The use of neural stem cells in cancer gene therapy: Predicting the path to the clinic

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Abstract

Gene therapy is a novel means of anticancer treatment that has led to preliminary positive results in the preclinical setting, as well as in clinical trials; however, successful clinical application of this approach has been hampered by the inability of gene delivery systems to target tumors and to deliver a therapeutic payload to disseminated tumor foci efficiently. Along with viral vector systems, various mammalian cells with tropism for tumor cells have been considered as vehicles for delivery of anticancer therapeutics. The discovery of the inherent tumor-tropic properties of neural stem cells (NSCs) has provided a unique opportunity to develop targeted therapies that use NSCs as a vehicle to track invasive tumor cells and deliver anticancer agents selectively to diseased areas. Many in vivo and in vitro studies have demonstrated that the targeted migration of NSCs to infiltrative brain tumors, including malignant glioma, provides a potential therapeutic approach. In this review, the development of NSCs as targeted carriers for anticancer gene therapy is discussed, and barriers in the path to the clinic, as well as approaches to overcoming such barriers are presented.

Keywords

Brain malignancy; cell carrier; gene therapy; glioma; NSC; neural stem cell; targeted tumor therapy

Introduction

Neural stem cells (NSCs) are defined as CNS progenitor cells that have the capacity for self-renewal and the potential to differentiate into three major types of CNS cells: (i) neurons; (ii) astrocytes; and (iii) oligodendrocytes [1]. NSCs are derived from fetal, neonatal or postnatal tissue, and have received substantial research attention because of their potential for treating neurodegenerative diseases. Researchers have speculated that it may be possible to formulate a novel cell replacement platform for such diseases by harnessing the multipotent nature of NSCs.

Since 2000, a number of in vitro and in vivo studies have demonstrated the unique migratory capacity of NSCs throughout the brain [2,3]. In 2000, data from several research groups demonstrated that NSCs transplanted into animal models of brain neoplasia were detected near metastatic tumor beds, far from the original transplant site [2,3]. This finding galvanized the initiation of research into stem cell-based delivery of anticancer agents targeted toward disseminated tumors in the brain. This review focuses on the characteristics of NSCs that make
these cells ideal as therapeutic delivery vehicles for CNS malignancies, and discusses possible barriers to the translation of NSC-based gene therapy into the clinic.

Neural stem cells as gene therapy carriers in CNS malignancies

The ideal cell carrier system for cancer gene therapy must exhibit three important characteristics [4]. First, the carrier cell must possess tumor-selective migratory capacity. Second, the carrier cell must be receptive to in vitro genetic manipulation to allow for the expression of a large quantity of selected therapeutic genes. Alternatively, if the carrier system is used to carry tumor-selective oncolytic viruses, then the carrier cell must be permissive to the virus and must be able to support viral replication. Finally, the carrier cell must be able to carry the therapeutic agent to the tumor while protecting it from the host immune system. In the following sections, the different properties of NSCs are described, to demonstrate their potential as cell carriers for anti-glioma gene therapy.

Inherent tumor tropism

The ability of NSCs to travel extensively throughout the brain and to migrate to tumor beds is central to their role as cellular vehicles for targeted anticancer therapies [2,5]. Most of the early preclinical studies investigating the tumor-homing properties of NSCs were conducted in intracranial glioma models [6]. When fluorescence-labeled NSCs were transplanted into rodent brains in the hemisphere contralateral to established tumors, the cells rapidly crossed the midline and migrated significant distances to locate the tumor mass [2]. The ability of NSCs to ‘seek out’ tumors in the brain is not limited to glial neoplasms; human NSCs can also target breast cancer [7] and melanoma brain metastases [8], as well as intracerebral medulloblastomas [9] and disseminated neuroblastomas [10].

