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OVERVIEW

The Roles of Hypoxia-Inducible Factors in Regulating Neural Stem Cells Migration to Glioma Stem Cells and Determinating Their Fates

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Abstract The mortality of patients with malignant gliomas remains high despite the advancement in multi-modal therapy including surgery, radio- and chemotherapy. Glioma stem cells (GSCs), sharing some characteristics with normal neural stem cells (NSCs), contribute to the cellular origin for primary gliomas and the recurrence of malignant gliomas after current conventional therapy. Accordingly, targeting GSCs proves to be a promising avenue of therapeutic intervention. The specific tropism of NSCs to GSCs provides a novel platform for targeted delivery of therapeutic agents. Tropism and mobilization of NSCs are enhanced by hypoxia through upregulating chemotactic cytokines and activating several signaling pathways. Moreover, hypoxia-inducible factors (HIFs) produced under hypoxic microenvironment of the stem cell niche play critical roles in the growth and stemness phenotypes regulation of both NSCs and GSCs. However, the definite cellular and molecular mechanisms of HIFs involvement in the process remain obscure. In this review, we focus on the pivotal roles of HIFs in migration of NSCs to GSCs and potential roles of HIFs in dictating the fates of migrated NSCs and targeted GSCs.

Keywords Hypoxia-inducible factors · Neural stem cells · Gliomas · Glioma stem cells · Migration

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Introduction

Malignant gliomas are the most common subtype of primary brain tumors, and glioblastoma multiforme (GBM) is uniformly fatal with a mean survival of 14 months after diagnosis despite aggressive surgery, radiation, and chemotherapies [1]. The discovery of a highly tumorigenic subpopulation of stem-like cells, termed glioma stem cells (GSCs), lents support to a new paradigm in cancer biology. GSCs are highly infiltrative and possess stem-like characteristics similar with normal neural stem cells (NSCs), including the expression of neural stem cell markers, the capacity for self-renewal and long-term proliferation, the formation of neurospheres and the ability to differentiate into multiple nervous system lineages [2–4]. However, GSCs exhibit significant distinctions from normal stem cells in chromosomal abnormalities, tumor formation and increased radio-/chemoresistance. GSCs contribute to the cellular origin for primary gliomas and the recurrence of malignant gliomas after current multi-modality therapies combining surgery, chemotherapy and radiotherapy, which suggests that targeting GSCs might offer a new avenue of therapeutic intervention [5–7].

Hypoxia is the essential characteristics of the solid tumors. Cellular responses to hypoxia are commonly regulated by the hypoxia-inducible factors (HIFs). Hypoxia has been identified to a critical aspect of the microenvironment in GSCs and generally signifies unfavorable clinical outcome [8–14]. The fraction of brain tumor stem

cells is increased under hypoxia in vitro [13, 15]. Moreover, hypoxia has been recognized as a major factor in resistance to radiation and chemotherapies because hypoxic cells prevent the radiation-induced DNA damage [16–19] and express multidrug resistance genes [20–23]. Consequently, hypoxia potentially provides therapeutic targets to sensitize glioma stem cells to cytotoxic therapies to improve glioma patient treatments [24–27].

Recent researches indicate that NSCs can specifically target malignant gliomas, which provides a novel platform for targeted delivery of therapeutic agents to gliomas with significant antitumor effects [28–32]. Chemotactic cytokines induced by hypoxia-inducible factors (HIFs) are responsible for directed migration of neural stem cells and other stem cells to hypoxic areas [33–37]. Hypoxia induced SDF-1/CXCR4, VEGF/VEGFR signaling pathways and Matrix metalloproteinases (MMPs) have been identified to mediate increased NSC tropism [38, 39]. The expression of such chemotactic cytokines are more upregulated in GSCs than their differentiated counterparts [7]. In this review, we focus on the pivotal roles of hypoxia-inducible factors (HIFs) in migration of NSCs to GSCs and the potential roles of HIFs in dictating the fates of migrated NSCs and targeted GSCs.

