

# Neural Stem Cells - A Promising Potential Therapy for Brain Tumors

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**Abstract:** Brain tumors can be highly aggressive and debilitating for many patients and lead to an untimely death in just a few months. Unfortunately, due to the location of many brain tumors, therapy with ionizing radiation, chemotherapeutic agents and/or surgery has limited rewards. In addition, the probability of totally removing highly infiltrative tumors, particularly gliomas, is extremely low and rarely provides a cure. The need for directed targeting and ablation of tumors with minimal damage to nearby healthy tissue has led to the most recent findings and uses of neural stem cells for therapeutic treatment of brain tumors. Recently, some very promising studies have demonstrated that exogenous neural stem cells have the remarkable ability to migrate very long distances towards sites of metastasis after transplantation. These studies also show that intravascular injections of neural stem cells may lead to preferential migration towards central nervous system tumors. It has also been demonstrated that genetically modified neural stem cells, engineered to produce anti-tumor molecules, upon transplantation, have the ability to migrate towards tumors and reduce tumor mass directly or through a “bystander” effect. Here we review the current literature examining the promise of utilizing genetically modified neural stem cells as vehicles for CNS tumor therapy.

**Keywords:** Neural stem cells, brain tumors, gliomas, therapy, review.

## INTRODUCTION

Malignant brain tumors, particularly gliomas, can be devastating to patients and shorten their lives to just a few months after diagnosis [1]. These tumors have a remarkable ability of being highly invasive and resistant to current methods of treatment, like surgical resection, irradiation and chemotherapy. In the recent past, there have been several reports documenting the ability of transplanted neural stem/progenitor cells to migrate towards a tumor mass in animal model of brain tumors, primarily gliomas (Fig. 1) [2-10]. More recently, there has been evidence demonstrating that endogenous precursors from the subventricular zone of the forebrain will respond and migrate towards experimentally induced tumors in the forebrain [3]. In this review, we will discuss the implications of these findings and the potential future of this novel approach to treating malignant brain tumors.

## NEURAL STEM CELLS

Neural stem/Progenitor cells (NSC), by definition, have the ability to self-renew and generate neurons, astrocytes and oligodendrocytes during development in-vivo and in the adult [11, 12]. One of the earliest reports demonstrating these functions in the mammalian central nervous system utilized NSC isolated from the forebrain subventricular zone and manipulated in-vitro [13]. Subsequently, we have been able to elucidate molecular mechanisms underlying the role of NSC during development and disease. The proliferation, differentiation, migration and survival of NSC is regulated, at least in part, through Epidermal growth factor

receptor (EGF-R) and Fibroblast growth factor receptor (FGF-R) signaling [14, 15]. In the adult mammalian brain, there are only two sites of neurogenesis from endogenous progenitors and they are the forebrain subventricular zone and subgranular layer of the dentate gyrus [12]. While neurogenesis in the adult is limited to these sites, the migration potential of progenitors from these regions is still being elucidated.

## ENDOGENOUS PROGENITOR MIGRATION

Recently, a wave of reports have demonstrated that endogenous neural progenitors from forebrain germinal zones have the ability to migrate towards sites of various brain injuries, including animals models of stroke, ischemia, and chemical induced lesions [16-22]. A recent report has also demonstrated that endogenous progenitors from the subventricular zone respond to experimentally-induced tumors by migrating towards, surrounding and infiltrating the primary tumor mass [3]. The specific factors that regulate the migratory potential of endogenous progenitors in response to injury or disease are relatively unknown. In some cases, exogenous delivery of growth factors like Transforming growth factor-alpha, TGF- or Platelet-derived growth factor, PDGF, to forebrain structures could promote the migration of subventricular zone progenitors into nearby structures and subsequent differentiation into neurons in animal models of neurodegeneration [18, 23].

## EXOGENOUS NEURAL STEM CELLS FOR TUMORS

The migratory potential of NSC subsequent to transplantation in the damaged brain has been described by several reports, reviewed by Emsley *et al.* [24]. One of the first reports to demonstrate NSC ability to migrate towards

