Glioblastoma and stem cells
Minireview

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This review presents compelling evidence that human glioblastoma is a heterogenous tumor composed from tumor cells and small portion of cancer stem cells – tumor-initiating cells, which have a high tumorigenic potential and a low proliferation rate. Glioma cancer stem cells are phenotypically similar to the normal stem cells, they express CD133 gene and other genes characteristic of neural stem cells and posses the self-renewal potential. Cancer stem cells derived from glioblastoma are capable recapitulate original polyclonal tumors when xenografted to nude mice. They are chemoresistant and radioresistant and therefore responsible for tumor progression and recurrence after conventional glioblastoma therapy. Cancer stem cells contribute to glioma radioresistance by an increase of DNA repair capacity through preferential activation of the DNA damage response checkpoints. Potential therapies that modulate or target cancer stem cells are also reviewed. Mesenchymal stem cells and/or neural stem cells were shown to target brain tumors therefore these cells are considered as an effective delivery system to target and disseminate therapeutic agents to brain tumors. Stem cell-based gene therapies for glioblastoma were shown in experiments to be effective way to target brain tumors. Effects of bone morphogenetic protein (BMP4) on glioma cancer stem cells are also reviewed. BMP4 reduces effectively proliferation of CD133 positive cells *in vitro* and the tumor growth *in vivo*. BMP4 may act as a key inhibitory regulator of cancer initiation and therefore may be used in combined stem cell-based therapy as a non-cytotoxic therapeutic agent.

Key words: Glioblastoma, cancer stem cells, CD113 marker, chemoresistance, radio-resistance, rat glioma models, vascular niche, mesenchymal stem cells, stem cell-based gene therapy, BMP4.

Malignant astrocytic gliomas including the most common subtype, glioblastoma multiforme (GBM), are the most common and lethal intracranial tumors. These tumors exhibit a devastating malignant progression characterized by widespread invasion throughout the brain [1]. The tumor invasion is facilitated by normal brain parenchymal cells which secrete ligands that can stimulate receptors on invasive glioma cells. These secreted factors are able to diffuse through the peritumoral stroma, thereby influencing parenchymal cells that surround the tumor mass thus creating a permissive microenvironment for malignant progression [2, 3]. .

The traditional therapies, surgery and radiotherapy provide palliative benefit, while the value of chemotherapy has been controversial. Brain tumors are resistant to the most traditional chemotherapeutic cytotoxic therapies. For a subset of glioblastoma patients a novel chemoradiotherapy approach, consisting of alkylating agent temozolomide administered concurrently during radiotherapy followed by adjuvant systemic temozolomide, has recently demonstrated modestly improving the overall survival for newly diagnosed GBM patients.[4]. The efficacy of targeted therapies that inhibit receptor tyrosine kinases, which have shown to be a promising anticancer activity in other neoplasms, due to coactivation of receptor tyrosine kinases in the GBM has been modest [5]. Glioblastoma is usually fatal within a year of diagnosis.

Identification of cancer stem cells in brain tumors. Biological properties of glioblastoma cells like resistance to chemotherapy and radiotherapy, their infiltrative nature, proliferative behavior, and progressive character strongly supported the suspicion that glioblastomas contain cancer stem cells – tumor initiating cells. Cancer stem cells share many of the properties of normal stem cells [for a review see 6]. These include resistance to toxic drugs through the expression of several ABC transporters, an active DNA repair capacity, resistance to apoptosis, and lack of relative quiescent cell stages. Tumor mass is formed by dividing tumor cell clones and by cancer stem cells (CSCs), rare tumor cells within a tumor, designated also as tumor-initiating cells. CSCs are character-

ized as the population of cells within a tumor that posses the ability to:

- self-renew,
- aberrantly differentiate,
- initiate tumorigenesis,
- migrate,
- regenerate a phenocopy of the original tumor when injected *in vivo*.

