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An overview of therapeutic approaches to brain tumor stem cells

Alireza Khoshnevisan[1]

Department of Neurosurgery, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran.

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Abstract

Primary and secondary malignant central nervous system (CNS) tumors are devastating invasive tumors able to give rise to many kinds of differentiated tumor cells. Glioblastoma multiform (GBM), is the most malignant brain tumor, in which its growth and persistence depend on cancer stem cells with enhanced DNA damage repair program that also induces recurrence and resists current chemo- and radiotherapies. Unlike non-tumor stem cells, tumor stem cells lack the normal mechanisms that regulate proliferation and differentiation, resulting in uncontrolled production and incomplete differentiation of tumor cells. In current paper recent developments and new researches in the field of brain tumor stem cells have been reviewed.

Keywords: Brain tumor, Stem cells, Glioma.

Introduction

Several different types of tumors, benign and malignant, have been identified in the central nervous system (CNS). The prognoses for these tumors are related to several factors, such as the age of the patient, and the location and histology of the tumor. In adults, about half of all CNS tumors are malignant, whereas in pediatric patients, more than 75% are malignant. For most benign CNS tumors that require treatment, we can offer curative resections or at least provide significant relief from mass effect. Unfortunately, we still lack effective treatments for most primary and secondary malignant CNS tumors. However, the past decade has witnessed an explosion in the understanding of the early molecular events in malignant primary CNS tumors, and for the first time in history, oncologists are seeing that a plethora of new therapies targeting these molecular events are being tested in clinical trials. There is hope on the horizon for the fight against these deadly tumors (1). Over the past few years, the traditional view of brain tumorigenesis has been revolutionized by advances in genomic medicine, molecular biology, stem cell biology, and genetically-engineered small-animal modeling (2,3). The concept of cancer stem-like cells (CSCs) has gained considerable attention in various solid tumors including glioblastoma (GBMs) (4,5). Glioblastomas are the most common primary brain tumors with poor prognosis (6). CD133, nestin and recently CD90 (7) have been considered the putative markers of (CSCs) in malignant cancers, including GBMs. Unlike non-tumor stem cells, tumor stem cells lack the normal mechanisms that regulate proliferation and differentiation, resulting in uncontrolled production and incomplete differentiation of tumor cells

1. **(Corresponding author)** Department of Neurosurgery, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran. akhoshnevisan@yahoo.com

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(8,9). Some data suggest that CD133(+) glioma stem cells (GSCs) exhibit more aggressive invasion in vitro and GSCs in vivo probably disseminate along the long axis of blood vessels and transit through the white matter tracts (10,11). Recent studies have suggested that cancer stem cells cause tumor recurrence based on their resistance to radiotherapy and chemotherapy (12,13). This sub-population of tumor cells has been intensively investigated and their role in therapy resistance as well as tumor recurrence has been demonstrated. In that respect, development of therapeutic strategies that target CSCs (and possibly also the tumor bulk) appears a promising approach for patients suffering from primary brain tumors. Here we explored new researches that have been conducted in the field of brain tumor stem cells.

Review of literature

In vivo evidences for glioblastoma cancer stem cells

In order to test the relative tumorigenicity of CSCs and non-stem tumor cells in the same microenvironment, matched tumor populations were purified from a primary human tumor transplanted into a xenograft mouse model and competitive in vivo tumor growth studies using serial in vivo intravital microscopy were monitored. While CSCs were a small minority of the initial transplanted cancer cell population, the CSCs, not the non-stem tumor cells, drove tumor formation and yielded tumors displaying a cellular hierarchy. It has been found that in the resulting tumors, a fraction of the initial transplanted CSCs maintained expression of stem cell and proliferation markers, which were significantly higher compared to the non-stem tumor cell population and this evidence shows that CSCs generated cellular heterogeneity within the tumor (14,15). These comparisons between matched CSCs and non-stem tumor cells provide the first functional evidence using live imaging that in the same microenvironment, CSCs more than non-stem tumor cells are responsible for tumor propagation, confirming the functional definition of a CSC.