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intratumorally into a rodent model of glioma significantly reduced the tumor mass [5]. This study was supported by a subsequent study that further examined the anti-tumor effects of genetically modified human NSC that express TRAIL [9]. These genetically modified NSC were transplanted into the brains of rodents with experimentally induced glioma and the authors were able to utilize eukaryotic luciferases, the firefly (*Photinus*) and sea pansy (*Renilla reniformis*) luciferases, Fluc and Rluc, to mark the cell types respectively, and examine the migratory potential of NSC, as well as, potential changes in tumor size. The authors were able to demonstrate enhanced migration of NSC and a reduction in tumor size over time in the living animal. This dual enzyme substrate bioluminescence imaging allows for labeling of both the NSC and glioma cell line for sequential and differential imaging in the living organism [32]. In addition, the authors, utilized a more soluble form of S-TRAIL, that was shown to be more efficient at inducing apoptosis in tumor cells [33]. This advanced imaging analysis provides a new standard for demonstrating the efficacy of utilizing genetically engineered NSC for the purpose of treating intracranial tumors. In fact, the use of this imaging technology to study many disease paradigms will prove to be essential in providing a better understanding of the dynamic and plastic responses of brain tissue during disease and repair.

#### DOES CXCR-4/SDF-1 SIGNALING PLAY A ROLE?

While the above studies have investigated the potential of NSC to act as vehicles for anti-tumor gene delivery, they did not identify the potential signals responsible for the homing ability of NSC for tumors. One report has examined the potential role of stromal derived factor-1 (SDF-1) and Chemokine receptor-4 (CXCR4) signaling in the homing ability of NSC for tumors [34]. CXCR4, a chemokine receptor that governs cellular migration and homing in hematopoietic, neural and tumor cell lines, has been shown to be expressed by neural progenitors during development [35-40]. Stromal cell-derived factor-1 (SDF-1) a ligand for the CXCR-4 receptor has been shown to be secreted by highly invasive tumors and is correlated to tumor survival and invasiveness [41-43]. Ehtesam *et al.*, showed that human fetal NSC transplanted intratumorally in experimentally induced GL26 glioma mice, disseminated into the neighboring parenchyma, following "islets" of tumor cells that had migrated away from the primary tumor inoculation site. In addition, they also showed that the migrating NSC cells were strongly immunopositive for CXCR-4, while the non-migrating NSC and primary tumor mass were weakly immunopositive [34]. The authors also suggested that the tumor-tropic NSC were immature astrocytes based on immunohistochemical analysis and positive expression of A2B5 and GFAP, while the non-migrating NSC that remained at the primary tumor inoculation site were more differentiated astrocytes, as they were immunopositive for excitatory amino acid transporter 1 and 2, EAAT1 and EAAT2, proteins suggested to be expressed by mature astrocytes [44]. The authors were also able to demonstrate by in-vitro analysis, that NSC will migrate towards conditioned media generated from glioma cell lines and this migration could be inhibited if SDF-1

neutralizing antibody was added to the tumor conditioned media. These data suggest that SDF-1/CXCR-4 signaling, at least in part, plays some functional role in NSC's tumor tropism.

Another recent report by Schmidt *et al.* has implicated vascular endothelial growth factor (VEGF) in promoting NSC tropism towards tumors [45]. The authors were able to demonstrate through in-vitro analysis of human brain tumor extracts that VEGF protein was up-regulated in the tumor samples compared to normal human brain controls. Additionally, the authors infused VEGF protein into the striatum of nude mice. Two days later, human and mouse NSC were transplanted into the contralateral striatum. Within one week, NSC showed long range attraction and migration towards the site of VEGF infusion in the contralateral hemisphere. These data suggests that VEGF plays a role in NSC tumor tropism.

Taken together, secreted molecules shown to be up-regulated in brain tumors are beginning to be examined for their potential role in NSC migration and tumor tropism. Continued investigation in this area will be the next critical step to better understand the molecular mechanisms underlying NSC attraction towards sites of tumorigenesis and angiogenesis.

#### ENDOGENOUS NEURAL PROGENITORS FOR TUMORS

To date, the transplantation of NSC into the parenchyma, ventricular system or systemic circulation of experimentally induced rodent glioma models, has clearly demonstrated that NSC have a tropism for the primary tumor mass and invasive tumor cells that have migrated away from the primary tumor inoculation site. In addition, intratumor delivery of NSC, in glioma rodent models, has demonstrated the migrational capabilities of NSC within the tumor mass and to track tumor satellites that have migrated away from the primary tumor mass. A more recent report has also demonstrated in a experimentally induced glioblastoma murine model that endogenous precursors generated from the subventricular zone may also migrate towards the primary tumor mass [3]. The authors used a transgenic mouse expressing enhanced green fluorescent protein under the control of the nestin promoter to identify endogenous neural precursors [46, 47] and showed that two weeks after unilateral glioblastoma inoculation into the caudate-putamen, nestin-GFP positive cells could be identified throughout the tumor inoculated hemisphere compared to the non-inoculated contralateral side. The authors also showed that nestin-GFP positive cells were associated with tumor cells that had migrated away from the primary tumor site. Glass *et al.* also stated that approximately one-third of the nestin-GFP cells that surrounded the tumor mass were immunopositive for Ki-67, a marker for actively dividing cells [48]. In addition, one-third of the nestin-GFP positive cells co-expressed Mushashi, a marker for neural precursors [49], one-third co-expressed chondroitin sulfate proteoglycan, NG-2, a marker for glial precursors and neoplastic cells [50], and one-third co-expressed PSA-NCAM or double-cortin, markers for migrating neuronal precursor cells [51, 52]. While the authors state that sixty percent of the nestin-GFP positive