Hypoxia-Inducible Factors (HIFs)

Hypoxia occurs in tumors due to rapid cell proliferation and aberrant blood vessel formation. Cellular responses to hypoxia are commonly regulated by the hypoxia-inducible factor (HIF) family of transcriptional factors [40, 41]. HIFs consist of an alpha (HIF-α) and a beta (HIF-β) subunit. Under conditions of abundant oxygen (>8–10 %), HIF-α proteins are translated but rapidly degraded. As oxygen levels decrease below 8–10 %, HIF-α proteins become increasingly stabilized. Once stabilized, HIF-α proteins bind to constitutively expressed HIF-β subunits in the nucleus, thus binding to DNA and activating transcription of hundreds of downstream genes that modulate cell survival, motility, metabolism, and angiogenesis [40, 42]. The consequent stabilization of HIF proteins in hypoxic cancer cells is thought to promote tumor progression, largely by inducing the localized expression of specific target genes encoding vascular endothelial growth factor (VEGF) and proteins regulating cell motility and metastasis (CXCR4, E-cadherin) [43–47]. HIF-1α is universally expressed while HIF-2α shows a more restricted expression pattern. HIF-1α and HIF-2α share some target genes, including VEGF, whereas genes encoding glycolytic enzymes (PGK1, ALDA) are unique HIF-1α targets and those encoding TGF-α and cyclin D1 appear to be unique HIF-2α targets, at least in certain cell types [48].

NSC Tropism to Glioma Cells is Enhanced by HIFs

Transplantation of neural stem cells (NSCs) for therapeutic purposes was initially applied in Parkinson's disease [49, 50]. Since then, a number of in vitro and in vivo studies have proved the promising application of NSC transplantation in the treatments of human CNS diseases, particularly for Parkinson's and Huntington's disease, spinal cord injury, stroke and multiple sclerosis [51–56]. Until 2000, several researches demonstrated that NSCs possessed the unique migratory capacity and could efficiently cross the blood–brain barrier to target brain tumors far from the original transplanted site [57–59]. Subsequently, studies had proposed that NSCs might possess some natural abilities to suppress tumor growth and induce tumor cell apoptosis [28, 29]. These attractive findings soon ignited the conjectures of a novel therapeutic strategy to target these intractable brain tumors. As a result, the NSC inherent tropism towards brain tumors had led to the pursuit of applying NSC as a promising therapeutic tool and/or vehicle for tracking and suppression of malignant gliomas [32, 60–62].

Increasing evidences showed that stem cell migration was largely dependent on integrin binding to the extracellular matrix (ECM), various chemotactic cytokines and several involved signaling pathways. During this progress of migration, hypoxia has been identified to play a critical role in promoting tropism and mobilization of multiple stem cells, including NSCs (Fig. 1).

Several studies have found that hypoxic preconditioning increased stem cell mobilization. Exposure of mesenchymal stem cells to 1–3 % oxygen increased expression of the CXC chemokine receptor-4 (CXCR4) and stem cell migration rates [34, 35, 63–65]. Increased expression of CXCR4 after exposure of NSCs to hypoxia was also identified [38]. Ceradini et al. [66] and Chang et al. [67] found that CXCR4 positive stem/progenitor cells showed enhanced tropism to ischemic areas or tumor lesions, where stromal cell-derived factor (SDF-1) was induced by HIF-1 and overexpressed. Increasing data demonstrated that SDF-1/CXCR4 signaling induced by HIFs could be crucial for homing and migration of multiple stem cell types.

Chemokines induced by hypoxia, such as VEGF, EGF and several other factors, have also been identified to enhance NSC tropism. Zhao et al. [38] demonstrated that knockdown of HIF-1α in glioma cells blocked the hypoxia-induced migration of NSCs, which was due to decreased expression of SDF-1, VEGF and urokinase-type plasminogen activator (uPA) in glioma cells. Schmidt et al. [68] showed that tumor-upregulated VEGF was able to induce a long-range attraction of transplanted human NSCs toward brain tumors from distant sites. Data from our group showed that GSCs, compared to their differentiated cells, secreted much greater amounts of VEGF and bFGF [7].

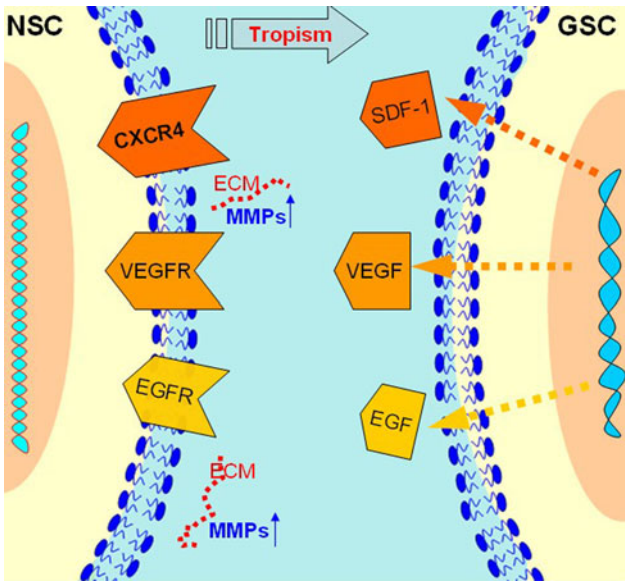

Fig. 1 Chemokines from GSC and activities of MMPs induced by HIFs enhance NSC tropism. Various chemotactic cytokines are overexpressed in hypoxia GSCs. The SDF-1/CXCR4, VEGF/VEGFR, and EGF/EGFR signaling pathways enhance NSC tropism. Whilst, MMPs upregulated by hypoxia promote NSC mobilization