MicroRNA-34a is tumor suppressive in brain tumors and glioma stem cells

MicroRNAs (miRNAs) are evolutionarily conserved, endogenous, small, non-coding RNA molecules of about 22 nucleotides in length that function as posttranscriptional gene regulators. They are deemed to play a crucial role in the initiation and progression of human cancer, and those with a role in cancer are designated as oncogenic miRNAs (oncomiRs) (16,17,18). Recently it has been found that microRNA-34a (miR-34a) is downregulated in human glioma tumors as compared to normal brain, and that miR-34a levels in mutant-p53 gliomas were lower than in wildtype-p53 tumors. This finding shows that miR-34a is a potential tumor suppressor in brain tumors that acts by targeting multiple oncogenes (19). The new data show that miR-34a expression inhibits various malignancy endpoints in glioma stem cells. Importantly, it has been shown for the first time that miR-34a expression induces glioma stem cell differentiation (20). MicroRNA (miRNA)-34a (1p36.23) is generally expressed at lower levels in unfavorable primary neuroblastoma (NB) tumors and cell lines relative to normal adrenal tissue and reintroduction of this miRNA into three different NB cell lines causes a dramatic reduction in cell proliferation through the induction of a caspase-dependent apoptotic pathway. Altogether, the data suggest that miR-34a is a tumor suppressor and a potential potent therapeutic agent that acts by targeting multiple oncogenic pathways in brain tumors and by inducing the differentiation of cancer stem cells.

Nonetheless, the microRNA145 with cationic polyurethane-short branch PEI to inhibit cancer stem cell-like properties

It has been shown that expression of miR145 (a tumor-suppressive miRNA) is inversely correlated with the levels of Oct4 and Sox2 (SRY (sex determining region Y)-box 2, also known as SOX2, is a transcription factor that is essential to maintain self-

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renewal of undifferentiated embryonic stem cells) in GBM-CD133(+) cells and malignant glioma specimens. It has been demonstrated that miR145 negatively regulates GBM tumorigenesis. Using polyurethane-short branch polyethylenimine (PU-PEI) as a therapeutic-delivery vehicle, PU-PEI-mediated miR145 delivery to GBM-CD133 (+) significantly inhibits their tumorigenic and CSC-like abilities. Furthermore, PU-PEI-miR145-treated GBM-CD133 (+) effectively suppresses the expression of drug-resistance and anti-apoptotic genes and increases the sensitivity of the cells to radiation and temozolomide. Finally, the in vivo delivery of PU-PEI-miR145 alone significantly suppresses tumorigenesis with stemness, and improves the survival rate when used in combination with radiotherapy and temozolomide in mice (21,22). Expression of Sox2 at transcriptional level has also been reported to decreases during arsenic trioxide [As(2)O(3)]-induced glioma cell apoptosis (23,24). Therefore, PU-PEI-miR145 and arsenic trioxide can be a novel therapeutic approach for malignant brain tumors.

Glioma tumor suppression by Pro-neural miR-128

The MiR-128 represses glioma-initiating neural stem cells (giNSCs) growth by enhancing neuronal differentiation. The MiR-128 represses growth and mediates differentiation by targeting oncogenic receptor tyrosine kinases (RTKs) epithelial growth factor receptor and platelet-derived growth factor receptor-α. Using an autochthonous glioma mouse model, it has been demonstrated that miR-128 repressed gliomagenesis (25). MiR-128 has been identified as a glioma tumor suppressor that targets receptor tyrosine kinases (RTK) signaling to repress giNSC self-renewal and enhance differentiation.