cells co-expressed GFAP, they did not identify any nestin-GFP cells co-expressing S100 $\beta$ , a marker for both maturing glia and glial progenitors [53, 54], or Calbindin, a neuronal marker [12], suggesting that these cells were not terminally differentiated. Glass *et al.* also demonstrated that endogenous neural precursor tropism for glioblastoma decreased with age and could be correlated with a subsequent decrease in survival.

Taken together, Glass *et al.* suggest that the tropism for tumor cells by endogenous neural precursors may represent an intrinsic tissue response that is very specific for tumor cells and not normal tissue. In addition, the fact that many of these cells migrated long distances away from the subventricular zone to reach the primary tumor inoculation site in the caudate-putamen, supports earlier studies demonstrating similar long distance effects with exogenous transplanted NSC and may suggest that some aspects of immune signaling may be involved. The idea of immune signaling playing a role in the tropism of endogenous progenitors towards a tumor mass was suggested by Glass *et al.* and they made reference to a previous study demonstrating an age-related decrease in survival, in an experimental glioblastoma mouse model, correlated to a significant decrease in CD8 $^{+}$  T-cell infiltration [55].

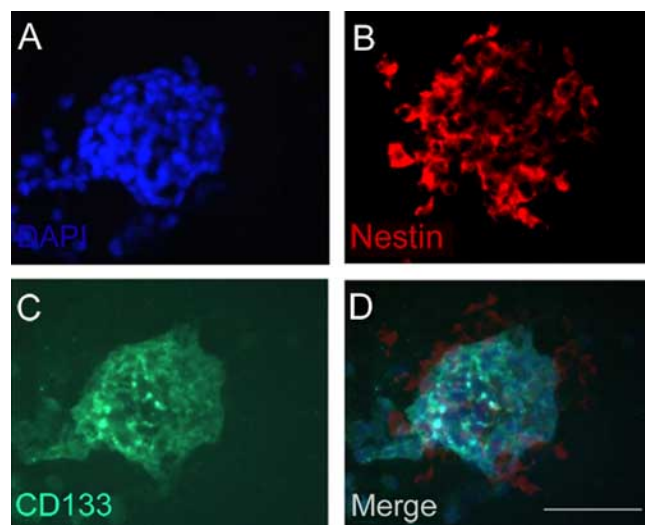
#### ALTERNATIVE SOURCES FOR NEURAL STEM CELLS

In order to translate these pre-clinical findings into clinical therapies we must begin to examine the potential obstacles related to the source of NSC for the purpose of transplantation. Using NSC lines as a source of cells for transplantation has many advantages. For example, these cells may be uniform, well characterized and readily available, however, there is some evidence that NSC lines may have tumorigenic potential after transplantation [56]. Additionally, if NSC lines, embryonic or fetal derived NSC are to be utilized for transplantation to treat brain tumors, patient would have to be immunosuppressed in order to

minimize tissue rejection. Ideally, autologous cells would be the preferred choice and presumably avoid the need for immunosuppression.

In the recent past, many reports have demonstrated that bone marrow derived cells have the potential to generate NSC [57-60]. Semi-adherent cells derived from bone marrow and maintained under neural stem cell growth media conditions, overtime, may generate neurospheres that express proteins markers suggested to identify NSC, like nestin or CD133 (Fig. 2). The cell fate potential of bone marrow derived NSC is still under investigation, as well as, their ability to engraft into the brain and generate functional neurons. If it is determined that these cells truly have the potential to generate functional neurons, astrocytes and oligodendrocytes after transplantation in-vivo, then they would be an ideal autologous cell source for neural replacement therapy, as well as, delivery vehicles for treating brain tumors.

