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Review Article

Stem cells as cellular vehicles for gene therapy against glioblastoma

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Abstract: Glioblastoma (GBM) is the most common and deadliest primary tumor in adults, with current treatments having limited specific and efficient delivery of therapeutic drugs to tumor sites or cells. Therefore, the development of alternative treatment options is urgently needed. Stem cells are considered as ideal cellular vehicles for gene therapy against glioblastoma. In this paper, we reviewed the recent studies investigating the use of different types of stem cells as cellular vehicles and the gene of interests against the glioblastoma, as well as the future directions of the application of cellular vehicles mediated therapy for glioblastoma.

Keywords: Glioma, stem cell, cellular vehicle, gene therapy

Introduction

Glioblastoma makes 25% of all malignant nervous system tumor, which occurs about 3 per 100,000 population in United States [1]. Because of its aggressive characteristics and low specific and efficient delivery of therapeutic drugs to tumor sites, treatments for glioblastoma include surgery, radiotherapy and chemotherapy lead to only 25% of patients surviving about 2 years even with advanced technology [2]. Thus, the development of better therapeutic strategies to enhance the survival rate is desperately needed [3].

Stem cells are a group of cells with self-renewal and multilineage differentiation. A large number of studies have demonstrated that stem cells derived from various sources could specifically migrat to tumor sites [4-7]. Therefore, stem cell is a promising vehicle loaded with anti-tumor drugs or gene of interests against tumor home to tumor site [8].

Stem cells as cellular vehicles

Neural stem cells

Neural stem cells (NSCs) are central neural system (CNS) progenitor cells, which have self-renewal ability and can differentiate into all of the three types of cells in CNS: neurons, oligodendrocytes and astrocytes [9]. Recent studies showed that NSCs could migrate through the brain and target to tumor site, which indicated that NSCs was a cellular vehicle for delivering anti-brain therapeutic drugs or gene of interests [10]. The possible mechanism was that cytokines and other factors produced in the tumor microenvironment, such as hepatocyte growth factor (HGF), hypoxia-inducible factor-1alpha (HIF-1α) and vascular endothelial growth factor (VEGF) act as chemoattractants for NSCs [11]. On the other hand, several studies have demonstrated that injected NSCs release soluble molecules to promote immuno modulation in the CNS [12, 13]. Because NSCs reduce the activity of immune system, they are easy to carry and deliver anti-tumor drug and gene of interests.

Mesenchymal stem cells

Mesenchymal stem cells (MSCs) are multipotent cells which is able to differentiate into a number of cell types. These cells have been another potential vehicle for delivering anti-tumor therapy [14]. MSCs can be expanded *in*

vitro with a low intrinsic mutation rate, are manipulated easily and well tolerant to the human immune system. They can also be autologously transplanted into the same patient where therapy taken to avoid immune response after administration [15]. Interestingly, MSCs have been proved to migrate into many different types of tumor microenvironments including glioma [16-18]. However, the exact migratory mechanism of MSCs is not completely understood. It is suspected that chemokines, cytokine, growth factors and metalloproteinase secreted by the tumor guide MSCs' tumor-targeting ability [19, 20]. Additionally, MSCs can be engineered to express homing ligands, which improves their target specificity [21].

Actually, bone marrow, adipose tissues, peripheral blood and embryonic stem cell-derived mesenchymal stem cells are the most common types [15, 22]. However, it has come up a new mesenchymal stem cells obtained from menstrual blood called menstrual blood-derived mesenchymal stem cells recently [23, 24]. These cells express stem cell markers such as SSEA-4, Oct-4, c-kit (CD117), and Nanog, and have the potent ability to differentiate into a variety of cell types, such as the heart, nerve, bone and liver [25, 26]. These cells secrete many growth factors to display recurrent angiogenesis [26]. This provides an easy way to get MSCs, indicating a potential application in cell carrier of gene therapy against glioma.

Gene of interest

Gene therapy for GBM is rapidly developing. The functions of genes of interest can result not only in tumor cell death, but also enhance immune responses to tumor antigens, as well as disruption of the tumor microenvironment, including inhibition of angiogenesis and neovascularization [27-29]. The genes of interest include the cytotoxic gene and immune stimulatory gene as follows.

Cytotoxic gene

Cytotoxic, radio- and chemotherapy have been the standard care for GBM patients. Most of the failure was because of their negative impacts on neighboring healthy tissue and small therapeutic indexes. Suicide gene therapy includes delivery of a prodrug activating enzyme (suicide gene) that is able to convert nontoxic prodrugs to cytotoxic forms [30].