The precise mechanism governing the tumor-tropic properties of NSCs is not fully understood. It is possible that gradients of agents such as chemokines and pro-angiogenic growth factors produced in the tumor microenvironment may act as chemoattractants for NSCs [11]. For example, stem cell trafficking toward ischemic tissue is mediated by hypoxia through the associated upregulation of the transcription factor hypoxia-inducible factor-1α (HIF-1α) [12]. Similar to ischemia, hypoxia is a critical feature of gliomas that results in HIF-1α-mediated upregulation of numerous pro-angiogenic factors and chemoattractants [13,14]. In 2008, Zhao et al investigated the role of hypoxia in NSC migration and observed that NSCs preferentially distribute to hypoxic areas within intracranial glioma xenografts [15]. SiRNA-mediated knockdown of HIF-1α in glioma cells reduced the expression of stromal cell-derived factor-1 (SDF-1), urokinase-type plasminogen activator (uPA) and VEGF, resulting in blocked tumor-tropic migration of the NSCs [15]. Numerous other cytokines, growth factors and receptors have been implicated in the tumor-homing properties of NSCs, including stem cell factor (SCF)/c-Kit [16], monocyte chemotactic protein-1 (MCP-1)/CCL2 [17], annexin A2 [18], hepatocyte growth factor (HGF)/c-Met [19] and VEGF/VEGFR [20] (summarized in Table 1). The multiple homing mechanisms used by NSCs support their use as delivery vehicles over other targeting strategies that primarily use a single-factor approach, such as antibody conjugation or tumor-selective recombinant viral vectors, as NSCs should enable dynamic targeting of heterogeneous malignancies. Although the reason why NSCs are recruited to tumor beds remains unclear, one hypothesis is that the cells migrate to the tumor site to repair damaged tissue [5,21]. By pursuing a better understanding of this process, approaches leading to improved neurological recovery following anti-glioma therapy can likely be formulated.

Although there is sufficient evidence from rodent tumor models to support the glioma-tropic properties of NSCs, data to demonstrate whether NSCs can track and target glioma cells in the human brain are lacking. Because of the size difference between the rodent and human brain, the distances that delivery agents are required to travel in order to locate disseminated tumor...
cells in human brains will be considerably further from the site of transplantation than in rodent brains. Moreover, it is not clear how tumor size will influence the migration kinetics of NSCs. Careful preclinical characterization of these parameters will be critical for the successful translation of NSC-based cell carriers to the clinical setting.

**Immunosuppressive properties**

As noted, the clinical outcome of an anticancer gene therapy depends on the successful delivery of the therapeutic payload at tumor sites, as well as the three-way interaction among the delivery vehicle, tumor microenvironment and host immune system [4]. The majority of currently available cancer gene therapies fail to sustain antitumor effects in the tumor microenvironment for a sufficient length of time to achieve clinically relevant therapeutic efficacy, partly because of the development of a host immune response against the administered therapeutic agents [22]. For example, in both preclinical [23] and clinical [24] settings, the anticancer activity of an oncolytic adenovirus (ONYX-015) was significantly restricted by the host immune response. Attempts to suppress the host immune system with cyclophosphamide in order to enhance the effects of anticancer gene therapy have been successful in rat models [23].

A significant amount of preclinical data suggests that in vivo transplanted NSCs can act as immunosuppressants [25]. Results from several studies in both rodent and non-human primate models of experimental autoimmune encephalomyelitis (EAE) indicate that NSCs transplanted by either intrathecal or intravenous injection promote bystander immunomodulation within the CNS through the release of various soluble molecules [25-27]. The NSCs migrate to areas of inflammation [28], where their presence is associated with a significant downregulation of the effector functions of EAE-specific reactive T-cells, APCs and microglia [27,29] and, thus, contribute to a reduction in the clinical severity of EAE.

The immunosuppressive properties of NSCs represent an attractive attribute for a therapeutic delivery agent, as they allow oncolytic viruses and other therapeutic agents to be shielded from host immunosurveillance. In theory, NSCs can suppress the immune system locally at delivery sites, allowing the therapeutic gene/oncolytic virus to be expressed, or to replicate for a longer time period, thereby killing tumor cells without immune interference. In 2009, Mader et al demonstrated that a mesenchymal stem cell (MSC) carrier system, which possesses similar immunosuppressive properties to NSCs, protected an oncolytic measles virus from antibody neutralization in an orthotopic ovarian cancer model in mice [30]. Further characterization of the molecular nature of NSC-mediated immunosuppression and its potential application to enhance the therapeutic efficacy of cancer gene therapy will likely support the argument for the use of NSCs as a cell carrier system.