Generally, the identification of tumor stem cells has important implications for understanding of tumor biology. These cells may be crucial cellular targets for curative tumor therapy generally and particularly in treatment of brain malignant tumors. The evidence for cancer stem cells existence came first from pediatric brain tumors. Uchida et al. [7] isolated clonogenic stem cells from fresh human fetal brain tissue by fluorescence-activated cell sorting, Single $CD133^+$, $CD34^+$, $CD45^+$ sorted cell initiated neurosphere cultures. These cells after transplantation into brain of immunodeficient mice showed potent engraftment, proliferation, migration, and neural differentiation at the single-cell level. Further proof of cancer stem cells existence came from studies of pediatric brain tumors by isolation of neurospheres with ability to self-renew and to be passaged at clonal density. Unlike normal neural stem cells, tumor-derived stem cells had an unusual capacity to proliferate and sometimes differentiate into abnormal cells with multiple differentiation markers. The cells expressed many genes characteristic for stem cells like CD133, Sox2, musashi-1, bmi-1, maternal embryonic leucine zipper kinase, and phosphoserine phosphatase [8].

Several approaches were used to identify and/or isolate cancer stem cells from pediatric brain tumors, ependymoma and adult glioblastoma multiforme [9, 10, 11, 12, 13]. Neural stem cell surface antigen CD133 (120kD five-transmembrane cell-surface protein) was found to be expressed not only on normal neural stem cells but also on cancer stem cells of several brain tumors. CD133 antibody-coated magnetic beads were used for enrichment of tumorigenic cells from tumor mass. CD133 positive cells from brain tumors have been shown that may play an important role in tumorigenesis. Crucial proof for stem cells origin of CD133 positive cells came from experiment when these cells were inoculated to immunocompromized mice where they formed tumors containing both CD133 positive and CD133 negative cells, recapitulating thus the original tumor polyclonality. Taken together human glioblastomas appear to be established and expanded by cancer stem cells, which are endowed with tumor-initiating and perpetuating ability.

In order to assess the discrepancy between growth and differentiation properties and the same histological phenotype of individual cases of human glioblastomas, tumor cells from 22 glioblastomas were cultured in medium favoring the growth of neural and cancer stem cells. The results of this study provide evidence that CD133 positive cancer stem cells maintain only a subset of primary glioblastomas. The other subpopulation of CD133 negative tumor cells possessed also stem cell-like properties. Both subtypes were similarly tumorigenic in nude mice *in vivo*, but differed in proliferation index being lower for CD133 negative cells. GeneArray analysis revealed 117 genes to be differentially expressed by these two subtypes [14]. Clement et al. [15] found that in human glioma cells HEDGEHOG – GLI signaling regulates the expression of stemness genes and the self-renewal of CD133 positive glioma cancer stem cells. This signaling is also required for sustained glioma growth and survival.

Recently the cellular origin of normal CD133-presenting cells in neurogenic regions of the embryonic and adult brain was studied [16]. It was found that CD133 is a marker for embryonic neural stem cells, an intermediate radial glial/ependymal cell type in the early postnatal stage, and for ependymal cells in the adult brain, but not for neurogenic astrocytes in the adult subventricular zone These findings suggest two principal possibilities for the origin of brain tumor stem cells: a derivation from CD133-expressing cells, which are normally not present in the adult brain or from CD133-positive ependymal cells in the adult brain [16].

Subpopulations of cancer stem-like cells were identified also in clinical specimens and two cell lines of retinoblastoma. These cells expressed neuronal stem cell markers, such as Oct3/4, Nanog, CD133, and Musashi-1 and they form neurospheres and retain BrdU label as indicators of self-renewal [17].

The CD133 positive cells with stem cells properties were identified also in colorectal cancer [18]. CD133 positive population accounted for about 2.5% of the tumor cells. Subcutaneous injection of colon cancer CD133 positive cells readily reproduced the original tumor in immunodeficient mice, whereas CD133 negative cells did not form tumors. Unlike CD133 negative cells, CD133 positive colon cancer cells grew exponentially *in vitro* as undifferentiated tumor spheres in serum-free medium, maintaining the ability to engraft and reproduce the same morphological and antigenic pattern of the original tumor [18].

Cancer stem cell model of glioma tumorigenesis was recently reviewed [19].