Herpes simplex virus-thymidine kinase (HSV-TK)

HSV-TK/ganciclovir (GCV) is one of the most widely used prodrug activation systems. In this suicide gene therapy system, GCV is non-toxic and can readily cross the blood-brain barrier, converted into active drug in the tumor cells. Then GCV will be phosphorylated and incorporated into replicating DNA, leading to cell death. The phosphorylated GCV can pass through the gap junction of adjacent cells, and kill neighboring tumor cells. This ability was called the "bystander effect", which was defined as death of tumor cells adjacent to modified cells [31, 32]. As the bystander effect could cover the low transduction rate of retroviral system, clinical studies have used the retrovirus-mediated HSV-TK/GCV gene therapy, resulting in only clinical safety but not therapeutic benefits [33, 34].

However, in a previous study, a potent bystander effect between NSCs transduced with HSV-TK gene (NSCtk cells) was observed inintracranial tumor. NSCtk cells were injected at the intracranial site distant from the tumor implantation inducing the contralateral hemisphere to the tumor in rates. Results demonstrated a potent migratory and tumor hunting ability of NSCs and a potent in vivo anti-tumor effect of thymidine kinase through the bystander effect [31]. Furthermore, they found out that the strategy using mesenchymal stem cells transduced with HSV-TK (MSCtk cells) and ganciclovir (MSCtk therapy) is more feasible and practical for clinical application than the method using neural stem cells [35]. Recently, human embryonic stem cell-derived MSCs were evaluated as another alternative option in stem cells HSV-TK therapy [36].

Secretable trimeric form of tumor necrosis factor-related apoptosis-inducing ligand (stTRAIL)

Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) based therapy strategy involves treatment with recombinant TRAIL (rTRAIL) or an adenovirus bearing the *TRAIL* gene anti glioma. The artificial *TRAIL* gene, that is secretable trimetric TRAIL (stTRAIL), encodes a fusion protein composed of three functional elements including a secretion signal, a trimerization domain and an apoptosis-inducing moiety of the *TRAIL* gene sequence [37]. Adenoviral vectors delivering the *stTAIL* gene (Ad-stTRAIL)

had higher tumor suppressor rate compared with adenoviral vectors delivering the full-length sequence of *TRAIL* gene in vivo and in vitro [38]. Other studies also showed that TRAIL and secreted TRAIL dominant with or without fused to hFlt3L instead of stTRAIL also had profound anti-tumor effects in vivo [39-41].

Cytosine deaminase (CD)

Cytosine deaminase: uracil phosphoribosyltransferase (CDy:UPRT) engineered human adipose tissue-derived mesenchymal stem cells (AT-MSCs), short as CDy-AT-MSCs, are able to convert non-toxic 5-fluorocy-tosine (5-FC) to the active toxic form [42]. Then they demonstrated that CDy-AT-MSCs/5-FC system of suicide gene therapy significantly inhibited glioblastoma growth [43, 44].

Interleukin-24 (IL-24)

The mda-7 gene, renamed as interleukin-24 (IL-24), was isolated from human melanoma cells induced to undergo terminal differentiation treating with fibroblast interferon and mezerein [45], which is a member of the interleukin-10 (IL-10) gene family [46-48]. Considering its cancer cells' specific apoptosis-inducing and tumor growth suppressing ability in human tumor animal models, mda-7/IL-24 was regarded in application in patients with advanced cancers [49, 50]. The pathways by which Ad.5-mda-7 causes cell death in tumor cells are not well understood, however, it seems that proteins important in the onset of growth inhibition and apoptosis, such as BCL-XL, BCL-2, and BAX [48, 51-53], are involved, which lead to mitochondrial dysfunction [54] and endoplasmic reticulum stress signaling [55].

A recent study employed a recombinant adenovirus that comprises the tail and shaft domains of a serotype 5 virus and the knob domain of a serotype 3 virus expressing MDA-7/IL-24 (Ad.5/3-mda-7) to combine both inhibition of cytoprotective pathways and tropism modification, and provided a means of developing an improved therapy for GBM [56].

Interleukin-13 (IL-13)

Human IL-13 was fused to the *Pseudomonas* exotoxin (hIL-13-PE; Cintredekin Besudotox) to target IL13Rα2-expressing GBM cells [57] as 50% to 80% of human GBMs express a number of the IL-13 receptor, IL13Rα2 [58, 59]. A recent study developed Ad.mhIL-13-PE to provide sustained expression, effective anti-GBM cytotoxicity, and minimal neurotoxicity leading to a significant advance in the implementation of targeted toxins for glioma therapeutics [60].

EphrinA1-PE38

EphrinA1-PE38 is a specific immunotoxin against the EphA2 receptor which is a member of the Eph receptor tyrosine kinase family, whose 16 members can be further divided into "A" and "B" classes, based on sequence homology and binding affinity to their ligand, the Ephrin [61]. A recent study demonstrated that the intratumoral injection of hMSCs engineered with EphrinA1-PE38 was effective in inhibiting tumor growth in a glioma tumor model [62].