**Tumor-selective therapeutic gene delivery approaches using neural stem cells**

In the past 10 years, NSCs have been used primarily in two ways as delivery vehicles for anticancer gene therapy. In one approach, NSCs have been genetically engineered to express various therapeutic genes and to carry these products selectively to tumor foci. A number of therapeutic systems have been evaluated in preclinical studies for this purpose, including prodrug-activating enzymes, immunomodulatory cytokines and proteins with anti-angiogenic activity. In a second approach, NSCs have been used as tumor-specific carriers for oncolytic viruses or other viral vectors, protecting the viruses from host immunosurveillance and selectively delivering the therapeutic agent to the tumor site. The genetically engineered approaches of suicide gene therapy and immunomodulatory gene therapy, and the tumor-specific carrier approach involving oncolytic virus-loaded NSCs, are discussed in more detail in the following sections.
Suicide gene therapy approaches

The majority of studies on NSC-based anticancer therapy have used an enzyme-prodrug suicide gene therapy system in which NSCs are modified to express genes coding for an enzyme that can convert a systemically administered inactive prodrug into toxic metabolites at tumor sites [31]. Two systems have been used to modify NSCs for this purpose. The most commonly used system involves the HSV-thymidine kinase (HSV-tk) gene, which converts the inactive prodrug ganciclovir (GCV) into its toxic metabolite GCV-triphosphate [32]. This system has been tested in several orthotopic malignant glioma models using various immortalized NSC lines. In 2010, Zhao and Wang delivered HSV-tk-expressing immortalized human NT2 NSCs to a mouse glioblastoma model, and observed a significant increase in the survival of treated animals relative to controls [33]. One of the earliest suicide gene therapy systems used to modify NSCs involved the cytosine deaminase (CD) gene, which converts inactive 5-fluorocytosine (5-FC) into highly toxic 5-fluorouracil (5-FU) [2]. Aboody and colleagues used this system extensively to modify HB1.F3 NSC lines, demonstrating a decrease in the tumor volume of mice bearing orthotopic gliomas or intracranial melanomas of 70 to 80% [34].

One of the attractive characteristics of suicide gene therapy is the in vivo bystander effect, defined as the ability of surrounding tumor cells that do not carry the therapeutic transgene to be killed [32,35]. This approach enables the amplification of the antitumor activity of NSCs carrying a suicide gene. Moreover, the inherent tumor-homing properties of NSCs allow these cells to seek tumor sites that are at a far distance from the original mass, and to kill non-transduced tumor cells via this potent bystander effect. In addition to these benefits, the majority of the inactive prodrug, delivered systemically, is able to cross the blood-brain barrier when carried by NSCs; thus, this approach is particularly well suited for the treatment of CNS malignancy [2]. In the future, it will be critical to improve the understanding of the molecular mechanisms underlying the tumor-tropic properties of NSCs, and to develop ways to improve their migratory capacity so that a greater number of engineered NSCs can track multiple disparate tumors for more effective therapy.

Immunomodulatory gene therapy approaches

Immortalized NSCs have been engineered to express immunomodulatory genes that have been established to act as effective anticancer agents. IL-4 [3], IL-12 [36], IL-23 [37] and IFNβ [36] produced by NSCs have been demonstrated to be effective in controlling tumor progression. For example, in rats with glioma, IFNβ-expressing NSCs in combination with CD resulted in a 60% reduction in tumor volume with 100% survival, compared with a rate of 70% survival with CD alone [38]. However, inflammatory cytokine-induced cellular signals alter the NSC properties of self-renewal and progenitor cell differentiation [39], with potential implications for the intrinsic tumor-homing properties of the cells. The immunomodulatory gene to be expressed must be selected carefully to ensure that the tumor-tropism of NSCs is not negatively affected, thus avoiding suppression of the sustained migration to the tumor and to distant sites.

