 | OVs-MEDIATED ANTITUMOR RESPONSES IN CANCER CELLS

It has been reported that OVs elicit antitumor functions via different mechanisms including direct cytotoxicity, transgene expression, triggering anticancer immunity, replication-mediated cytolysis,[29] and sensitization to radiotherapy and chemotherapy.[30] In agreement with these findings, Cai et al[31] demonstrated that oncolytic M1 virus which was potentiated by the second mitochondria-derived

activator of caspases mimetic compounds, increases apoptosis via sensitizing tumor cells to cytokines in cellular, animal and in ex vivo systems. Similarly, Kim et al[32] showed that oncolytic adenovirus conjugated with Arg-Gly-Asp(RGD)-poly(cystaminebisacrylamide-diaminohexane) (poly CBA-DAH) biopolymer could selectively target fibrosarcoma cell line, HT1080, leading to induction of apoptosis, suppression of angiogenesis, inhibition of tumor migration, invasion, and growth. In another study conducted by the same group, hepatoma-specific adenovirus (YKL-1001) conjugated with arginine-grafted bioreducible polymer (ABP) selectively killed liver cancer cells, Huh7 and HepG2, expressing α-fetoprotein with high specificity compared with naked adenovirus, suggesting that adding polymers on the surface of viruses enhance therapeutic efficacy of OVs specifically targeting cancer cells.[33] Consistently, Passaro et al showed that the oncolytic adenovirus dl922 to 947 induced anaplastic thyroid carcinoma (ATC) cell death in vitro and tumor regression in vivo. They showed that dl922 to 947 decreased interleukin-8 (IL-8) and monocyte chemo-attractant protein 1 (MCP-1) production in the ATC cell lines, 8505-c, and BHT101-5, leading to the inhibition of cell proliferation, survival, invasion, and angiogenesis in thyroid carcinoma cells.[34] Moreover, it was shown that genetically modified vaccinia virus called LIVP-GFP elicited antitumor activity via oncolysis induction of tumor cells in human cervical carcinomas, KB-3-1 (MDR^-), or KB-8-5 (MDR^+), and in murine melanoma, B-16 (MDR^-), cells.[35]

Furthermore, combination of OVs with standard antitumor drugs can potentiate therapeutic efficacy for cancer treatment. Consistent with this hypothesis, it has been shown that oncolytic Rhabdovirus Maraba-MG1 combined with Paclitaxel, one of the most common drugs used to treat patients with breast cancer, showed excellent compatibility against EMT6, 4T1, and E0771 murine breast cancer cells. Not only did this combination had synergistic cytopathic activity, but Paclitaxel also led to increased virus production in both EMT6 and 4T1 tumors.[36] In agreement with these findings, it has been demonstrated that combination therapy of oncolytic herpes simplex virus type 1 with doxorubicin triggered a potent suppression of tumor growth with increased median survival period compared with each treatment given alone ($P < 0.05$).[37] Consistently, it has been shown that administration of oncolytic adenovirus ZD55 carrying short hairpin RNA targeting special AT-rich sequence-binding protein-1 (SATB-1), a promising therapeutic target for prostate cancer, significantly inhibited the tumorigenic properties of human prostate cancer in both cellular and animal systems.[38] These results clearly support the therapeutic potency of OVs against cancer cells in several tumors.