Correlation between tumor vascular niche and glioblastoma stem cells

It is believed that formation of abnormal, dysfunctional tumor vasculature and glioblastoma stem-like cells (GSCs) are the major obstacles to treat these tumors effectively. Brain tumor stem cell markers CD133 and nestin are expressed in tumor and endothelial cells in GBM samples. Double immunofluorescence stainings showed that the two different marked GSCs were found accumulated around the CD31+ blood vessels and CD133/CD31 or nestin/CD31 co-expression was found in the endothelial cells and GSCs. Additionally, the vascular endothelial growth factor (VEGF) and the endothelial marker CD31 were co-expressed in GSCs (26,27). This findings demonstrate that GSCs contribute directly to the tumor vasculature by endothelial cell differentiation, and a significant portion of the vascular endothelium has a neoplastic origin and therefore GSCs and tumor vascularization are closely related to each other, not only in the regional distribution but also in biological function (28,29). These evidences show a new mechanism for tumor vasculo-genesis and may provide new insights for targeted therapy against brain tumors.

NOTCH ligands that are provided by endothelial cells create a stem cell niche in glioblastoma. NOTCH ligands (The notch receptor is a single-pass transmembrane receptor protein. It is a hetero-oligomer composed of a large extracellular portion, which associates in a calcium-dependent, non-covalent interaction with a smaller piece of the notch protein composed of a short extracellular region, a single transmembrane-pass, and a small intracellular region) are expressed in endothelial cells adjacent to nestin and NOTCH receptor-positive cancer cells in primary GBMs (30,31). Coculturing human brain microvascular endothelial cells (hBMEC) or NOTCH ligand with GBM neurospheres promoted GBM cell growth and increased CSLC self-renewal. RNAi-mediated knockdown of NOTCH ligands in hBMECs abrogated their ability to induce CSLC self-renewal and GBM tumor growth, both in vitro and in vivo (32-34). These findings establish that NOTCH activation in GBM

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CSLCs is driven by signaling between tumor cells and their surrounding endothelial cells in the tumor microenvironment, suggesting that targeting both CSLCs and their vascular niche may provide a new way to deplete CSLCs and improve GBM treatment.

Targeting of the MEK-ERK-MDM2-p53 pathway in combination with temozolomide

Overcoming the resistance of glioblastoma cells against temozolomide a chemotherapeutic agent, is a major therapeutic challenge in the management of this tumor. The gene encoding O(6) - methylguanine DNA methyltransferase (MGMT), which removes the methyl group attached by temozolomide, is expressed in a significant fraction of glioblastomas and is therefore regarded as one of the mechanisms of resistance against temozolomide. Evidences show that the mitogen-activated protein/extracellular signal-regulated kinase (MEK)-extracellular signal-regulated kinase (ERK)--murine double minute 2 (MDM2)-p53 pathway plays a critical role in the regulation of MGMT expression.it has been shown that, in stem-like glioblastoma cells, MEK inhibition reduced MDM2 expression and that inhibition of either MEK or MDM2 resulted in p53 activation accompanied by p53-dependent downregulation of MGMT expression (35). MEK inhibition makes resistant stem-like glioblastoma cells sensitive to temozolomide, and combination of MEK inhibitor and temozolomide treatments effectively deprives stem-like glioblastoma cells of their tumorigenic potential.

Antiglioma effects of oncolytic adenoviruses

Antiglioma effect of the tumor-selective oncolytic adenovirus Delta-24-RGD has been previously reported (36). It has also been shown that Delta-24-RGD infects, replicates in, and induces cell death in brain tumor stem cells (BTSCs). Interestingly, adenoviral-infected cells undergo autophagy and that autophagy-related cytoplasmic vacuolization might be part of the lysis process (37).

Role of CD44v6 through the AKT-mediated pathway

CD44 is a cell surface protein linked to tumorigenesis in various cancers. Patients with CD44 (high) GBM exhibited significantly poorer prognoses. Among various variant forms, CD44v6 is the only isoform that was detected in BTSC and its knockdown inhibited in vitro growth of BTSC from CD44 (high) GBM but not from CD44(low) GBM (38). Stimulation with a CD44v6 ligand, osteopontin (OPN), increased expression of phosphorylated AKT in CD44 (high) GBM, but not in CD44 (low) GBM. In summary, data indicate that a subset of GBM expresses high CD44 in BTSC, and its growth may depend on CD44v6/AKT pathway.

