Chapter 9

Stem Cell Research for the Treatment of Malignant Glioma

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Additional information is available at the end of the chapter

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Abstract

Glioblastoma is the most aggressive brain tumor. Gene therapies, such as cytokine-based, suicide gene, and oncolytic virus therapies, are different types of treatments from chemotherapy such as using temozolomide as a standard treatment. However, overall survival was not prolonged in some clinical trials because of the low efficiency of gene transduction and viral infection. Neural stem cells (NSCs) have tumor trophic migratory capacity and can be cellular delivery vehicles of cytokines, suicide genes, and oncolytic virus. NSCs can be differentiated from embryonic stem cells. In addition, mesenchymal stem cells can be another cellular delivery vehicle. Recently, induced pluripotent stem cells (iPSCs) have been established. iPSCs are multipotent; hence, they can efficiently differentiate to NSCs and can possibly overcome ethical and practical issues in clinical application. In this study, current topics about stem cell therapy for malignant glioma are reviewed.

Keywords: malignant glioma, gene therapy, stem cell

1. Introduction

Malignant glioma is the most aggressive brain tumor that accounts for approximately 30% of all brain tumors [64]. It is incurable by a conventional standard therapy (maximal tumor resection, adjuvant chemotherapy, and irradiation) because brain tumor stem cells have infiltrative growth and resistance to irradiation and tumoricidal agents [63].

Gene therapies, such as cytokine-based, suicide gene, and oncolytic virus therapies, are different types of treatments from chemotherapy, such as using temozolomide, an alkylating agent, as a standard treatment for glioblastoma [15, 25, 56]. Some clinical trials have been previously conducted; however, prolonged overall survival was not attained. This result was caused by the low efficiency of gene transduction and viral infection [56].

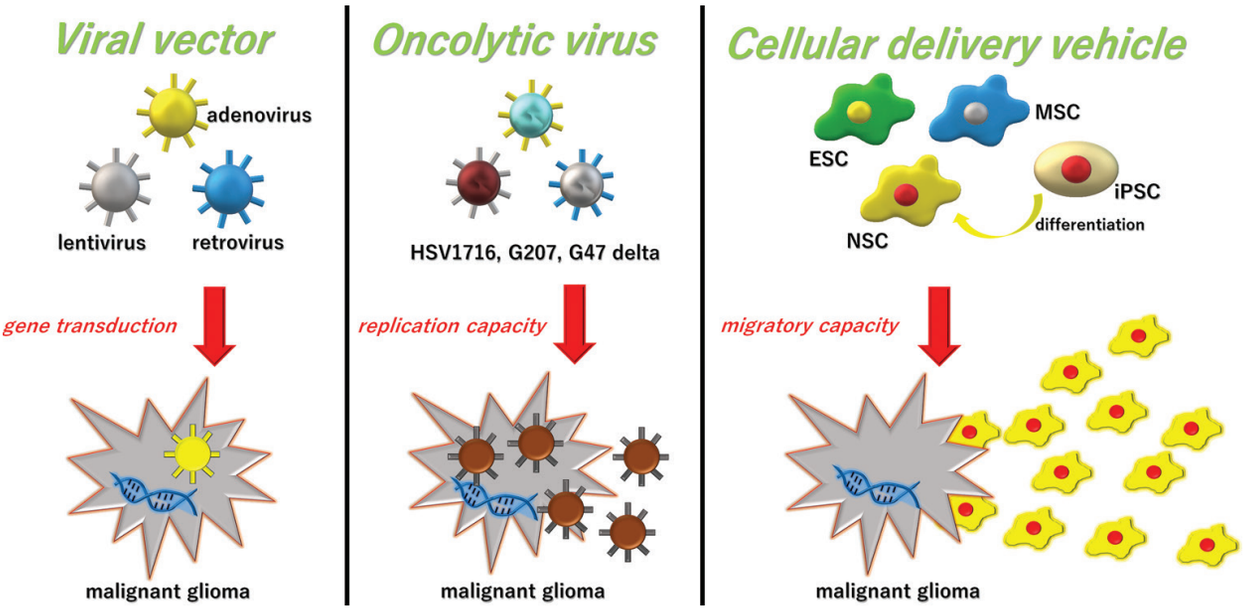

Figure 1. Viral vectors are tools commonly used to deliver genetic material into tumor cells. However, the efficiency of gene transduction by the viral vectors is not high enough to cover the invaded area of malignant glioma. Replication-competent virus is used for oncolytic virus therapy. Genetically modified oncolytic virus can selectively replicate in tumor cells. Viral particles are released and spread to surrounding tumor cells. Some stem cells have tumor trophic migratory capacity, which can be possible cellular delivery vehicles of cytokines, suicide genes, or oncolytic virus to tackle malignant gliomas. Stem cells have the possibility to cover the large invaded area of malignant glioma.

