Stem cells tropism for malignant gliomas

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Abstract: Various studies have demonstrated the tremendous tropism of stem cells for malignant gliomas, making these cells a potential vehicle for delivery of therapeutic genes to disseminated glioma cells. However, little is known about the mechanisms underlying the glioma-induced tropism of stem cells. Soluble factors including chemokines or growth factors released and expressed by glioma cells at least mediate the tropism of stem cells for gliomas. Here we review the possible mechanisms of stem cells tropism for malignant gliomas.

Keywords: stem cell; tropism; glioma

1 Introduction

Malignant gliomas are the most prevalent type of primary brain tumors. The prognosis of patient with malignant gliomas, such as glioblastoma multiforme (GBM) or anaplastic astrocytoma, is extremely poor, despite their extensive surgical excision and adjuvant radio- and chemotherapy^[1-3]. The median survival is 1 year or less for patients with GBM and 3 years for those with anaplastic astrocytoma^[4]. This treatment resistance is partly due to their infiltration and invasion into surrounding brain architecture. Surgical resection is almost always followed by regrowth of tumor cells residing in adjacent regions of normal brain because it is impossible to eliminate successfully all of glioma cells from normal brain under current circumstance^[5-7]. Single tumor cells, which deeply infiltrate the surrounding tissue, are thought to be responsible for tumor relapse. New therapies should specifically target to tumor cells, especially those cells that have escaped from the main tumor mass^[8-10].

Neural stem cells (NSCs) administered intracranially possess extensive tropism for experimental glioma^[11,12]. This behavior of NSCs has been exploited as a tumor targeting strategy for glioma gene therapy^[11-19]. Recently, it has been

suggested that mesenchymal stem cells (MSCs) may represent an alternative source of NSCs for regeneration^[20,21]. In brain glioma models, intracranially implanted or intravenously injected MSCs can migrate away from the initial injection site towards tumor beds^[22-25]. The ability of stem cells of various lineages to migrate to gliomas have become attractive vehicles to improve therapeutic gene delivery to gliomas.

Although the migratory behavior of stem cells has now been extensively documented, little is known about the mechanisms underlying the glioma-induced tropism of stem cells. A better understanding of the interactions between tumor cells and stem cells would be of clinical interest in using stem cells as tumor targeting strategy for glioma gene therapy. In this review, we will discuss possible mechanisms of stem cells tropism for malignant gliomas.

2 Exogenous stem cells tropism for gliomas

The first report to demonstrate that NSCs exhibit tumor-homing capability was described by Aboody and colleagues^[11]. The authors showed that the immortalized murine NSC line C17.2 subsequently distributed themselves within and surrounded the tumor when implanted directly into glioma-bearing rodents. In addition, NSCs appeared to track infiltrative tumor cells escaping from the primary tumor mass into normal brain tissue. The authors also transplanted NSCs into the brain parenchyma, the contralateral hemisphere, and the ventricle system in order to assess their migratory potential. The NSCs were able to migrate

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towards, infiltrate and surround the primary tumor inoculation site, irrespective of the location of initial implantation. Another interesting feature in the same report, was that NSCs injected into the systemic circulation were also able to “home in” and infiltrate the primary tumor mass but were not identified within the surrounding normal brain parenchyma. This may suggest that tumor-homing ability of NSCs is specific and efficient. Taking advantage of the efficient tumor targeting capabilities, investigators have used genetically engineered NSCs to disseminating tumors. Genetically modified NSCs from different sources have been shown to exhibit the same gliomatropic effect in glioma-bearing models and effectively to reduce tumor bulk and prolong host survival^[13-19].