PFKFB4 as a key molecule is important for cancer cell survival

RNA interference (RNAi) has been used to screen the complete human kinome and phosphatome (682 and 180 targets, respectively) in order to identify genes and pathways relevant for the survival of brain CSCs and thereby potential therapeutical targets for glioblastoma. 46 putative candidates have been reported including known survival-related kinases and phosphatases. A number of genes identified are involved in metabolism, especially glycolysis, such as PDK1 and PKM2 and, most prominently PFKFB4. Essential role of PFKFB4 in the maintenance of brain CSCs has been confirmed by in vitro studies (39). Additionally, high PFKFB4 expression is associated with shorter survival of primary glioblastoma patients (4). Findings support that glycolytic pathway is important in the maintenance of malignant glioma cells and brain CSCs and therefore tumor metabolism can be a promising therapeutic target in glioblastoma.

Girdin and its role in the stemness of GSCs

Hyperactivation of the PI3K-Akt path-

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way, a pro-tumorigenic signaling cascade,is usually seen in GBM and contributes to its pathogenesis. Girdin (an actin-binding protein) that is a substrate of Akt , regulates the sprouting of axons and the migration of neural progenitor cells during early postnatal-stage neurogenesis in the hippocampus. Girdin is highly expressed in human glioblastoma (GBM). Stable Girdin knockdown in isolated GBM stem cells resulted in decreased expression of stem cell markers, including CD133, induced multilineage neural differentiation, and inhibited in vitro cell motility, ex vivo invasion and in vivo tumor formation. Furthermore, exogenous expression of the Akt-binding domain of Girdin, which competitively inhibits its Akt-mediated phosphorylation, diminished the expression of stem cell markers, SOX2 and nestin, and migration on the brain slice and induced the expression of neural differentiation markers glial fibrillary acidic protein/βIII Tubulin (40). These results reveal that Girdin is required for GBM-initiating stem cells to sustain the stemness and invasive properties.

Blockade of TGF-β signaling by the TGFβR-I Kinase Inhibitor LY210976112

TGF-β is a modifier of radiation response. Antitumor effects of the TGF-β receptor (TGFβR) I kinase inhibitor LY2109761 in combination with radiotherapy have been studied. In vivo studies show that LY2109761 reduces clonogenicity and increases radio-sensitivity in GBM cell lines and cancer stem-like cells and augments the tumor growth delay produced by fractionated radiotherapy in vivo. In an orthotropic intracranial model, LY2109761 significantly reduced tumor growth, and extended the prolongation of survival induced by radiation treatment. Histologic analyses showed that LY2109761 inhibited tumor invasion promoted by radiation and reduced tumor microvessel density. These results show that a selective inhibitor of the TGFβR-I kinase can potentiate radiation responses in glioblastoma by coordinately increasing apoptosis and cancer stem-like cells targeting while blocking DNA damage repair, invasion and angiogenesis (41). TGFβR kinase inhibitors can be considered as radiosensitizers to improve the treatment of glioblastoma. There are some reports also which show that first-generation kinase inhibitors that selectively disrupt single kinases have failed to demonstrate clinical benefit in most patients with GBM. One strategy to solve this problem is to target multiple kinases by multitargetedkinase inhibitors or combinations of single targeted kinase inhibitors (42).

PKCδ signaling and fractionated-radiation-induced expansion of glioma-initiating cells

Reports have indicated that treatment of human glioma cells with fractionated radiation increases Abl (Abelson murine leukemia viral oncogene homolog) (Abl) and protein kinase Cδ (PKCδ) activity, expandes the CD133-positive (CD133(+)) cell population that possesses tumor-initiating potential and induces expression of glioma stem cell markers and self-renewal-related proteins. Moreover, cells treated with fractionated radiation were resistant to anticancer treatments. Knockdown of PKCδ expression with small interfering RNA (siRNA) blocked fractionated-radiation-induced CD133(+) cell expansion and suppressed expression of glioma stem cell markers and self-renewal-related proteins. It also suppressed resistance of glioma cells to anticancer treatments. Similarly, knockdown of Abl leads to a decrease in CD133 (+) cell populations and restores chemotherapeutic sensitivity (43,44). Collectively, these data indicate that fractionated radiation induces an increase in the glioma-initiating cell population, decreases cellular sensitivity to cancer treatment and implicates activation of Abl-PKCδ signaling in both events. These findings might be important in the context of ionising-radiation-based therapeutic interventions for brain tumors.