Oncolytic virus-loaded neural stem cells for antglioma therapy

Oncolytic virus (OV) therapy for cancer is a novel approach in which viruses are modified to replicate preferentially in tumor cells. These viral vectors have the ability to amplify a therapeutic gene in a tumor-selective manner, and can also kill neoplastic cells through tumor cell-specific replication. In the past 20 years, several promising OVs with antglioma activity have been developed [40]. The human immune system, however, poses a significant challenge in the development of effective oncolytic viral therapy against gliomas. Early in vivo experiments with OVs demonstrated that infected virus-producing cells could enhance antitumor activity when administered instead of naked virus [41,42]. This finding led to the hypothesis that carrier cells can be used to conceal the therapeutic virus from the host immune
system and amplify its volume while being transported toward the target site. In 2009, Tyler et al demonstrated the enhanced delivery of an oncolytic adenovirus when loaded into NSCs in a mouse xenograft model [43]. Tumors receiving virus-loaded NSCs exhibited an overall reduction in the mean tumor volume compared with tumors treated with the virus alone [43].

**Choosing a neural stem cell line for cancer gene therapy**

There is substantial diversity among the NSC lines currently available, with some being potentially unsuitable as delivery vehicles. The cell lines differ in their source, required culture conditions, tumor-tropic migratory kinetics, ability to express therapeutic genes, and even in their methods of immortalization. A comprehensive approach is necessary to compare the various cell lines to assess these parameters in order to select the most suitable NSC line for clinical application. By 2008, only NSCs from fetal tissue-derived cells had been scaled up under GMP grade conditions, and these were the only NSCs available for clinical trials [44]. The use of these GMP-grade cell lines may be favorable for generating consistent experimental outcomes, and for potentially accelerating the translation of NSC-based anticancer therapies into the clinic. In addition, once each cell line has been genetically manipulated, its phenotype and karyotype, as well as its microbiological status, should be carefully assessed. According to existing EMEA and FDA guidelines, information detailing the source of the stem cell line and its method of manipulation should also be freely available to the public and the scientific community [45,46]. In the future, an important challenge for the rapid clinical translation of NSC-based anticancer therapy will be the consensus among researchers worldwide on a common set of parameters for different NSC lines (eg, culture conditions and characterization criteria).

**The use of immortalized neural stem cells**

An ideal cell delivery system should be stable in tissue culture and be capable of the sustained expression of therapeutic molecules. A primary cell must be immortalized by the introduction of an oncogene in order to become stable in culture; such stability allows the cell to continue to expand beyond the time at which senescence would usually be reached. Several genes have been used to immortalize NSCs for their use as cell carriers, including the human telomerase gene (hTERT) [47], SV40 (simian vacuolating virus 40) large T-antigen [48] and the proto-oncogene v-myc [49]. Although most of these immortalized cells are well characterized, and have been demonstrated not to result in the formation of tumors in SCID mice for up to 12 months [6], there are concerns regarding the safety of such cells in the clinical setting. Results from earlier cell-based gene therapy clinical trials have suggested that the most serious toxicity related to this approach is the potential of developing secondary malignancies [48]. In 2009, it was reported that a boy with ataxia telangiectasia (AT) had been diagnosed with a donor-derived multifocal brain tumor 4 years following treatment with intracerebellar injections of allogeneic human fetal NSCs [50]. Although the stem cell line used in that study was not well characterized, and patients with AT have a higher incidence of cancer as a result of their severely compromised immune systems [51], the findings described in this report provided the first clinical evidence that such concerns may be valid. In addition, the most common method of introducing therapeutic genes into NSCs is through retro- and lentiviral vectors. This method can induce insertional mutagenesis, which may also lead to secondary malignancies [52]. To circumvent these problems, clonal populations of modified NSCs must be isolated and expanded, and the site of DNA integration must be mapped prior to the clinical use of NSCs.