Glioma stem cells and chemoresistance. Another approach used for CSCs identification is based on their putative high chemoresistance. This property of CSCs was reflected in their identification by flow cytometry as a "side population", distinct cells with the ability to efflux the Hoechst 33342 dye [20]. Recently the link between CSCs and chemoresistance was established [21]. In this study a small subpopulation of human GBM cancer cells was isolated after exposure to a lethal dose of 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU). BCNU-resistant subpopulations derived from GBM had cancer stem-like cell properties. These cells were able to form tumors after transplantation into severe combined immunodeficient (SCID) mouse brain. The cells had the capacity for multipotency and contained subpopulations of stem-like cells, expressing CD133, CD117, CD90, CD71, and CD45 cell-surface markers. Taken together BCNU-resistant subpopulations derived from GBM have cancer stem-like cell properties [21].

Analysis of gene expression and chemoresistance of CD133 positive cancer stem cells in glioblastoma confirmed the link between their chemoresistance and cancer stem cell origin of these cells [22]. The percentage of CD133 positive cells in three primary cultured cell lines established from glioblastoma patients can vary substantially being in range of 10 to 70 percent. The average mRNA levels of markers associated with neural precursors on CD133 positive cells compared to autologous CD133 negative cells increased. The main difference was observed in chemokine receptor CXCR4 and in MELK mRNA. Additionally, CD133 positive cells express higher levels of BCRP1 and MGMT mRNA, as well as higher mRNA levels of genes that inhibit apoptosis. Furthermore, CD133 positive cells were significantly resistant to chemotherapeutic agents used in glioma treatment. CD133 expression was significantly higher in recurrent GBM tissue obtained from five patients as compared to their respective newly diagnosed tumors. All these observations are in agreement with conclusion that CD133 positive cells posses the characteristics of cancer stem cells [22].

Heterogeneity of gliomas as regards their chemoresistance was recently comprehensively reviewed [23].

Cancer stem cells and resistance to radiation. Radiation is the most successful non-surgical treatment of brain tumors, medulloblastomas being the more sensitive to radiation than gliomas. Gliomas usually respond to radiation treatment but subsequently radiation resistant cells recur. The analysis of the radio-resistant cancer cell subpopulations of GBM had shown that these cells abundantly express CD133, CD117, CD71, and CD45 surface markers. The cancer stem cells character of these radio-resistant cell subpopulations was supported by their capacity for extensive proliferation, self-renewal, and pluripotency. When they were transplanted into SCID mouse brain they initiate tumorigenesis. Interestingly these cells could differentiate to endothelial cells; that is why tumors contained both vascular and cancerous tissue structures [24]. Glioma cancer stem subpopulations promote tumor angiogenesis through increased expression of vascular endothelial growth factor (VEGF) [25]. Bao et al. [26] observed that stem cell-like glioma cells consistently secreted markedly elevated levels of vascular endothelial growth factor, which was further induced by hypoxia. The proangiogenic effects of these cells on endothelial cells were specifically abolished by bevacizumab, the clinically used anti-VEGF monoclonal antibody. Furthermore the role of VEGF in human CSCs was followed [3, 26]. The property of self-renewing cells, derived from fresh human glioblastoma, after infection with a VEGF-expressing retrovirus did not change. On the other hand the transplantation of VEGF-expressing stem cells into mouse brains induced the massive expansion of vascular-rich glioblastoma with tumor-associated hemorrhage [3].

It was proved that cancer stem cells – tumor-initiating cells, derived from human glioblastoma surgical specimens and xenografts display resistance to radiation due to increased in DNA repair capacity [27] by activation of the DNA damage checkpoints, including phosphorylation of the checkpoint proteins Chk1 and Chk2.. The CD133-expressing tumor cells preferentially activate the DNA damage checkpoint in response to radiation, and repair radiation-induced DNA damage more effectively than CD133-negative tumor cells. Chalmers [28] proposed that upregulated and hyper-responsive cell cycle checkpoint pathways in gliomas derived cancer stem cells may be potential target for therapy.

Glioblastoma stem cells and the vascular niche. Cell microenvironment, the so-called stem cell niche plays an important role in maintenance of stem cells. Vascular endothelial growth factor promotes the proliferation of vascular endothelial cells and the neurogenesis of neural stem cells. From the experiments when CSCs derived from glioblastoma were infected with VEGF expressing retrovirus [3, 29] seems likely that stem cells of glioblastoma are dependent on cues from aberrant vascular niches that mimic the normal neural stem cell niche. This finding implies that the tumor microenvironment may be a target for new therapies.