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P53-deficient mouse astrocytes dedifferentiates into brain cancer stem-like cells by Nanog

It has been reported that Nanog (a transcription factor critically involved with self-renewal of undifferentiated embryonic stem cells) has some role in the genesis of cancer stem-like cells. Evidences show that enforced Nanog expression can increase the cellular growth rate and transform phenotypes of p53-knockout astrocytes (p53(-/-) astrocytes) , in vitro and in vivo (45,46). In addition, Nanog drives p53(-/-) astrocytes toward a dedifferentiated, CSC-like phenotype with characteristic neural stem cell/progenitor marker expression, self-renewal activity, and tumor formation (47,48). These findings suggest that dedifferentiation of p53-deficient mouse astrocytes into cancer stem-like cells can be promoted by Nanog.

Effects of neural stem cells expressing TRAIL

Tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) is a member of the TNF/nerve growth factor superfamily that induces cell death in susceptible cells (49). It can be found in two forms: membrane-bound (mTRAIL) and soluble protein. Glioma cells appeared to be more prone to apoptosis in co-culture with NSCs-mTRAIL than to treatment with soluble TRAIL. In vivo, the survival of animals possessing intracranial glial xenografts was significantly improved by NSCs-mTRAIL (50). These evidence demonstrate that therapy with NSCs-mTRAIL is effective in treatment of glioma.

Hedgehog pathway

The Hedgehog (Hh) pathway has a major regulatory role in many fundamental processes in vertebrate embryonic development including stem cell maintenance, cell differentiation and cell proliferation. This pathway also regulates proliferation of cancer stem cells and increases tumor invasiveness. inhibition of Hh signaling may be effective in the treatment and prevention of many types of human cancers (51,52). Hh pathway inhibitors have significant clinical implications in novel cancer therapeutics. The oral compound, GDC-0449, is one of these inhibitors that has been shown to be effective and safe in Initial clinical trials (53,54).

Role of matrix metalloproteinases (MMP) and their collagen substrates in cancer

The MMP activity regulates the functionality of multiple extracellular matrix proteins, cytokines, growth factors and cell signaling and adhesion receptors. Enhanced MMP proteolysis affects multiple cell functions, including proliferation, migration and invasion. This aberrant MMP proteolysis is frequently seen in cancer. Collagen deposition, combined with an enhanced MMP activity in glioblastomas/gliomas, facilitates rapid invasion of tumor cells through the brain(55). It is hypothesized that mechanisms which control MMPs, TIMPs (MMPs tissue inhibitors) and collagens and, consequently, tumor cell invasion, may be promising drug targets and that in the near future these targets will be challenged pharmacologically.

Role of YB-1 in differentiation & cell growth

The Y-box binding protein 1 (YB-1) is essential for normal brain development, suggesting that YB-1 is part of a neural stem cell (NSC) network. It is also up regulated in many human malignancies including glioblastoma (GBM). Sox-2, nestin, and musashi-1 expression in the subventricular zone (SVZ) are reduced in YB-1 knockout mice. Although primary murine neurospheres were rich in YB-1, its expression is lost during glial differentiation. Silencing YB-1 with siRNA reduces neurosphere growth, and triggers differentiation. Furthermore, bone morphogenetic protein-4 suppresses YB-1 protein expression (56). Likewise, YB-1 expression is lost during differentiation of normal human NSCs. YB-1 correlatively expresses with NSC markers where it functions to promote

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cell growth and inhibit differentiation.