4 | OVs TARGET BRAIN TUMOR CANCER STEM CELLS

OVs improve survival rate and reduce the possibility of cancer recurrence by targeting both normal cancer cells as well as CSCs.[29] Several studies have investigated the efficacy of OVs in targeting CSCs and killing cancer cells. Consistently, Zhu et al[39] showed that a viral vector carrying an exogenous Endostatin-Angiostatin (Endo-Angio) fusion gene (VAE) could infect and inhibit activity and viability of glioma stem cells (GSCs), suggesting that the VAE-mediated virus-gene therapy is an effective strategy for glioma treatment. Similarly, it was shown that arming a genetically engineered oncolytic herpes simplex virus with an immunomodulatory cytokine, murine interleukin 12 (G47-mIL12), lysed human glioblastoma ($CD133^+$) CSC-like cells, and targeted mouse GSCs in a murine glioblastoma stem cell model.[40] In another study, Friedman et al[41] showed that low CD111 oncolytic herpes simplex viruses failed to enter glioma progenitor cells, suggesting that CD111 plays crucial role in infecting and killing $CD133^+$ glioma progenitor cells by oncolytic herpes simplex viruses. Moreover, Bach et al developed a type of oncolytic measles virus, MV-141.7, which could infect and lyse cells expressing $CD133^+$, a cell surface marker of several tumor cells including glioblastoma, with high selectivity. They showed that MV-141.7 oncolytic measles viruses elicited a great antitumoral function against mouse models of orthotopic glioma tumor spheres.[42] Similarly, compared with inactivated virus-treated controls, oncolytic measles virus derivatives significantly replicated, and prolonged survival in glioma stem cell derived xenograft models.[43] In another study carried out by Wakimoto et al, the function of a triple knockout oncolytic herpes simplex virus, G47Delta (ICP6(-), gamma34.5(-), and alpha47(-) was evaluated on CSC-enriched cultures derived from human glioblastoma specimens. The results showed that the oncolytic virus not only killed glioblastoma-derived cancer stem-like cells, but also suppressed the formation of secondary tumor spheres, suggesting inhibition of self-renewal in infected viable cells. Further studies showed that intratumoral injection of the vector significantly prolonged survival in mice, supporting the therapeutic potency of oncolytic herpes simplex virus against human glioblastoma-derived cancer stem cells.[44]

Furthermore, Mahller et al designed a Nestin-targeted oncolytic herpes simplex virus termed rQNestin34.5 to kill neuroblastoma CSCs. Nestin is an intermediate filament protein recognized as a CSC marker in a number of cancers including brain tumors and neuroblastoma.[45] They found that rQNestin34.5 efficiently replicated and prevented neuroblastoma CSCs from forming tumors in athymic nude mice, suggesting OVs as next generation anticancer therapeutics against neuroblastoma CSCs.[46] In another study, it was shown that an oncolytic adenovirus, Delta-24-RGD, targeted the abnormal p16INK4/Rb pathway and effectively induced autophagic cell death in brain-tumor stem cells. Moreover, treatment of xenografts derived from brain tumor stem cells with the vector improved the survival of glioma-bearing mice (means: 38.5 vs 66.3 days, difference = 27.8 days, 95% confidence interval = 19.5 to 35.9 days, $P < 0.001$), supporting the potential role of Delta-24-RGD in mediating cell death via autophagy in cellular and animal models.[47] Similarly, Yu et al[48] found that a single intravenous injection of Seneca Valley virus-001 (SVV-001), a naturally occurring oncolytic picornavirus, eliminates medulloblastomas in primary tumor-based orthotopic xenograft mouse models, resulting in significantly increased survival (2.2-5.9 fold). Consistently, Skog et al[49] demonstrated that both adenovirus 16 and chimpanzee Ad (CV23) viruses could infect both the low-passage brain tumor cell lines and the positive or negative cancer stem cell marker, CD133, and primary tumor cells supporting the clinical potency of these viruses against brain tumors. In another study, administration of JX-594, a recombinant granulocyte macrophage colony-stimulating factor-expressing vaccinia virus, infected and killed BTIC. Further studies showed that JX-594 inhibited tumor growth and improved survival in rats-bearing RG2 intracranial tumors and mice-bearing GL261 brain tumors.