**The use of allogeneic neural stem cell lines**

As a result of HLA mismatch, the transplantation of allogeneic NSCs into patients may require immunosuppression to prevent host rejection. Despite the low expression of MHC class II and costimulatory molecules on NSCs, *in vitro* allore cognition of these cells by peripheral blood
lymphocytes has been reported in cell models [53]. In a phase II clinical trial in patients with Huntington’s disease, alloimmunization was observed in 4 out of 13 patients transplanted with fetal NSCs [54]. Furthermore, one patient exhibited a significant rejection reaction, although a full recovery was made following immunosuppressive treatment. These observations support the use of autologous NSC sources. However, currently available technologies for isolating and expanding autologous NSCs in culture exhibit serious limitations in terms of their ability to produce a sufficient number of viable cells for successful transplantation. The acquisition of autologous NSCs from an adult patient currently requires invasive procedures, which generally obtain only small numbers of cells that can be difficult to expand in culture [55,56]. In 2009, Casalbore and colleagues were able to isolate and expand NSCs from patients who had undergone unilateral olfactory bulb removal for benign conditions [57]; however, this process requires further optimization before it can be used routinely. Until technology allowing unlimited expansion of autologous primary cells to express a therapeutic gene becomes available, well-characterized NSC lines are the most viable option.

**Conclusion**

NSC derivatives have demonstrated potent inherent tumor-tropic properties in a variety of preclinical brain tumor models. The available evidence supports the theory that an NSC-based delivery system can be clinically useful in the targeted delivery of a therapeutic agent to widely disseminated tumors. Genetic manipulation of NSCs to express a variety of anticancer molecules has resulted in clinically relevant therapeutic efficacy in various xenograft animal models. However, the main issues that remain to be addressed in preclinical studies are the identification of an optimal NSC type and determination of the most effective therapeutic molecules. The tumor-homing efficiency of NSCs will likely be the most important aspect to consider for the successful translation of NSC-based cell carriers in the treatment of brain malignancies in humans. The number of NSCs that have the capacity to reach tumor satellites located a significant distance from the implantation site will likely be limited. Therefore, NSCs must not only maintain their natural tropism following modification, but may even require enhancement. The therapeutic molecule expressed by an engineered NSC must have strong antitumor activity to be able to suppress the spread of malignancies throughout the CNS. The amplification of therapeutic effects, through mechanisms such as oncolytic viruses or the bystander effect, would therefore significantly facilitate the successful translation of this strategy into the clinic. As a result of their intrinsic characteristics, NSCs are more suitable as therapeutic delivery vehicles for CNS malignancies compared with other cell types such as MSCs. Unlike MSCs, which might be the preferred cell carrier for other organs, such as the breast and ovaries, [30], NSCs have the ability to integrate into the host brain without disrupting usual brain function. However, this innovative therapeutic approach carries a substantial risk of secondary malignancy following transformation of the implanted NSCs. Thus, engineered NSCs must be extensively characterized before they can be considered appropriate for clinical use. Safety measures should be established for any potential NSC-based therapy, such as the introduction of a suicide gene (eg, encoding CD) that could facilitate the rapid killing of abnormally growing transplanted NSCs by the administration of a prodrug (eg, 5-fluorocytosine). Once these issues have been addressed in the preclinical setting, the implantation of genetically modified NSCs into the resection cavity wall during removal of the primary tumor might be sufficient to allow the NSCs to migrate to residual disseminated tumor sites and to deliver their associated therapeutic agent.

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References

• of outstanding interest

• of special interest


7. Joo KM, Park IH, Shin JY, Jin J, Kang BG, Kim MH, Lee SJ, Jo MY, Kim SU, Nam DH. Human neural stem cells can target and deliver therapeutic genes to breast cancer brain metastases. Mol Ther 2009;17(3):570–575. [PubMed: 19127251] • Provides important evidence, along with references [8] and [9], supporting the use of NSC-based therapies for a variety of CNS malignancies, both primary and secondary. Demonstrates that NSCs migrate to a variety of CNS pathologies effectively, thus encouraging further research into their therapeutic potential in other disease paradigms.