Nitric oxide synthase-2 and glioma stem cell proliferation

It has been demonstrated that glioma stem cells (GSCs) produce nitric oxide via elevated nitric oxide synthase-2 (NOS2) expression. GSCs depend on NOS2 activity for growth and tumorigenicity, distinguishing them from non-GSCs and normal neural progenitors. High NOS2 expression correlates with decreased survival in human glioma patients, and NOS_2 inhibition slows glioma growth (57). These findings suggest that NOS_2 inhibition may be an effective approach to treat this devastating disease.

Targeting III-Tubulin in Glioblastoma Multiforme

Overexpression of βIII-tubulin in GBM has been reported and it has been proposed that this aberrant expression may be linked to a disruption in microtubule dynamics associated with glioma tumorigenesis, tumor progression and transformation into GBM. βIII-tubulin can be considered as a target of GBM therapy. Epothilones, a new family of anticancer agents, has been shown to be active in βIII-tubulin-expressing tumor cells (58).

Role of immunotherapy in GSCs

The GSCs are resistant to resting natural killer (NK) cells because they express MHC class I molecules. However, lectin-activated NK cells kill GSCs. GSCs are also sensitive to antibody-mediated cytotoxicity. Sensitivity of GSC to cytotoxicity caused by IL2-activated NK cells and tumor-specific T cells has been shown. GSCs are more sensitive to NK and T cell-mediated lysis relatively to their corresponding serum-cultured GBM cells taken from the same initial tumor specimen (59). These results suggest that GSCs are suitable target cells for immunotherapy of GBM patients.

Other factors

The Oncostatin M (OSM) (a cytokine that belongs to the interleukin 6 group of cytokines.) and its receptor, OsmRβ, are both expressed in the subventricular zone (SVZ). Osm can inhibit clonal growth of glioblastoma-derived neurospheres (60).

HOX genes encode a family of homeodomain-containing transcription factors involved in the determination of cell fate and identity during embryonic development. They also behave as oncogenes in some malignancies. It has been observed that HOXD9 protein is expressed in human brain tumor tissues, including astrocytomas and glioblastomas. Decreased cell proliferation and cell cycle arrest, have been observed when expression of HOXD9 protein is silenced by HOXD9-specific siRNA. It has been suggested that HOXD9 contributes to both cell proliferation and/or cell survival and can be a potential therapeutic target (61).

Maternal embryonic leucine-zipper kinase (MELK) has been identified as a key regulator of survival of stemlike GBM cells in vitro. It has been demonstrate that a thiazole antibiotic, siomycin A, potently reduces MELK expression and inhibits tumor growth in vivo. Treatment of stemlike GBM cells with siomycin A inhibits self-renewal (62).

Recent evidence have supported the importance of hypoxia in glioma stem cell (GSC) niches. Hypoxia-inducible factors (HIFs) hypothetically require epigenetic-modifying proteins to promote tumor malignancy in GBM (63). GSCs reside in a specialized hypoxic niche, which can regulate the tumorigenic capacity of GSCs primarily through HIFs (64).

Mesenchymal stem cells and/or neural stem cells were shown to target brain tumors, therefore these cells can be used as an effective delivery system to target and disseminate therapeutic agents to brain tumors.

Stem cell-based gene therapies for glioblastoma were shown in to be an effective way to target brain tumors.

BMP4 reduces proliferation of CD133 positive cells in vitro and the tumor growth in vivo and may act as a key inhibitory regulator (65).

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Conclusion

Brain tumors remain one of the most deadly cancers in adults, with an average period between diagnosis and death of ~12 months. The discovery of brain tumor stem cells and their chemo- and radioresistance have provided a reasonable explanation for the difficulty in these tumors treatment and the high rate of relapse. Indeed, as GBM cells are highly invasive, surgery is not routinely curative. In recent years targeting brain tumor stem cells opened up the way for new therapies. These new strategies in addition to other treatment approaches (gene therapy, immunotherapy) may show promising results to help patients with brain tumors.

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