Animal glioma models. There are two widely used rat brain tumor models C6 glioma and 9L gliosarcoma, which closely simulated glioblastoma multiforme both in studies *in vitro* and *in vivo*.

When the 9L gliosarcoma cells were cultivated in serum-free medium supplemented with the mitogen epidermal growth factor and basic fibroblast growth factor, clonal-derived spheres were formed. These cells behaved like cancer stem cells, they express the neural stem cells markers Nestin and Sox2, self-renew, and differentiate into neuron-like and glial cells *in vitro*. Tumor-initiating character of these cells was confirmed by observation that they can propagate and recapitulate tumors when implanted into the brain of rats, and they display a more aggressive course compared with 9L gliosarcoma cells grown in monolayer cultures devoid of mitogens. [30].

The low effectiveness of radiation therapy of malignant gliomas in part explain the observation that irradiated C6 glioma cells induce angiogenesis *in vivo* and activate endothelial cells *in vitro* [31].

Stem cell based gene therapy using rat mesenchymal stem cells engineered with adenoviral vector encoding human interleukin-2 (IL-2) were shown to be effective treatment for 9L glioma cells both *in vitro* experiments and also *in vivo* [32].

Fisher et al. [33] showed on rats that primary adult progenitor cells isolated from adult bone marrow posses tumor-infiltrating capacity and can be genetically modified to stably produce retroviral lymphocytic choriomeningitis virus pseudotype vectors. In a rat glioma model, these packaging cells infiltrated the tumors extensively with high specificity. Thus bone marrow derived packaging cell line may be a useful tool to enhance specificity and efficacy of gene transfer to gliomas.

New directions in therapies for glioblastoma. Malignant gliomas are characterized by their local growth and aggres-

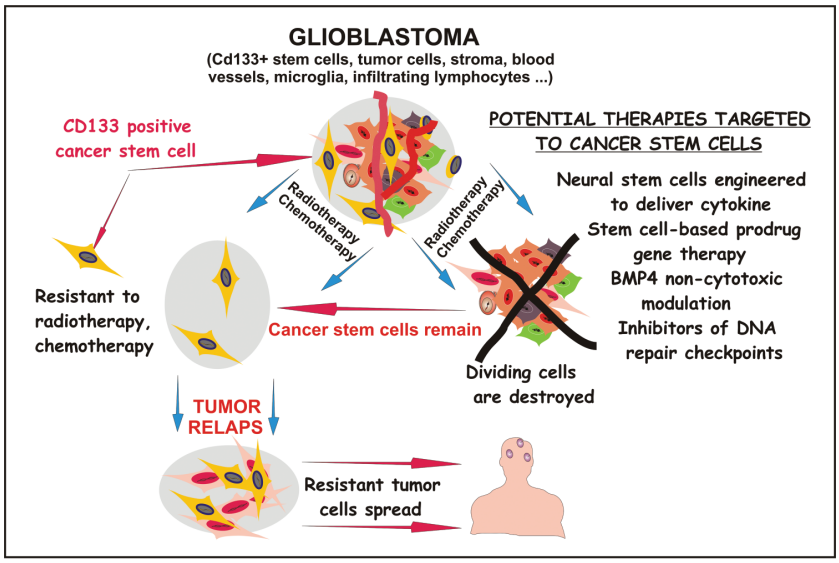

Figure 1. Human glioblastoma properties and its behaviour by conventional therapies and potential targeted therapies to eliminate cancer stem cells.

sive infiltration of the normal brain. There has been little improvement in outcome despite intensive clinical and laboratory research during recent decades. One reason for this failure is the lack of appropriate animal models that reflect the behavior of human glioblastomas. Therapeutic progress in management of malignant brain tumors has also been hindered by the limited delivery of effective therapeutic compounds to an extremely heterogenic tumor cell population. There is general agreement that therapies should be targeted to glioma cancer stem cells, which are responsible for tumor initiation. Glioma driving cancer stem cells – CD133 marker positive cells were already identified. Efforts are made to discover unique CSCs markers that may distinguish between normal stem cells and CSCs and thus allow targeted cancer treatments. The functional role of CD133 marker in stem cells as well as in cancer stem cells is needed to be assessed. Several approaches for elimination of cancer stem cells have been proposed. One treatment modality broadly studied in leukemia is differentiation therapy by retinoic acid (ATRA), an approach forcing cancer stem cells to terminal differentiation [34]. Glioblastoma growth and consequencies of conventional therapies and potential therapies targeted to the cancer stem cells are schematically depicted in Figure 1.