These findings strongly suggest that GSCs potentially possess enhanced chemotaxis for NSC tropism compared with the differentiated cells, which had been further identified in our recent study (data unpublished).

The HIFs mediated NSCs tropism may involve activation of MMPs, VEGF, and some other molecular pathways. Activation of MMPs induced by hypoxia around injured tissues and tumors are identified to enhance NSC mobilization. Ingraham et al. [39] demonstrated that in 1 % O2, levels of HIF-1α were increased and adherence of NSCs to basement membrane-coated plates was reduced. Notably, a fivefold increase in MMP-9 mRNA was confirmed and specific inhibition of MMP-9 activity prevented the increase in proliferation and migration of NSCs. The increased MMP-9 expression and NSC migration were induced via activated Wnt/β-catenin signaling pathway. In line with this finding, several other studies showed that low O_2 affected cell proliferation and activated the canonical Wnt signaling pathway, the downstream effectors of which had a wide variety of transcriptional gene targets, including MMP-9 and VEGF [69–71]. Existent data suggested that upregulated expression of chemokines and activation of MMPs by injured tissues and tumors act as signals for attraction of NSCs in hypoxic circumstance [33, 38, 72]. HIFs played an essential and pivotal role in hypoxia-induced NSC mobilization, possibly via the involvement of their downstream genes including MMPs and VEGF. These provide a novel insight into the mechanisms responsible for NSC mobilization and may be of great help in the development of new clinical mobilizing agents.

Taken together, large numbers of studies have been exploring the tropism of NSCs especially during the progress of neural injuries and brain tumors. HIFs have been identified to play important roles in initiating and promoting the process. Nonetheless, the definite mechanisms remain to be elucidated.

Influences of HIFs on NSC Fates

Neural stem cells (NSCs) have been recognized as the progenitor cells of the nervous system possessing a self-renewing capacity to differentiate into neurons, astrocytes and oligodendrocytes in the mature nervous system. In the mammalian central nervous system, oxygen plays a critical role in regulating the growth and differentiation state of neural stem/progenitor cells [73–79] (Fig. 2). Commitment of NSCs toward specific phenotypes is strongly pre-conditioned by oxygen tension. Physiological hypoxia (2.0–5.0 %) enhances both NSC self-renewal and neurogenic abilities through HIF-1α [80–82], while atmospheric culture conditions (20 % O2) promotes NSC differentiation to astrocyte [82, 83]. In the brain, oxygen sensing is found to be integrated into normal signaling pathways controlling NSC proliferation and cell fate choice in their niche. Gustafsson et al. [84] showed that hypoxia blocked neuronal and myogenic differentiation in a Notch-dependent manner. The notch signaling pathway is a highly conserved cell signaling system present in most multicellular organisms. Hypoxia activated Notch-responsive promoters and increased expression of Notch direct downstream genes. The Notch intracellular domain (NICD) interacts with HIF-1α, thereby blocking terminal differentiation of neural precursors. Under increased oxygen concentrations, such interaction is abolished, allowing neural precursors to differentiate. This interaction between HIF-1α and Notch was also found in medulloblastoma stem cells in another study by Pistollato et al., in which they found that hypoxia, by maintaining Notch1 in its active form, maitained medulloblastoma stem cell viability and expansion [85]. Moreover, Mukherjee et al. [86] demonstrated that HIF-1α, being independent of HIF-β, interacted with NICD to promote development and survival of drosophila blood. These data indicate that HIFs may have a crucial influence on the development and survival of NSCs, and canonical notch pathway is largely involved in the process.

