Glioblastoma multiforme: can neural stem cells deliver the therapeutic payload and fulfill the clinical promise?

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Neural stem cells (NSCs) are defined as progenitor cells of the CNS. They have the capacity for self-renewal and multipotent potential to differentiate into three major types of CNS cells: neurons, astrocytes and oligodendrocytes. Recently, NSCs have received a great deal of attention owing to their therapeutic potential for neurodegenerative and oncologic diseases. It has been speculated for many years that it may be possible to formulate a novel cell replacement platform for these diseases by harnessing NSCs’ multipotent nature. In the last decade, many in vitro and in vivo studies have demonstrated the unique migratory capacity of NSCs throughout the brain. In 2000, Aboody et al., along with several other groups, were able to show that NSCs transplanted into animal models of brain neoplasia were found near metastatic tumor beds far from their site of original transplantation [1,2]. These observations galvanized the concept of stem cell-based targeted delivery of anticancer agents to disseminated tumors in the brain. The ability of NSCs to migrate to tumors is central to their utility as carriers of therapeutic, antineoplastic modalities.

Most of the earlier preclinical studies investigating the tumor-homing properties of NSCs were performed in various animal models of intracranial glioma [1,2]. However, the ability of NSCs to seek out tumors is not limited to gliomas. Human NSCs have also been shown to target breast cancer [3] and melanoma brain metastases [4], as well as disseminated neuroblastoma [5]. The precise mechanism governing the tumor-tropic properties of NSCs is not fully understood. It is speculated that gradients of factors such as chemokines and proangiogenic growth factors produced in the distant tumor microenvironment may act as chemoattractants for NSCs. The multifaceted homing mechanisms employed by NSCs favor their use as delivery vehicles over other, largely one-dimensional, targeting strategies. Nevertheless, it remains to be seen whether NSCs can track and target glioma in the human brain. Owing to the size difference between the rodent and human brain, the distance required to track disseminated tumor cells in the human brain will be vastly larger than in the rodent brain. Ultimately, a careful characterization of these parameters in the preclinical setting will be critical for the successful translation of NSC-based cell carriers to the clinic.

Most of the currently available cancer gene therapies have failed to sustain anti-tumor effects in the tumor microenvironment long enough to achieve clinically relevant therapeutic efficacy. This is partly due to the host immune

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Response against the administered therapeutic agent. A wealth of preclinical data suggests that in vivo transplanted NSCs can act as immunosuppressants [6]. NSCs do not express major histocompatibility complex (MHC) class II and express low levels of CD80 and CD86 costimulatory molecules, which make them partially resistant to immune-mediated killing. This immunosuppressive quality of NSCs is a very attractive attribute for a cell carrier given that it will allow therapeutic payloads such as oncolytic viruses or other gene therapy vectors to be shielded from host immunosurveillance. In theory, NSCs can suppress the immune system locally at delivery sites, thus allowing the therapeutic gene/oncolytic virus to express/replicate longer and kill tumor cells with limited immune interference. We have recently observed that in response to oncolytic adenovirus infection/loading, NSCs unexpectedly express immunosuppressive cytokines such as IL-10, and the delivery of these virus-loaded NSCs into the animal brain significantly reduces vector-mediated neuroinflammation [7]. The immunosuppression offered by stem cells adds to their novelty as a cell carrier and further characterization of the molecular nature of NSC-mediated immunosuppression will support the use of NSCs as a bona fide cell carrier for anticancer therapy.

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The available preclinical data strongly argue in favor of the hypothesis that a stem cell-based delivery system can be clinically effective in targeted delivery of a therapeutic agent to the disseminated tumor burden in the brain. So far, stem cells expressing a variety of anticancer agents have resulted in clinically relevant therapeutic efficacy in several xenograft animal models [8]. However, one remaining issue that needs to be addressed before this novel therapeutic strategy can be considered in the clinical setting is the identification of an optimal stem cell system and determination of the most effective therapeutic payload that can be delivered by this system. To date, the majority of studies on NSC-based anticancer therapy have used an enzyme-prodrug suicide gene therapy system. In this approach, NSCs are genetically modified to express genes for an enzyme that can convert an inactive prodrug, when administered systemically, into toxic metabolites at tumor sites. One of the attractive characteristics of suicide gene therapy is the in vivo bystander effect: the ability of these systems to kill surrounding tumor cells that do not carry the transgene. This is very appealing because it has the potential to amplify the anti-tumor activity of NSCs carrying a suicide gene. Based on such encouraging preclinical results, the US FDA recently allowed Aboody and colleagues from City of Hope (CA, USA) to conduct the first human Phase I study of genetically modified NSC-based therapy carrying a suicide gene, cytosine deaminase, for recurrent high-grade glioma [9]. This clinical trial has just begun, with the goal of enrolling 12–20 patients with high-grade gliomas.

