Journal of Stem Cells Research, Reviews & Reports

Austin Publishing Group

Open Access Full Text Article

Review Article

Stem Cells in Gliomas

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Received: August 20, 2014; **Accepted:** September 16, 2014; **Published:** September 16, 2014

Abstract

Gliomas are central nervous system tumors exhibiting marked cellular heterogeneity, invasiveness and resistance to any therapeutic intervention. Experimental evidence suggests that most of these properties of gliomas are due to the presence of glial stem cells within the gliomas. Markers of glioma stem cells include Nestin, CD133 and CD15. The anatomic location of stem cells within gliomas is predominantly the perivascular areas. Glioma patients with high percentage of glial stem cells have poor survival. Although eradication of the glioma stem cells could extend survival it is difficult to succeed due to their high resistance to therapy. Apart from the glioma stem cells, normal neural stem cells that can be induced from pluripotential stem cells may be used therapeutically for gliomas as carriers for various antitumor agents due to their tropism for neural tissue, if their safety can be attained.

Keywords: Stem cells; Glioma; Brain tumor

Introduction

Gliomas are central nervous system (CNS) tumors of glial origin, exhibiting a profound cellular heterogeneity with tumor cells showing various degrees of differentiation, and genetic heterogeneity with dissimilar gene alterations in neighbourhood cells of the same tumor [1]. This heterogeneity could be due to possible origin of glioma from neural stem cells (NSCs) which after pre-existing or acquired genetic abnormalities drive the NSCs to malignant transformation and formation of glioma stem cells [2]. Glioma stem cells exhibit increased invasiveness, angiogenesis and resistance to therapeutic interventions [3-5]. These glioma stem cells are eventually responsible for tumor malignancy, growth and recurrence [6].

Normal stem cells are capable of infinite proliferation like cancer cells. Apart to the well-known hematopoietic stem cells from bone marrow, stem cell stores exist in other adult tissues. Thus, subcutaneous fat and dermis consist of accessible sources for obtaining stem cells, with minimal discomfort to the patient [7]. Stem cells niche denotes the anatomic location or microenvironment where stem cells are located, and this microenvironment interacts with the stem cells to regulate various cell functions [8]. Recent evidence suggests that human glioma niches are localized in the perivascular areas within gliomas [9].

Study of both normal stem cells and glioma stem cells are important during therapy of gliomas: Normal stem cells may be used during treatment for gliomas, mainly as vehicles to transfer various therapeutic agents to the tumor; study of glioma stem cells is also important to assess the tumor behavior, response to treatment and prognosis.

Stem Cell Markers

Glioma stem cells and NSCs co-express similar markers essential for similar functions in both types of cells (Table 1) [10]. Markers of glioma stem cells include Nestin, CD133 and CD15 [11]. Nestin, is a type-VI intermediate filament that is briefly expressed in glioma tissue during brain development. A study in 70 patients with gliomas that had surgery showed that nestin was expressed in astrocytic gliomas and correlated with the degree of malignancy [12]. Similarly, another immunohistochemichal study in 87 primary CNS tumors showed that nestin was expressed in 95.8% of gliomas with higher expression in malignant tumors and inversely correlated with patient survival. Interestingly, the immunohistochemical staining of nestin in a xenograft model demonstrated its location mainly in the invasive tumor cells at the tumor periphery rather than tumor center [13].

Prognostic significance of glioma stem cells

Immunohistochemical analysis in 125 patients with gliomas of various grades revealed that the presence of glioma stem cells in the tumor, as manifested by Nestin and/or CD133 expression, especially the co-expression of both, was an independent predictor of poor survival [14]. Another study in 95 gliomas of various grade revealed that both the proportion of CD133-positive cells and their ability to organize in clusters were significant independent negative prognostic factors. In addition, the presence of CD133-positive cells was an independent risk factor for tumor recurrence [15].

There is evidence for a crucial role of the expression of glioma SC genes and tumor recurrence as well as response to therapy [16]. Bmi1, an oncogene that is expressed in stem cells and associated with increased cell proliferation and invasion potential of gliomas was able to be downregulated by miR-218, a microRNA involved in its function. These findings suggested that miR-218 may be functioning as tumor suppressor, inhibiting invasion and proliferation of glioma cells [17].

Glioma stem cells mediating resistance to therapy

Gliomas, are tumors highly resistant to chemotherapy [18] or any other therapy [19]. Evidence suggests that GSCs may play a significant role mediating such a resistance [20]. Established human glioblastoma cell lines, such as U-87 MG possess subpopulation of glioma stem cells expressing CD133 and resistant to Fas-activated apoptosis in contrast to the non stem glioma cells that exhibit sensitivity to Fas-mediated apoptosis [21]. The apparent heterogeneity of glial tumors [1,2] appears to be a crucial element for in vitro studies in glioma cell

Citation: Assimakopoulos A, Polyzoidis K and Kyritsis AP. Stem Cells in Gliomas. J Stem Cells Res, Rev & Rep. 2014;1(2): 1009.