Recent studies demonstrated that neural stem cells (NSCs) and mesenchymal stem cells (MSCs) have tumor trophic migratory capacity [45, 62]. NSCs and MSCs would be possible cellular delivery vehicles of cytokines, suicide genes, or oncolytic virus to tackle gliomas [45, 62]. NSCs can be differentiated from certain types of stem cells. Embryonic stem cells (ESCs) are established from the inner cell mass in human embryos; however, ESCs have ethical issues [73]. MSCs can be easily harvested from the adult bone marrow and the fatty tissue. However, further investigation is needed for the affinity of MSCs to the human brain [31]. Induced pluripotent stem cells (iPSCs) were established from human adult fibroblasts in 2007 [65, 67]. iPSCs have multipotency; hence, they can efficiently differentiate to NSCs. iPSCs can possibly overcome ethical and practical issues in clinical application [6, 66].

In this study, current topics about stem cell therapy for malignant glioma are reviewed (**Figure 1**).

2. Gene therapy using viral vector

The characteristics of gene therapies are summarized in **Table 1**.

2.1. Cytokine-based therapy

Viral vectors such as retrovirus and adenovirus with genes encoding immunostimulatory cytokines have been used to treat malignant glioma. This therapy can increase the proliferation

Gene therapy	Characteristics	Types
Cytokine based therapy	Cytokine based therapy can increase the proliferation of cytotoxic T cells and natural killer cells, enhancing anticancer immune response.	IL-2, IL-4, IL-12, IL-18, GM-CSF, IFN-γ, B7-1, and TGF-β antisense
Oncolytic virus therapy	Genetically modified oncolytic viral vectors can selectively replicate in tumor cells. Viral particles are released and spread to surrounding tumor cells.	First generation: HSV1716: γ34.5 gene deleted HSV-1 Second generation: G207: a doubly mutated HSV-1, which has deletion of both γ34.5 loci and insertional inactivation of UL39 Third generation: G47 delta: a new type of oncolytic HSV-1 derived from G207, with an additional deletion of ICP47 and the promoter region of US11
Suicide gene therapy	Suicide genes can change a nontoxic prodrug into a toxic substance that triggers apoptosis of tumor cells.	Suicide gene/prodrug • HSVtk/ganciclovirl • CD/5-flucytosine

CD: cytosine deaminase, GM-CSF: granulocyte–macrophage colony-stimulating factor, HSV: herpes simples virus, IFN-γ: interleukin interferon-gamma, IL: interleukin, TGF-β:transforming growth factor-beta, tk: thymidine kinase.

Table 1. Characteristics of gene therapies.

of cytotoxic T cells and natural killer cells, enhancing anticancer immune response. Cytokines delivered by viral vectors such as interleukin (IL)-2, IL-4, IL-12, and IL-18, granulocyte-macrophage colony-stimulating factor (GM-CSF), interferon-gamma (IFN-γ), costimulating factor such as B7–1, and enhancer of immunogenicity such as transforming growth factor-β antisense have been previously investigated. These studies demonstrated the local augmentation and ability of the immune response against glioma cells [53, 71, 74].

Recently, tumor suppressor genes are also used for gene therapy to treat malignant glioma. p53, which is known as a common mutagenic target in the development of malignant glioma, was evaluated using a replication-deficient adenoviral vector [32]. Phosphatase and tensin homolog (PTEN) negatively regulates PI3K. PTEN gene alterations are also associated with poor prognosis of malignant glioma. PTEN expression induced by adenoviral vector also showed an antitumor response in some experiments [1]. A clinical trial using an adenoviral vector with INF-β has also been conducted. However, the efficacy of that clinical trial in patients is limited. Therefore, improvement of the vector is certainly necessary to deliver the genes [14]. On the contrary, some studies suggested the advantages of the combination of cytokine-based and standard chemotherapies. In the future, combinatorial gene therapy might be effective in the treatment of malignant glioma [11, 33, 44, 76].

2.2. Oncolytic virus therapy

Replication-competent viral vectors have been previously used for oncolytic virus therapy. The transduction efficiency of replication-competent viral vectors is higher than that of replication-deficient viral vectors [2]. Genetically modified oncolytic viral vectors can selectively

replicate in tumor cells. Viral particles are released and spread to surrounding tumor cells. Oncolytic viral vectors cannot replicate in normal cells. Herpes simplex virus (HSV)-1 is the most famous oncolytic virus that has lower immunogenicity and stronger tumoricidal effects than adenovirus [22, 70].