Our laboratory has extensively investigated the possibility of utilizing the inherent tumor tropic properties of NSCs to deliver glioma-restricted oncolytic adenovirus selectively to the disseminated tumor burden [10]. In theory, oncolytic viruses (OVs) have particular characteristics that make them an ideal anticancer agent to be loaded onto cell carriers. First, OVs can replicate selectively in the tumor cells and thus should be able to amplify the therapeutic gene at the tumor sites. Second, once OVs release from the loaded NSC at the delivery sites, they can also distinguish tumor from normal tissues and induce tumor cell-specific oncolysis. Our recent data indicate that distance delivery of NSCs loaded with oncolytic adenovirus significantly prolongs the survival of animals in the orthotopic murine model of human glioblastoma [7]. In the future, it will be crucial to improve our understanding of the molecular mechanisms underlying the tumor-tropic properties of NSCs and find a way to improve their migratory capacity so that a greater number of engineered NSCs carrying their therapeutic payload can home to the disseminated tumor burden for more effective therapy.

Methods to generate antibodies against cancer cell-specific antigens have revolutionized our understanding of cellular transformation, disease diagnosis and treatment. Antibodies are used with increasing success against many tumors. However, the success of antibody therapy against brain tumors is limited owing to:

- The inability of the therapeutic antibodies to cross the BBB;
- Poor distribution of the therapeutic antibodies in the solid tumor;
- The failure to target disseminated tumor burdens.

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Thus, current therapeutic approaches require repeated administration of large quantities of therapeutic antibodies in order to achieve clinically relevant therapeutic efficacy. The inherent tumor tropisms of NSCs and their ability to cross the BBB are very attractive for targeted delivery of therapeutic antibody in the disseminated brain tumor. NSCs can be genetically modified to express intact or single-chain antibodies, and if the modified NSCs retain their tumor-specific migratory properties, upon arrival to the tumor foci each NSC has the potential to become a therapeutic antibody-producing factory. Recently, human NSCs have been modified to express the heavy and light chain of breast cancer-specific anti-HER2 antibody [11]. Similarly, our laboratory has been able to modify mesenchymal stem cells (MSCs) to express a cell surface-bound single-chain antibody targeting glioma associated with EGF receptor variant II [12]. Coinjection of these genetically modified MSCs with glioma cells in the orthotopic murine model of human glioblastoma significantly improved the survival of diseased mice. NSC-mediated anticancer antibody therapy has the potential to sustain a high level of therapeutic antibody concentration at the tumor site without repeated systemic administration, which

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will not only reduce the toxicity related to such therapy, but will also allow the therapeutic antibody to target the disseminated tumor burden more effectively. An ideal cell-delivery system should be stable in tissue culture and capable of sustained expression of therapeutic molecules. In order to make a primary NSC line that is stable in culture, it must be immortalized by introducing an oncogene. Several genes have been used to immortalize NSCs for their use as cell carriers. Although most of these cells are well characterized and have not been observed to form tumors in severe combined immune deficiency mice up to 12 months [13], there is a safety concern about the utilization of immortalized cells in the clinical setting with regard to secondary malignancy. In addition, the most popular way of introducing therapeutic genes into NSCs is by means of retro- and lenti-viral vectors. This method can induce insertional mutagenesis, which also may lead to secondary malignancies. To circumvent these problems, clonal populations of modified NSCs must be isolated and expanded and the site of DNA integration must be mapped. From a clinical perspective, it may be prudent to have some safety measures, such as the introduction of a suicide gene that could facilitate the killing of abnormally growing transplanted NSCs by administration of a prodrug. Indeed, such is the case in the Aboody clinical trial.

In conclusion, NSC-based delivery systems for anticancer therapy represent an exciting and novel approach in neuro-oncology. Even though most of the research is still in the preclinical stages, a new clinical trial utilizing NSC expressing cytosine deaminase is currently underway. Others are likely to follow given the availability of an NSC line for use in clinical trials. Ultimately, whether these approaches result in clinically meaningful results remains to be seen, but it goes without saying that such approaches represent a new and exciting forum for patients with glioblastoma multiforme.

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References