There is a compelling evidence suggesting that the combination of a chemotherapeutic agent with OVs not only increases the treatment efficacy of brain tumors, but also decreases toxicities of chemotherapy regimens to normal tissues. In line with this, the oncolytic herpes simplex virus G47Δ armed with low-dose etoposide, a chemotherapeutic drug, exerted significant antitumor activity in glioblastoma cell lines as well as in the most etoposide-resistant human glioblastoma-derived cancer stem cells such as BT74. They also showed that the combination therapy significantly extended survival of mice-bearing etoposide-insensitive human glioblastoma stem cell xenografts.[50] Similar to these findings, Kanai et al showed that coadministration of a chemotherapeutic alkylating agent, temozolomide, with oncolytic herpes simplex virus G47Δ was highly effective in killing glioblastoma stem cells and significantly increased survival rate of mice bearing glioblastoma stem cell-derived intracranial tumors. They also showed that the synergistic effect of combinatorial therapy was at least partially mediated by localization of ataxia telangiectasia mutated, a DNA damage response gene, to oncolytic herpes simplex virus DNA replication and could not participate in repairing temozolomide-induced DNA damage.[51] Moreover, coadministration of JX-594 with rapamycin, a specific pharmacological inhibitor of mammalian target of the rapamycin signaling pathway, enhanced replication potency of the vector and further prolonged survival in immunocompetent rodent models of malignant glioma.[52] Consistent with these findings, Zemp et al investigated the therapeutic potency of oncolytic Myxoma virus either alone or in combination with rapamycin against human brain tumor-initiating cells (BTIC). They showed that Myxoma virus killed BTIC and prolonged survival of BTIC-bearing mice in cellular and animal models. Moreover, the combination of Myxoma virus with rapamycin effectively improved antitumor activities of Myxoma virus, even in mice bearing "advanced" BTIC tumors.[53] Furthermore, coadministration of MG18L, a new oncolytic herpes simplex virus containing a U(S)3 deletion and an inactivating LacZ insertion in U(L)39, with PI3K/Akt inhibitors, LY294002, triciribine, GDC-0941, and BEZ235, synergistically induced apoptosis in glioma stem cells. Compared with using either agent alone, this combinatorial treatment also prolonged survival of a mouse model of stem cell–derived glioblastoma.[54] To further support the therapeutic potency of combinatorial treatment strategies, it has been demonstrated that combination of virotherapy with radiotherapy improves killing glioma CSCs. In line with this, Nandi et al[55] reported that a combination of low-dose of radiotherapy with a novel oncolytic adenovirus, CRAd-Survivin-pk7, enhanced the toxicity of the vector approximately 20% to 50% against malignant glioma stem cells. Moreover, cotreatment with radiation and CRAd-Survivin-pk7 inhibits tumor growth in U373MG $CD133^+$ stem cells. These results support the clinical significance of administration of OVs either alone or in combination with standard regimens as a novel therapeutic strategy against brain tumors.

5 | CONCLUSION

CSCs play key roles in several brain tumor characteristics including tumor growth, metastasis, and nonstop proliferation potential. It has been validated that

targeting CSCs is essential for eradicating brain cancers and long-term patient treatment.[56] CSCs possess diverse features including slow cell cycle kinetics, efficient DNA repair, upregulation of antiapoptotic proteins, and multidrug resistance-type membrane transporters which make them resistant to conventional therapies.[29,57] Thus, novel therapeutic strategies should be developed to improve therapeutic effects and prolong the disease-free survival of patients with cancer. Here, we summarized the therapeutic potency of OVs-induced cancer stem cell targeting as a novel strategy against brain tumors. OVs are able to target brain CSCs, conditionally replicate in these cells and disrupt the CSC niche via increasing production of immune-stimulating cytokines or small molecules toxic to CSCs and their progeny. (Figure 1)

Consistently, several OVs have been developed and investigated in brain cancer clinical trials. In line with this, G47Δ has completed clinical phase I-IIa in patients with recurrent glioblastoma successfully. Moreover, it has also finished phase I study in patients with castration-resistant prostate cancer too.[10] Similarly, combination therapy with Reolysin, a reovirus, and paclitaxel and carboplatin demonstrated substantial improvement in a randomized double-blinded phase III trial in patients with regional head and neck cancer, supporting the significant efficacy of OVs in brain cancer treatment.[58] Several clinical trial studies have been performed to evaluate the potential role of oncolytic viruses in treatment of glioblastoma tumor.[59] In line with this, a phase I study using combination therapy of TG6002 OV with 5-flucytosine (5-FC) has been started in France. All patients will be treated with the same dose schedule of TG6002. After first and second infusion of TG6002, patients will be given 5-FC for 3 days which is initiated on days 5 and 12 and terminated on days 7 and 14, respectively. This will be followed by third infusion of TG6002 on Day 15 and another given oral 5-FC for 21 days from day 19 to 39 (NCT03294486). Consistently, a clinical phase 2 trial using DNX-2401, a genetically modified oncolytic adenovirus, in combination with pembrolizumab, an immune checkpoint inhibitor, is administered in patients with brain tumors. Through this study, DNX-2401 will be injected directly into the brain tumor at an intratumoral dose of 1.0 mL. After 7 to 9 days, patients will receive intravenous pembrolizumab, 200 mg every 3 weeks for 105 weeks (2 years) (NCT02798406). Moreover, adenovirus E1B-55kDa is approved for the treatment of squamous cell head and neck cancer.[60] In normal cells adenovirus is affected by p53-mediated cell cycle arrest, resulting in inhibition of virus replication. However, p53 mutated cancer cells are subjected to viral replication leading to cancer cells death.[61]