Mesenchymal stem cells have been shown as an attractive cell-based therapeutic vehicle for cancer gene therapy [35]. Human mesenchymal stem cells derived from bone marrow [36], from adipose tissues [35] and/or neutral stem cells [37] were found to be effective vehicle for drugs delivery to tumors and prodrug gene therapy.

Bone marrow stromal cells show an extensive tropism for gliomas both *in vitro* and in vivo. It was shown that gliomas have the capacity to actively attract MSC by secreting a multitude of angiogenic cytokines. These include vascular endothelial growth factor, interleukin-8, transforming growth factor-ss1 and neurotrophin-3 [37].

Human neural stem cell based therapy using cytosine deaminase/5-fluorocytosine prodrug system was experimentally tested for human medulloblastoma, a malignant pediatric brain tumor. The immortalized, clonal human neural stem cell line engineered to secrete the prodrug activating enzyme cytosine deaminase retains the migratory ability toward tumor cells. *In vivo* therapeutic studies on nude mice bearing intracranial medulloblastoma with cytosine deaminase transduced neural stem cells followed by systemic 5-flourocytosine treatment resulted in a 76% reduction of tumor volume in the treated animals [38].

The efficacy of gene therapy prodrug system herpes simplex virus type I thymidine kinase (HSV-TK) /ganciclovir depends on cell-cell contact. The presence of gap junction is required for bystander effect. It was reported that HSV-TK-transduced neural stem cells can circumvent this problem. Glioma cells in this system were eliminated purely by means of the bystander effect [39].

The fate of human neural stem cells (NSC) *in vivo* can be visualized after CM-DiI-labeling. The pattern of NSC distribution showed a gradient with higher densities toward the center of the tumor mass. Authors estimated that NSC-mediated therapy would eradicate 70-90% of the primary tumor mass and the majority of invasive tumor foci [40]. Neural stem cells can be also magnetically labeled *in vitro* with the bimodal gadolinium-based contrast agent, gadolinium rhodamine dextran. The labeled cells can be used for visualizing of tumor development and its progression *in vivo* by magnetic resonance imaging [41].

Bone morphogenetic proteins. Interesting therapeutic non-cytotoxic possibility opens the finding that bone morphogenetic protein 4 (BMP4) trigger a significant reduction in the stem-like, tumor-initiating precursors of human glioblastomas [42]. Family of biomorphogenetic proteins are involved, beside other biological activities, in bone formation [43]. Piccirillo et al.[44] found that *in vivo* delivery of BMP4 effectively blocks the tumor growth and associated mortality that occur in 100% of mice after intracerebral grafting of human GBM cells. Studying the involved BMP4 molecular mechanisms they proofed transient activation its cognate receptors and triggering the Smad but not the MAP38 kinase signaling cascade in cells isolated from human glioblastomas [44]. This is followed by a reduction in proliferation and increased expression of differentiated neural markers, without affecting cell viability. The concomitant reduction in the clonogenic ability, both in the size of the CD133 positive side population and in the growth kinetics of GBM cells, indicates that BMP4 triggers a reduction in the *in vitro* cancer stem cell pool. These findings show that the BMP-BMP receptor signaling system, which controls the activity of normal brain stem cells, may also act as a key inhibitory regulator of cancer-initiating [43]. Obviously, BMP4 may be used to prevent growth and recurrence of GBMs in humans through abolishment of the tumor's self-renewal due to depletion of the tumor stem cells. BMP4 treatment may render the stem cells more susceptible to a conventional therapy.

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The clinical utility of stem cell-based gene therapy was recently excellently reviewed [45].

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