HSV1716 is γ34.5 gene deleted HSV-1, constructed from wild-type strain. The γ34.5 gene of HSV-1 encodes ICP34.5. ICP34.5 gene counteracts the double-stranded RNA-dependent protein kinase (PKR)-mediated block to virus replication in post-mitotic cells. HSV1716 effectively kills tumor cells because tumor cells have weaker defenses mediated by PKR pathway. The safety and toxicity of HSV1716 in patients have been demonstrated in a phase I clinical trial for recurrent malignant glioma. Moreover, major neurological manifestation was not noted [55]. However, HSV1716 has the risk of being converted to the wild-type strain HSV-1 because HSV1716 has only single gene deletion [18, 52].

G207 is a doubly mutated HSV-1, which has deletion of both γ34.5 loci and insertional inactivation of UL39. Ribonucleotide reductase (RR) encoded by UL39 is crucial for virus replication by catalyzing ribonucleotide formation. The lack of viral RR expression in G207 specifically targets tumor cells because tumor cells have high RR activity. In addition, G207 did not have the risk of being converted to the wild-type strain HSV-1. G207 was safe when it was inoculated into patients with recurrent malignant glioma in phase I or Ib clinical trials. Treatment-related toxicity or serious adverse events and evidence of HSV-1 encephalitis were not shown [39, 40, 42].

G47 delta is a new type of oncolytic HSV-1. G47 delta has an additional deletion of the gene encoding ICP47. G47 delta has the ability to enhance major histocompatibility complex class I antigen and immune response. In addition, this deletion causes promoter shift for the unique short 11 gene, which blocks the effect of IFNs and increases viral replication in tumor cells. A phase I/IIa clinical trial using G47 delta, which enhances specificity, and safety was conducted for recurrent or progressive glioblastoma in 2009 [72]. A phase II clinical trial using G47 delta was initiated from 2015 in a physician-led clinical trial.

OncoVEX^{GM-CSF} is a first-in-class oncolytic vaccine approved by the FDA in 2015. It helps stimulate host immune response. ICP34.5 and ICP47 were deleted from HSV-1, and the gene encoding GM-CSF was inserted. A phase I clinical trial using OncoVEX^{GM-CSF} was conducted for patients with breast, head and neck, and gastrointestinal cancers and malignant melanoma who had unsuccessful prior therapy. In the clinical trial, the virus had a good safety profile [24]. A phase II clinical trial for patients with unresectable metastatic melanoma showed 26% response rate [60]. Moreover, a phase III clinical trial showed significant prolonged overall survival for unresectable metastatic melanoma [27, 54].

Reovirus (Reolysin), which is a naturally occurring nonpathogenic, double-stranded RNA virus, has oncolytic activity and was also approved by the FDA. It was evaluated in phase I–III clinical trials in squamous cell carcinoma of the lungs and non-small-cell lung, pancreatic, and ovarian cancers. Its favorable toxicity profile, deficiency of viral shedding, and therapeutic effect have been shown in those clinical trials. A phase III trial of Reolysin combined with paclitaxel and carboplatin for treatment of head and neck squamous cell carcinoma was completed in 2014 [43].

The 55-kda protein from the E1B region of an adenovirus binds to and inactivates the p53 gene. ONYX-015 is an adenovirus modified to selectively replicate and kill cells that harbor p53 mutations [20]. A phase I clinical trial was conducted for patients with recurrent malignant glioma. ONYX-015 showed promising safety profile; however, there was no significant therapeutic benefit [10].

Oncolytic virus therapy has been centered on various types of cancers and is expected to be applied for brain tumors. However, diffuse infiltration capacity of oncolytic virus to cover a large area invaded by malignant glioma might be one of the issues to solve.

2.3. Suicide gene therapy

Suicide genes can change a nontoxic prodrug into a toxic substance that triggers apoptosis of tumor cells [8, 69]. Herpes simplex virus thymidine kinase (HSVtk) + ganciclovir and cytosine deaminase (CD) + 5-flucytosine is the most famous combination. This therapy has a bystander killing effect, which results in the killing of a larger portion of cells than is transduced with the suicide gene [57]. In the 1990s, some clinical trials were conducted using viral vectors and fibroblasts that produce retrovirus for gene transduction. However, this therapy did not prolong the overall survival of patients with glioblastoma. This was considered to be caused by the vector's low efficiency of gene transduction [9]. Toca 511, a retroviral replicating vector that delivers yeast CD, showed good results under the Toca FC administration in experimental brain tumor models, leading to a clinical trial [51].