Although the tropism of stem cells for gliomas was first demonstrated by observing the behavior of NSCs, this capacity might not be limited to only stem cells of neuroectodermal origin or to CNS tumors. Nakamura *et al.* have shown that rat MSCs are capable of exhibiting tumor-tropic behavior comparable to that demonstrated by fetal NSCs^[24]. The authors showed that MSCs migrated toward glioma cells through the corpus callosum when inoculated into the contralateral hemisphere. Moreover, MSCs implanted directly into the tumor localized mainly at the border between tumor cells and normal brain parenchyma, and also infiltrated into the tumor bed. Recently, Nakamizo and colleagues showed that human MSCs specifically localized to human glioma intracranial xenografts in nude mice regardless of whether injected into the ipsilateral or contralateral carotid artery^[25]. In addition, these MSCs were able to migrate into glioma xenografts when injected into the contralateral cerebral hemisphere. Gene-modification of MSCs with therapeutic cytokines clearly prolonged the survival of tumor-bearing animals^[24,25].

Other stem cells tropism for gliomas also included haematopoietic progenitor cells. The recent report by Tabatabai *et al.* demonstrated that human CD34+ haematopoietic progenitor cells injected intravenously into nude mice with experimentally-induced glioma, can be traced within intracerebral gliomas, but not within normal brain^[26]. Further examination revealed no expression of glial or neuron marker but sustained expression of CD34+ on the progenitor cells that homed to glial tumor.

3 Endogenous progenitors tropism for gliomas

Glass and colleagues recently demonstrated that in a

murine experimental glioblastoma model, endogenous neural progenitors migrated from the subventricular zone toward the tumor and surrounded it^[27]. The authors used transgenic mice expressing enhanced green fluorescent protein under the control of the nestin promoter to identify endogenous neural precursor cells^[28,29] and showed that two weeks after inoculation of glioblastoma cells into the caudate-putamen of transgenic mice, nestin-GFP positive cells were highly abundant in the tumor-containing hemisphere compared with the contralateral side and accumulated around the tumor. Furthermore, nestin-GFP positive cells were associated with tumor cells that migrate away from the main tumor mass. The authors also stated that approximately 30% of nestin-GFP positive cells around the tumors were immunopositive for Ki-67, an antigen specifically present during cell division^[30]. In addition, approximately 35% of the nestin-GFP positive cells co-expressed Musashi, an RNA-binding protein that is restricted to precursor cells^[31], 35% co-expressed the chondroitin sulfate proteoglycan NG-2, a marker for glial precursors and neoplastic cells^[32], and 30% co-expressed PSA-NCAM or doublecortin (DCx), markers for migrating neuronal precursor cells^[33,34]. While the authors stated that sixty percent of the nestin-GFP positive cells co-expressed GFAP, they did not identify any nestin-GFP cells co-expressing S100 β , a marker for mature astrocytes^[35], or Calbindin, a neuronal marker^[36], suggesting that these cells were not terminally differentiated. The authors also demonstrated that endogenous neural precursor tropism for glioblastoma decreased with age of the recipient, and this correlated with increased tumor size and shorter survival times in aged mice.

4 Possible mechanisms responsible for tumor-homing

While several studies have investigated the potential of stem cells to act as vehicles for anti-glioma gene delivery, they did not identify the potential signals responsible for the tropism of stem cells for gliomas. The mechanisms are likely multifactorial. Factors released and expressed by the glioma cells, by the tumor stroma, by tumor-derived endothelium as well as the damaged surrounding normal brain itself all contributed to stem cells gliomatropism.

4.1 Chemokines Upregulation of chemokine synthesis by activated astrocytes and microglia is associated with neuroinflammatory response^[37,38]. The chemokine stromal cell-derived factor 1 α (SDF-1 α) released following CNS in-

jury (particularly by reactive astrocytes and endothelium) directs the migration of NSCs expressing CXCR4, the cognate receptor for SDF-1 α , through the brain parenchyma to the damaged area^[39]. The same binding partners have also been shown to play a role in directing the migration of neural progenitors in the developing brain^[40-43] and peripheral nervous system^[44].