Table 1: Characteristics of normal stem cells and glioma stem cells.

	Normal neural stem cell	Normal mesenchymal stem cell	Glioma stem cell	Glioma cell
Nestin	+	+	+	-
CD-133	+	+	+	-
Capable to infinite proliferation	+	+	+	+
Malignant	-	-	+	+
Invasive	-	-	+	+
Affect patient prognosis	-	-	+	+
Resistance to chemotherapy	Unknown	Unknown	++	+
Resistance to radiotherapy	+/-	Unknown	++	+
Resistance to apoptotic agents	-	-	++	+
Localization	Subventricular zone of brain	Umbilical cord blood, adipose tissue, muscle, cornea	Perivascular area of glioma	N/A
Tropism to glioma	+++	+	+	-
Carrier of anti-glioma agents*	+++	+++	-	-

* Chemotherapy, therapeutic genes, viruses, or tumor-toxic molecules

lines, since most of them consist of only a small cell subpopulation of the original tumor, making tissue culture results of preclinical test of new therapeutic agents difficult to interpret. Thus, establishment of glial stem cell lines would be more appropriate to test potential therapeutic agents for further in vivo testing.

GSCs have been also resistant to TRAIL even at high concentration of 100-2,000 ng/ml, in contrast to glioma cells with non stem cell characteristics. Their resistance to TRAIL has been attributed to hypermethylation of caspase-8 promoter and low caspase-8 levels for TRAIL-mediated apoptosis. However, reversion of expression of caspase-8 by 5-Aza-2'-deoxycytidine was not enough to reinstate TRAIL effectiveness suggesting interplay of additional mechanisms to TRAIL resistance [22].

The serine/threonine kinase maternal embryonic leucine-zipper kinase (MELK) is an enzyme encoded by the *MELK* gene, highly expressed in gliomas and significantly associated with the malignant phenotype. MELK expression is reduced by p53 expression leading to increased GSCs apoptosis. MELK is able to form a complex with the oncoprotein c-JUN in GSCs but not normal stem cells and mediate the JNK-driven MELK/c-JUN signaling to maintain tumor survival and resistance to therapeutic interventions [20]. GSCs but not normal neural stem cells synthesize nitric oxide through nitric oxide synthase-2 (NOS2) that is associated with tumor growth and reduced patient survival. Thus, NOS2 inhibition may be a possible target for glioma treatment [23].

Although GSCs exhibit prolonged cell cycle and checkpoint, there appears to be no enhanced DNA repair capability during the checkpoints to explain cell resistance due to DNA repair [24]. After radiotherapy of GSCs in vitro, early postradiation resistance was noted in cells under the presence of EGF and FGF-2, but late postradiation apoptosis was encountered in cells with non-functional p53 [25].

Survivin, a protein encoded by the *BIRC5* gene, is expressed during G2-M phase of the cell cycle and abundant in malignant glioma cells and GSCs, mediating inhibition of apoptosis through caspase inactivation. Comparison of Survivin immunohistochemical expression in glioblastomas of 44 untreated and 31 recurrent post-chemoradiation and resistant to chemotherapy patients, demonstrated higher expression in the tumors of the recurrent patients especially in the perivascular areas [26].

Glioma SCs exhibit a deregulated balance between cell proliferation and differentiation, specifically increased cellular proliferation and decreased cellular differentiation, partially mediated by the Notch signaling pathway. Inhibition of this pathway by Notch-1 small interfering RNA (siRNA), it was able to inhibit growth of glioma SCs in vitro and in vivo in nude mice, suggestive that Notch-1 gene may represent a possible target for glioma therapy [27]. Stem cells isolated from glioma specimens could induce tumors in immunocompromised mice that secreted vascular endothelial growth factor (VEGF) leading to endothelial cell migration and excessive angiogenesis. These angiogenic effects could be suppressed by bevacizumab a potent inhibitor of angiogenesis and currently used therapy for gliomas [28].

Experimental evidence in nude mice bearing C6 gliomas suggests that disruption of GSC niche by antiangiogenic therapy could sensitize the GSCs to chemotherapy [25]. Furthermore, clinical evidence indicates that radiotherapy of the stem cell niches in patients with gliomas could extend survival. Thus, a study in 55 patients with malignant gliomas treated with radiotherapy showed that patients subjected to bilateral subventricular zone that harbors the GSCs niches had a significant improvement in progression-free survival (15.0 vs 7.2 months) than patients whose radiotherapy field did not include these areas. In addition, higher radiation fractions may be more efficient that lower fractions [29].