Other potential cell sources from bone marrow are Sca1 $^{+}$  cells [61]. The recent report by Anderson *et al.* demonstrated that nanoparticle labeled Sca1 $^{+}$  bone marrow cells injected intravenously into severe combined immunodeficient SCID mice with experimentally-induced gliomas, migrated towards sites of angiogenesis, including the intracranial tumor site. The authors suggested that many of the nanoparticle containing cells that migrated towards the tumor mass, differentiated into endothelial-like cells, as they were immunopositive for CD31 and von Willebrand factor. Additionally, a recent report has demonstrated that bone-marrow stromal cells transfected to over-express EGF-R and subsequently transplanted intracranially in an experimentally-induced GL261 glioma mouse model showed enhanced migratory response towards tumor compared to non-transfected controls [62]. Sato *et al.* also demonstrated that bone marrow stromal cells adenovirally transduced to secrete interferon- $\gamma$ , upon intra-tumor transplantation resulted in significantly prolonged survival compared to controls. These reports further demonstrate and support the



**Fig. (2).** Immunocytochemistry of Cultured Human Bone Marrow derived cells (A-D). (A.) DAPI stain of undifferentiated human bone marrow derived cells maintained for two weeks in neural stem cell proliferation media containing 20ng/ml for both FGF-2 and EGF and B-27 supplement. (B.) Nestin immunocytochemistry of human bone marrow derived cells (C). CD133 immunocytochemistry of human bone marrow derived cells. (D). Merged image. Scale bar: 160 $\mu$ m.

idea of utilizing bone marrow derived cells as sources for tumor targeting and therapy. The potential benefit of isolating bone marrow cells from a patient is that these cells can be readily isolated from a brain tumor patient, manipulated *ex-vivo* and then transplanted back into the patient for brain tumor therapy. Presumably minimizing the need for immunosuppression or tissue rejection from an autologous transplant.

## CONCLUSIONS

Using NSC as vehicles for gene delivery for the treatment of gliomas has great therapeutic potential. Mounting pre-clinical evidence of this potential demonstrates that NSC upon transplantation into a tumorigenic brain have both a direct apoptotic effect on tumor cells, as well as, an ability to “track down” infiltrating tumor cells. This kind of therapy could prove very useful when considering the limitation with current therapies, including surgical resection, irradiation and chemotherapy. However, many questions still need to be answered before we can examine the true potential of the cells to treat human patients with brain tumors. For example, while it has been demonstrated that NSC have a direct anti-tumor apoptotic effect, there is no direct evidence of the molecular mechanisms underlying this function. In addition, the molecules primarily responsible for NSC’s tumor tropism are still being identified and characterized. Many more molecules will probably be implicated and their specific role in NSC attraction towards tumor cells determined. While there is some demonstration that CXCR-4/SDF-1 or VEGF signaling plays a role in NSC tropism for tumors, these molecules also effect migration and communication between many other cell types. In addition, the cell fates of NSC transplanted into the brains of experimentally induced tumors has not been fully elucidated. The reports we have discussed here, have provided some evidence that the NSC remain relatively undifferentiated at the primary tumor inoculation site or become more differentiated glia upon tracking infiltrating tumor cells that migrate away from the primary tumor mass and a relatively small percentage of these NSC may represent immature neuronal precursors [3, 34]. Determining the fate and functional integration process of transplanted NSC in response to experimentally induced intracranial tumors is critical, if we are to better understand and prepare for the potential side effects of using NSC for brain tumor therapy.

Several of the above stated reports have demonstrated the efficacy of genetically engineered NSC to express anti-tumor molecules to reduce tumor mass and increase survival in animal models of brain tumors, however, the direct effects that these anti-tumor molecules have on NSC function and fate, must be characterized thoroughly as well. Genetically modified, transplanted NSC cells may persist in the brain well after their therapeutic benefit and continued expression of these therapeutic molecules may have deleterious effects on normal neighboring tissue.

Therefore, modifying NSC to have regulated expression by either endogenous promoters or utilizing regulatable viral vectors to transduce NSC may provide more useful and practical applications for their potential therapeutic use for brain tumors.

The endogenous precursor response is very interesting and brings more questions than answers when trying to understand the pathology of brain tumors. Clearly, endogenous progenitors do not provide enough protection for patients with malignant gliomas, but what, if any, protection do they provide? Do they respond differently to different tumors, and if so, why? Can they also be manipulated to act as vehicles for gene delivery, and if so, is their tropism strong enough to utilize them as a potential cell source for brain tumor therapy? We look forward to future reports regarding what stimulates their tropism towards tumors.

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