It has been reported that high-grade gliomas secrete significant levels of SDF-1 α , and that the expression of this protein and the CXCR4 receptor correlated with the histological grade and invasive capacity of these tumors, as well as tumor cell survival^[45-47]. Expression of SDF-1 α by tumor-derived endothelium serve to attract the migration of NSCs^[48,49]. Recently, Ehtesam *et al.* demonstrated that SDF-1 α /CXCR4 interactions play a functional role in gliomatropic migration of NSCs^[50]. The authors showed that human fetal NSCs transplanted intratumorally in glioma-bearing mice, migrated away from the site of inoculation in proximity of islets of tumor cells that were disseminating into and through normal brain parenchyma. The authors also demonstrated expression of both A2B5 and GFAP within tumor-tropic NSCs along with an absence of differentiated morphology and negligible expression of the glutamate transporters EAATQ/EAAT2. In addition, the authors demonstrated that glioma-tracking NSCs with phenotypic expression profiles characteristic of astrocytic precursors, as well strong expression of CXCR4 and that the tumor-tropic capacity of these cells can be inhibited by neutralization of surface CXCR4. A more recent report also demonstrated that SDF-1 α /CXCR4 interactions appear to be essential for the gliomatropism of circulating adult haematopoietic progenitor cells^[26]. Most metastatic brain tumors are from cancers of the lung or breast. That the chemokine receptor CXCR4 has also found to be functionally expressed on metastatic breast cancer cells and its ligand SDF-1 α is present on brain endothelium could also provide the basis for the transmigration of circulating tumor cells through the blood-brain barrier^[51]. Indeed, inhibition of CXCR4 prevented breast cancer metastasis^[52].

Besides SDF-1 α , several chemokines have been described on glioma cells, including macrophage chemoattractant protein-1 (MCP-1/CCL2)^[53,54], interleukin-8 (IL-8/CXCL8)^[55], regulated on activation, normal T-cell expressed and secreted (RANTES/CCL5)^[56]. MCP-1 is known to be synthesized *in vivo* under neuroinflammatory circumstances, and it is important in the trafficking of leukocytes into the

brain^[57-59]. Recent studies have shown that chemokines such as MCP-1 play a role in the migration of progenitor cells toward sites of neuroinflammation^[60], but so far it is unknown whether the above chemokines mediate gliomatropism of progenitor cells.

4.2 Stem cell factor (SCF) In bone marrow, stem cell factor (SCF) is expressed on stromal cells as a membrane-anchored form and released by matrix metalloproteinase-9 (MMP-9), resulting in the activation of SCF/c-kit signaling in the progenitor cells^[61]. Recent studies demonstrated that various forms of brain injury induce neuronal expression of SCF, and that SCF mediates NSCs migration to the site of cerebral injury^[62]. Additionally, expression of SCF seems to be upregulated in gliomas in a grade-dependent manner^[63]. c-kit, a receptor tyrosine kinase for SCF ligand, is also expressed in neural stem cells^[62,64]. Accordingly, some researchers presumed that gliomas might use bone marrow cue to attract progenitor cells. Tabatabai *et al.* first demonstrated that SCF is involved in glioma-directed haematopoietic progenitor cells migration^[26]. The author also showed that SDF-1 α is the essential mediator of progenitor cells migration, and SDF-1 α attraction is enhanced by MMP-9-induced SCF cleavage.

4.3 Angiogenic cytokines Recent reports indicated that the recruitment and differentiation of neural precursors in the adult brain are linked to active angiogenesis^[65-67], which is also a pathologic hallmark of malignant gliomas^[68]. Angiogenic cytokines expressed by malignant gliomas are possible candidates for mediating the gliomatropism of progenitors.

Schmidt *et al.* recently demonstrated that upregulated vascular endothelial growth factor (VEGF) in brain tumors might serve as a signal for NSCs tropism to pathologic sites^[69]. The authors showed *in vitro* a highly significant correlation between the brain tumor-produced VEGF and the induction of NSCs attraction. Studies *in vivo* demonstrated that transplanted NSCs showed long range attraction and migration towards the site of VEGF infusion in the contralateral hemisphere. Additionally, the author also showed that hepatocyte growth factor (HGF), not placenta growth factor (PIGF), was able to stimulate NSCs migration *in vitro* in a dose-dependent manner. However, low doses of HGF by local intracerebral infusion were not able to induce a long-range attraction of transplanted NSCs *in vivo*. These data suggested that VEGF might additionally trigger other signals that are possibly relevant for allowing a di-

rected NSCs migration.