Normal stem cells as carriers of therapeutic agents to gliomas

Normal NSCs and mesenchymal stem cells (MSCs) may be used as cellular vehicles for targeted delivery of various agents to glioma cells (Table 1). However, the normal stem cells that carry anti-tumor substances may be used therapeutically only if their malignant transformation potential can be eliminated [30]. MSCs isolated from the umbilical cord blood could migrate towards glioma cells via a partially dependent on the PDGF/PGGFR system glioma tropism,

and provoke a Fas-mediated apoptosis in glioma cells [31]. NSCs secrete factors that inhibited the proliferation of glioma cells, both in vitro and in vivo in gliomas growing in the cisterna magna of mice [32]. In addition to secretion of growth inhibitory factors, NSCs could be used as cellular vehicles to deliver chemotherapy, therapeutic genes, viruses, or tumor-toxic molecules to malignant gliomas due to their tropism for glioma cells [33,34]. Preclinical comparison of the two cell lines revealed that although both NSCs and MSCs allowed adenoviral replication intracellularly, the efficiency of the NSCs was much higher to MSCs [35].

Difficult tumor areas to attain enough concentration of a therapeutic agent consist of hypoxic areas with necrosis and poor blood circulation, such as the tumor necrotic core and the adjacent to tumor areas that contain infiltrating tumor cells with still poor new blood vessel formation. Interestingly, NSCs tropism is predominantly directed towards the hypoxic areas of the malignant gliomas located both in tumor core and the periphery of the tumor. This function appears to be mediated via stromal cell-derived factor-1 (SDF-1) SDF-1/CXCR4, uPA/uPAR, VEGF/VEGFR2, and hepatocyte growth factor/c-Met signaling pathways [36].

Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) demonstrated glioma-directed killing activity suggestive of a promising antitumor treatment strategy in clinic [37,38]. Thus, employment of TRAIL-secreting human MSCs could represent a tumor specific targeted therapy for gliomas alone or in combination of a chemotherapeutic agent such as temozolomide [39]. Another example is the use of normal NSCs carrying secretable TRAIL in an orthotopic mouse model of gliomas in combination with systemically administered other specific therapies to enhance the anti-tumor effect [40].

Normal stem cells can be used to deliver enzymes that convert a chemotherapeutic prodrug to an active chemotherapy drug. An in vivo example of using normal NSCs to this effect consists of usage of a cytosine deaminase (CD)-expressing clonal human NSC line, HB1.F3.CD, to deliver the enzyme to gliomas growing in brains of mice in order to convert the systemically administered prodrug 5-fluorocytosine to the active chemotherapeutic 5-fluorouracil locally [41].

Facilitated delivery of gene therapy agents is another potential application of normal stem cell technology for treatment of gliomas. Animal experiments have demonstrated that transfer of the interleukin-4 gene into C57BL6J mouse NSCs and injection into syngeneic brain gliomas significantly increased the survival of most tumor-bearing mice [42]. Similarly, NSCs transduced with herpes simplex virus-thymidine kinase gene (NSCtk) were injected in distant sites of rat brains harboring C6 glioma cells, following by the systemic administration of ganciclovir (GCV), a drug against herpes virus. The reason for the injection in distant areas was to study the migratory potential of neural stem cells and their effectiveness to reach the glioma cells. The result was active migration of neural stem cells towards the tumors, even when implanted at the controlateral hemisphere, and marked inhibition of tumor growth and prolonged survival of the animals [43]. Induced pluripotent stem cells derived from primary mouse embryonic fibroblasts were used to generate NSCs. Subsequently, the NSCs were transduced with a baculoviral vector having the HSV TK gene and were injected into the controlateral to the tumor hemisphere in mice. Systemic administration of ganciclovir, resulted in inhibition of glioma growth suggesting that NSCs may be used as vehicles for gene therapy [44,45]. Apart from intratumoral delivery of normal stem cells, intravascular delivery of NSCs appears to be an effective strategy to target tumors of neural origin, inside the brain [46].

Conclusion

The profound cellular heterogeneity of gliomas in association with their invasiveness and resistance to therapeutic interventions is at least partially due to the presence of glioma stem cells within the malignant types of these tumors. The anatomic location or microenvironment where these cells are located is denoted as stem cell niches in the perivascular areas within gliomas. Study of glioma stem cells is important to assess the tumor behavior, delivery of chemotherapeutic agents, response to treatment and prognosis. In addition to glioma stem cells, normal neural stem cells exist in the brain of human beings in addition to other locations. These normal stem cells have high tropism for glioma tumors and can migrate even from distant areas towards gliomas. This property renders them good candidates as transfer vehicles to carry toxic agents to gliomas. Further research is needed to assess their safety prior to their routine utilization as carriers of therapeutic agents to humans.

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J Stem Cells Res, Rev & Rep - Volume 1 Issue 2 - 2014
ISSN : 2381-9073 | www.austinpublishinggroup.com

Citation: Assimakopoulos A, Polyzoidis K and Kyritsis AP. Stem Cells in Gliomas. J Stem Cells Res, Rev & Rep. 2014;1(2): 1009.