Immune stimulatory gene

The immune-privileged state of the brain is an important obstacle to immunotherapy against glioma [63]. The brain lacks antigen-presenting cells and is limited in lymphatics that impede immune cells from the brain parenchyma [64]. In addition, the GBM microenvironment is immunesuppressed, with elevated myeloid-derived suppressor cells and regulatory T cells [65]. Despite these challenges, significant progress with immunemediated gene therapy strategies has been achieved.

Interleukin-12 (IL-12)

IL-12 is one of the anti-tumor cytokines, driving from a T_H1 response [66]. A 34.5-deleted HSV-1 expressing mouse IL-12 (M002) was tested in non-human primates and proved to be nontoxic, but increased activation of nonhuman primates lymphocytes [67]. MSCs expressing IL-12 (MSC-IL12M) inhibited intracranial tumor growth and prolonged survival administered in the contralateral brain hemisphere [68].

Colony stimulating factor (CSF)

One of the immunotherapy strategies is to express cytokines to enhance adaptive immune system. JX-594 was a TK-deleted VV expressing granulocyte macrophage colony stimulating factor (GM-CSF) [69]. In two GBM models, JX-594 inhibited tumor growth and increased survival. It indicated to be linked with increased CSF-dependent inflammation [70].

Fms-like tyrosine kinase 3 ligand (Flt3L)

Flt3L is a cytokine associated with the development of hematopoietic precursors into both conventional (cDCs) dendritic cells and plasmacytoid (pDCs), as well as their migration out of bone marrow [71]. Replication-defective Ad expressing Flt3L enhanced survival in a rat glioma model and this was linked with increased infiltration of DCs [72]. A similar strategy has been performed using oHSV expressing Flt3L. G47D-Flt3L significantly prolonged survival in the mouse glioma model [73].

Future directions

Considering the cell carriers' tropism to tumor cells, integrins and chemokines have been regarded as important for cell hunting for tumors sites [74]. Chemokines, which induce migration and manipulating integrin function to stimulate lymphocyte movement are used to attract various cell types to the tumor [75]. It has demonstrated that these chemokine systems can improve the efficacy of migrating immunotherapeutic cell carriers to tumors, and would be applied to improve the delivery of cell carriers to brain tumors [76].

Additionally, signaling pathways including uPA/uPAR (urokinase receptor), c-MET receptors and VEGF/VEGFR2 seem to play roles in the migration of stem cell to cancer cells [77]. The upregulation of these signaling pathways would improve the migratory activity of these cell carriers in glioma treatment.

Keeping the cell carriers alive around the tumor site for a longer period of time is another important strategy that will improve cell-carried therapies. Coating the carrier cells with a synthetic extracellular matrix (sECM) promotes stem cell survival. This approach reduced tumor volume when used with TRAIL engineered stem cells in vivo successfully [78]. These results are particularly attractive because the efficacy of the sECM surrounded NSCs was determined in a resected tumor cavity. This study also domenstrated that encapsulating MSCs with a biodegradable sECM enabled their retention in the tumor resection cavity and allowed them to release tumor suppressing therapy for a longer period of time.

At last, when cell carriers are loaded with a therapeutic virus, the virus would better to remain quiescent until delivered to the tumor cells. Otherwise, the virus will destroy the cell carrier and potential therapeutic effect will be lost. Therefore, creating viruses that only replicate when they reach the tumor site will improve their clinical efficacy in patients with brain tumors.

Alternatively, differentiated cells can be induced into stem cell state. Cells derived from urine, and skin other tissues have been reprogrammed into induced pluripotent NSCs successfully [79]. These induced pluripotent stem (iPS) cell-derived NSCs have delivered gene therapy following contralateral intracranial injection in mice with glioma xenografts successfully [80]. Advantages of iPS cells instead of stem cells include their ability to escape from immune rejection and the absence of ethical concerns when using human embryonic cells. Additionally, iPS cells can be easily generated from somatic cells, which makes it excellent option for investigationsin many model systems. However, these cells still have the potential for tumorigenicity. Furthermore, which somatic cells provide the best source to generate iPS cells or which reprogramming technique is the most efficient and safest still remains uncertain [81]. While the treatment of brain cancer is in infancy using iPS cells as carriers of therapeutic agents, the clinical potential of iPS cells is promising.

Conclusions

Even with the advanced therapies for glioma, patients are still faced with a poor prognosis. The low efficiency of delivering molecular therapies to the tumor site has in large part resulted in unremarkable benefits to glioma patients in clinical trials. Stem cells as cellular vehicles have been used to improve the delivery of these therapies. The natural tumor tropism, loading capability and modifiable characteristics of stem cells are major advantages that augment molecular therapies. The genes of interest include Cytotoxic gene and Immune stimulatory gene. With a better understanding of the potential tumor tropism mechanism, modifications can be performed to improve clinical efficacy of cell carrier system. To avoid ethical concerns and get stem cells relative easily, using induced pluripotent stem (iPS) cell is another direction in the future.

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Disclosure of conflict of interest

None.

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