Table 1

Selected studies evaluating the tumor-tropism of neural stem cells in vivo

<table>
<thead>
<tr>
<th>Cell line</th>
<th>Model</th>
<th>Route of administration</th>
<th>Signals examined</th>
<th>Kinetics observed</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>hNT2RA2 (human)</td>
<td>Intracranial glioma (U87)</td>
<td>- Contralateral injection, Tail vein</td>
<td>n/a</td>
<td>Robust migration to contralateral hemisphere; Cells crossed the blood brain barrier to reach the intracranial tumor</td>
<td>[33]</td>
</tr>
<tr>
<td>HB1.F3 (human)</td>
<td>Intracranial glioma (U373)</td>
<td>Contralateral injection</td>
<td>n/a</td>
<td>Migratory fraction of 10% at 50 min after injection; significant migration continued to 15 days post injection</td>
<td>[58]</td>
</tr>
<tr>
<td>Primary murine NSC</td>
<td>Intracranial glioma (GL261, U87)</td>
<td>Contralateral injection</td>
<td>VEGFR1</td>
<td>Prominent migration along vascular tracts to interhemispheric fissure; 80% migration knockdown in vivo following anti-VEGFR1 treatment</td>
<td>[59]</td>
</tr>
<tr>
<td>HB1.F3 (human)</td>
<td>Brainstem glioma (F98)</td>
<td>Ipsilateral forebrain injection</td>
<td>n/a</td>
<td>Migration by 29.7 ± 5.4% of NSCs at 2 weeks after implantation</td>
<td>[38]</td>
</tr>
<tr>
<td>Bone marrow-derived neural progenitor/stem cells</td>
<td>Rat intracranial glioma (RG2)</td>
<td>Contralateral injection</td>
<td>CXCR4</td>
<td>Significant decrease in tumor tropism following anti-CXCR4 treatment</td>
<td>[60]</td>
</tr>
<tr>
<td>C17.2 (murine)</td>
<td>Intracranial infusion of MCP-1 in glial tumor cells</td>
<td>Injection contralateral to infusion site</td>
<td>MCP-1</td>
<td>Contralateral migration by a subpopulation of cells to the site of MCP-1 infusion</td>
<td>[17]</td>
</tr>
<tr>
<td>HB1.F5, A4, F3 (human)</td>
<td>Rat intracranial glioma (C6)</td>
<td>Ipsilateral injection away from tumor site</td>
<td>n/a</td>
<td>Migration initiated by day 3, tumor mass surrounded by NSCs by day 5 and infiltrated throughout by day 7</td>
<td>[61]</td>
</tr>
<tr>
<td>C17.2 (murine)</td>
<td>Rat intracranial glioma (C6)</td>
<td>Contralateral injection</td>
<td>TM-18</td>
<td>Significant increase in migration following induction of TM-18 overexpression</td>
<td>[62]</td>
</tr>
<tr>
<td>HB1.F3 (human)</td>
<td>Intracranial glioma (U251)</td>
<td>Contralateral injection</td>
<td>Hypoxia</td>
<td>NSCs clustered at the tumor-brain interface with preferential migration toward hypoxic tumor regions</td>
<td>[15]</td>
</tr>
<tr>
<td>C17.2 (murine)</td>
<td>Melanoma brain metastases (B16/F10)</td>
<td>Intracarotid or intracranial injections</td>
<td>n/a</td>
<td>Cells colocalized to brain metastases via both injection methods</td>
<td>[34]</td>
</tr>
<tr>
<td>HB1.F3 (human)</td>
<td>Intracranial medulloblastoma (Daoy)</td>
<td>Contralateral injection</td>
<td>n/a</td>
<td>Qualitative observation of cells migrating contralaterally and into the tumor bed</td>
<td>[9]</td>
</tr>
<tr>
<td>C17.2 (murine)</td>
<td>Intracranial glioma (U251)</td>
<td>Tail vein injection</td>
<td>n/a</td>
<td>Qualitative observation of cells migrating across the blood brain barrier to reach intracranial tumor</td>
<td>[63]</td>
</tr>
<tr>
<td>C17.2 (murine)</td>
<td>Rat intracranial glioma (CNS-1)</td>
<td>Distant ipsilateral site, contralateral,</td>
<td>n/a</td>
<td>Robust migration throughout the tumor mass and tracking of</td>
<td>[63]</td>
</tr>
<tr>
<td>Cell line</td>
<td>Model</td>
<td>Route of administration</td>
<td>Signals examined</td>
<td>Kinetics observed</td>
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<tr>
<td></td>
<td></td>
<td>intraventricular, or intravascular injection</td>
<td>Microsatellites observed; contralateral migration with no impact of tumor size observed</td>
<td>CXCR4 CXC chemokine receptor 4, MCP-1 monocyte chemotactic protein-1, NSC neural stem cell, TM-18 transmembrane protein 18</td>
<td></td>
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</table>