Similarly, Schichor *et al.* demonstrated that VEGF-A contributed to glioma-induced migration of human marrow stromal cells (hMSC)^[70]. The authors showed that VEGF-A, but not MCP-1, induced a concentration-dependent increase of hMSC migration. In addition, the chemokinesis-enhancing effect of glioma conditioned medium can be significantly reduced by addition of a VEGF-A neutralizing antibody. Nevertheless, glioma-cell-conditioned medium showed much stronger effects on hMSC migration than VEGF-A alone, thus indicating that additional cytokines might be involved as well. The same group later demonstrated that interleukin-8 (IL-8), transforming growth factor- β 1 (TGF- β 1) and neurotrophin-3 (NT-3) contributed to glioma-directed tropism of human MSCs, whereas several other neurocytokines did not seem to be involved^[71]. Contrary to their findings, Nakamizo *et al.* postulated that VEGF might not be the key mediators of the glioma tropism of human MSCs^[25]. These contradictory findings may be due to variations between donors, the isolation and expansion protocol and the lack of an MSC specific antibody.

Epidermal growth factor (EGF) and their receptor EGFR are thought to be important in the mediation of a variety of biological responses in gliomas via autocrine or paracrine mechanisms^[72]. Direct consequences of increased expression of a EGF/EGFR autocrine or paracrine loop in glioma cells include the enhanced motility of glioma cells^[73,74]. Moreover, EGFR has also been shown to regulate NSCs migration^[75]. Constitutive EGFR expression in NSCs enhanced downstream signaling via phospholipase γ C to facilitate stem cell migration. Therefore, relative EGF concentrations in tumor microenvironment could mediate NSCs migration toward the EGF source-location of brain tumor cells. In turn, EGFR-transfected stem cells could exhibit enhanced migratory response and therapeutic potential against brain tumors^[76].

4.4 Glioma-produced extracellular matrix (ECM) Although tumor-upregulated VEGF and SDF-1 α are serving as soluble chemotactic factors for inducing glioma tropism of NSCs, single invading glioma cells distant from the main tumor mass seem to be unable to establish a chemotactic gradient. Therefore, additional signals for the local guidance of NSCs may be present. Ziu *et al.* demonstrated that tumor-produced ECM was highly permissive for NSC migration^[77]. The authors also showed that laminin was the most permissive substrate for human NSCs migration, and

tenascin-C the strongest inducer of a directed human NSCs migration. In addition, a positive correlation between the degree of adhesion and migration of NSCs on different ECM compounds exists, as for glioma cells. Taken together, glioma modulated ECM may potentially function as an additional local guidance signal for neural stem cell migration.

5 Summary

The robust tropism of stem cells for intracranial gliomas makes them highly attractive as vehicles for the delivery of a wide variety of therapeutic gene products directly to tumor cells. However, despite encouraging results in preclinical models, many questions still need to be answered prior to clinical implementation of this strategy. The key among these is understanding the mechanisms underlying the tropism of stem cells for malignant gliomas. It can be assumed that stem cells home to neuroinflammatory sites in a similar, but somewhat distinct, manner to that of leucocytes via the utilization of selectins, chemokines, integrins and other adhesion molecules. As described above, many studies conclude that SDF-1 α /CXCR4 interactions play a role in stem cells tropism for gliomas. In addition, the affinity of stem cells for tumor specific endothelial integrins may contribute to tumor localization. Yet, there is still more work to be done to clarify many questions concerning the mechanisms of migration.

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干细胞向恶性胶质瘤的趋向性迁移

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摘要: 干细胞具有向恶性胶质瘤趋向性迁移的特性, 并可能成为恶性胶质瘤基因治疗的理想载体。然而, 对干细胞向胶质瘤迁移的机制仍知之甚少。胶质瘤细胞分泌的可溶性因子包括趋化因子或生长因子可以介导干细胞的胶质瘤趋向性。本文就干细胞的胶质瘤趋向性机制进行综述。

关键词: 干细胞; 趋向性; 胶质瘤