In spite of numerous advantages of using OVs against cancer cells, there are some hurdles for their application in cancer therapy.[62] Consistent with this, it

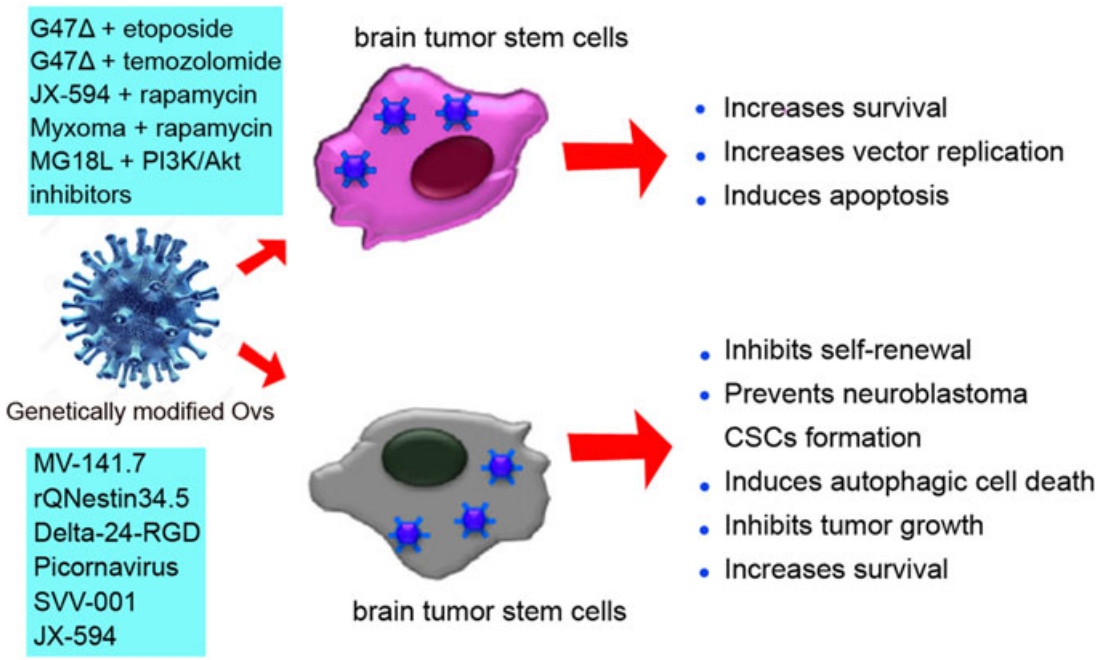

FIGURE 1 Schematic representation of OVs-mediated brain tumor cancer stem cell targeting. Oncolytic measles either alone or in combination with standard regimens increases antitumor responses in both cellular and animal models. OVs, oncolytic virotherapies

has been validated that effectual systemic delivery of OVs is still considered as one of the main remaining challenges in OVs usage.[63] It has been shown that OVs are neutralized through nonspecific attachment to serum proteins and circulating cells existing in the bloodstream.[63] Some organs including lung, spleen, and especially the liver, play a crucial role in removing virus from the bloodstream.[64] Moreover, several mechanisms have been widely used by immune system to prevent efficient systemic delivery of viruses to tumors. More interestingly, the tumor immunosuppressive microenvironment interferes with OV clinical efficacy and inhibition of this immunosuppressive condition is one of the significant issue which needs to be addressed in the OV therapy.[65] Tumors contain infiltrating Tregs and myeloid-derived suppressor cells and secret immunosuppressive cytokines such as IL-10 which maintain an immunosuppressive environment that interfere with OV efficacy.[66]

It is recommended that further investigation can be performed in this regard to evaluate the exact mechanisms of OVs in targeting CSCs and potential hazards of this approach to normal tissues. The information gained from all these studies will provide guidelines for designing novel selective viruses to limit CSC maintenance, tumorigenicity, and drug resistance which will improve management of cancer patients.

CONFLICTS OF INTEREST

The authors have no conflicts of interest.

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