2.4. Some types of stem cells

2.4.1. ESC

ESCs are derived from inner cell mass that can differentiate to triploblastic tissues. It has high telomerase activity that can persistently divide [30, 59]. Because the generation of ESCs involves the destruction of the preimplantation stage embryo, their use was controversial. In addition, ESCs can possibly lead to teratoma formation after transplantation. ESCs are also affected by immune rejection accompanied with ethical concerns because a fertile ovum is used. The first clinical trial that used ESCs was conducted in patients with severe subacute spinal injury in 2009. In that study, oligodendrocyte progenitor cells derived from ESCs were transplanted. Other clinical trials using ESCs have been previously conducted for some diseases such as age-related macular degeneration and Stargardt disease. However, it has not been applied for brain tumor [59, 80].

2.4.2. MSC

MSCs can be harvested from fetal Wharton's jelly adult bone marrow, synovialis, fatty tissue, placenta, heart and liver. MSCs can be established by patients themselves. MSCs are not affected by host immune rejection [75]. Therefore MSCs tend to be easily linked to clinical applications. For example, endocapillary cells, myocardium, skeleton muscle, liver cell, neuron, glial cell, insulin-producing cell and epithelial cell can be differentiated from MSCs. MSCs have been previously used for clinical trials such as head injury and cerebral infarction [23, 30].

2.4.3. iPSC

iPSCs can be established directly from adult cells. Four specific genes (Oct3/4, c-myc, Sox2, and Klf4) encoding transcription factors could convert adult cells into iPSCs. iPSCs hold great promise in the field of regenerative medicine. iPSCs can also overcome some problems such as ethical concerns and immune rejection. Recently, iPSCs can be established without c-myc and can prevent teratoma formation [46, 49]. An episomal vector is used for the transduction to prevent chromosomal insertion that cannot be accomplished by viral and plasmid vectors [50, 77]. In addition, iPSCs can be cultured under the feeder-free condition, and laminin-511 supports the stable culture of iPSCs [19]. The efficiency to culture iPSCs has been rapidly improved.

The first clinical trial for macular degeneration using autologous-induced stem cell-derived retinal cells has been completed in Japan in 2015. The feasibility of using iPSCs has been shown [38]. A clinical trial for Parkinson's disease is expected to use iPSCs in the near future [12, 13, 16, 26, 48].

All types of stem cells have two important effects. First is the trophic effect, that is, supplying various nutrients and tissue-protective cytokines, and the second is the repairing effect, that is, identifying the damaged area and differentiating to an organized tissue after homing [23, 30].

2.5. Gene therapy using stem cells as delivery vehicle

2.5.1. Cytokine-based therapy

IL-4-producing NSCs showed powerful antitumor effects compared with that of the virus-mediated delivery of IL-4 [7]. In addition, NSCs and MSCs that produce IL-2, IL-7, IL-12, and IL-23 have been evaluated for brain tumor [15, 17, 47, 61, 78, 79]. TNF-related apoptosis-inducing ligand (TRAIL) triggers caspase-8-dependent apoptosis. The tumor-specific therapeutic effects of TRAIL-producing NSCs, MSCs, and ESCs-derived astrocytes have been shown in experimental gliomas [29, 58].

2.5.2. Oncolytic virus therapy

Some studies showed the advantages of stem cells (NSCs and MSCs) to deliver replicating HSV and adenovirus because stem cells suppress the host immune response of the virus. In addition, stem cell therapy has become a promising approach because it can deliver viruses at further distance within the invaded malignant glioma [3, 5, 21, 68]. Actually, MSCs with replicating adenovirus showed that MSCs can suppress the immune response against the virus, which makes it possible to prolong viral activity and survival [4]. Some similar researches using NSCs with conditionally replicating HSV and adenovirus in preclinical studies were conducted [21].

2.5.3. Suicide gene therapy

Some reports showed that suicide gene therapy with HSVtk or CD using NSCs as cellular delivery vehicle could significantly prolong survival in animal models of brain tumor [28, 34, 37]. MSCs with HSVtk or CD were also used for the treatment of malignant glioma. Both NSCs

and MSCs could migrate even to the contralateral tumor [35, 41]. Mouse iPSC-derived NSCs with HSVtk have been previously reported and showed equivalent results as described above. However, the study using human iPSC-derived NSCs has not been reported, yet [36]. One pilot trial using NSCs with CD has been recently completed, but results are not yet available.

3. Future directions

The treatment concept of gene therapy was appropriate for malignant glioma; however, viral vectors are not enough to cover the large invasion area. The migration ability of stem cells has been expected. Some types of stem cells can be established recently. However, a comparative analysis on which type of stem cell has the strongest migration ability and the tumoricidal effect is needed. In brain tumor, NSCs may be considered as the most effective cellular vehicle because of their affinity to the brain. iPSCs are attractive tools because NSCs could be efficiently differentiated from iPSCs. Gene therapy using stem cells as cellular delivery vehicles is expected to be further developed in the future.

Conflict of interest

The authors have no personal financial or institutional interest in this article.

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