Survival and fate of transplanted NSCs are crucial in their applications for various therapeutic purposes, especially when NSCs are utilized as gene vectors migrating or grafted to the hypoxic microenvironment. Takeuchi et al. [87] showed the grafted NSCs, around the injured spinal cord, differentiated into neuronal and glial subpopulations at 21 days after transplantation. In another contusion injury model by Fujiwara et al. [88], transplanted NSCs were

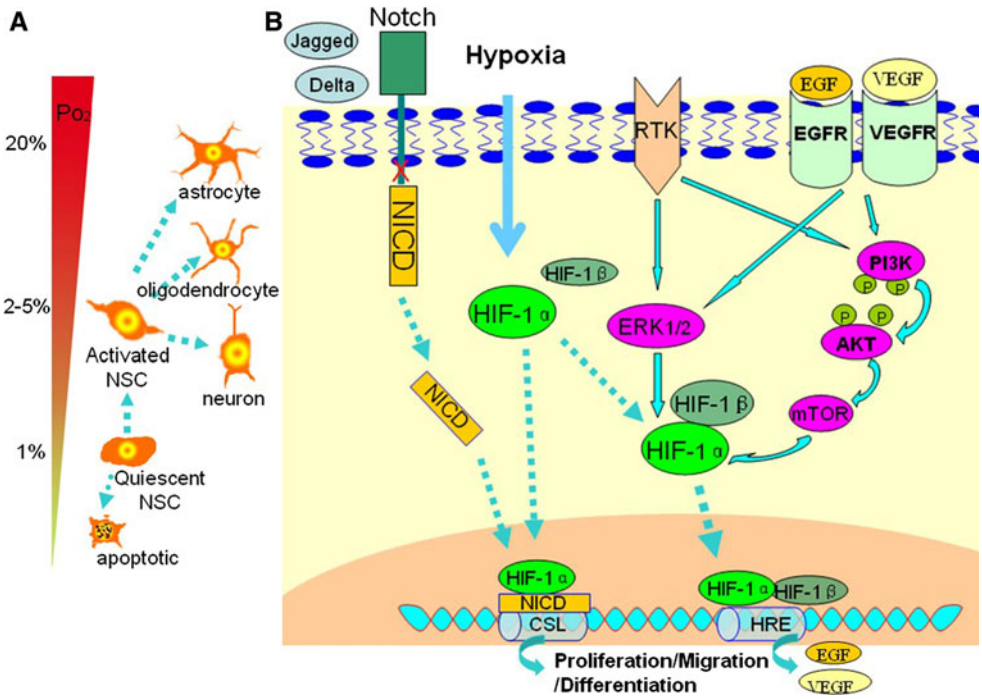

Fig. 2 The pivotal roles of HIFs in the proliferation, migration and differentiation of NSCs. **a** Changes of oxygen tension from normal atmospheric levels to severe hypoxia may regulate the proliferation, migration and differentiation of NSCs. **b** HIFs and interactions with Notch, ERK1/2, and PI3K/KT signaling pathways. *NICD* Notch intracellular domain, *CSL* DNA binding protein, also referred to as CBF-1, *RTK* receptor tyrosine kinase, *ERK1/2* extracellular signal-regulated kinase, *HRE* hypoxia-response element, *PI3K* phosphatidylinositol-3-kinase, *mTOR* mammalian target of rapamycin

shown to differentiate into neurons, astrocytes and oligodendrocytes, and survive at least for 56 days. However, the definite fate of transplanted NSCs in tumor microenvironment is still far from being clarified when applied in targeting the glioma cells for therapeutic purposes.

Regulation of GSC Phenotypes by HIFs

The hypothesis of GSCs implies that GSCs, which possess similar "stemness" as normal NSC but exhibit aberrant behavior, potentially derive from mutational NSCs or dedifferentiated mature cells [89–92]. Similar molecular mechanism and signaling pathways, being involved in hypoxic microenvironment, could be operative in both NSCs and GSCs. Notably, recent reports have identified that hypoxia is a critical aspect of the microenvironment in GSCs and generally signifies unfavorable clinical outcome [8, 10, 12, 13]. Hypoxia has been found to play a key role in the regulation of the GSC phenotypes through HIFs and subsequent induction of specific GSC signature genes. There are functional differences between HIF-1α and HIF-2α in the response of glioma cells or/and GSCs to hypoxia. HIF-1α is widely expressed in various tumors. However, the effect of HIF-1α deficiency on tumor growth has not been fully identified. Mendez et al. [27] reported that knock down of HIF-1α in human and murine glioma cells reduced their migration in vitro and their invasion in vivo. In addition, knock down of HIF-1α reduces the capability of glioma cells to form tumor spheres, which suggested that HIF-1α might play a role in the survival and self-renewal potential of GSCs. However, their data did not show any significant differences in overall survival or grafted tumor volume between animals transplanted with cells knocked down for HIF-1α expression and control cells. In another study, reduction of HIF-1α by siRNA in glioma cells grown in mouse flanks led to decreased glioma growth, which involved the reduction of VEGF and GLUT-1, two known downstream targets of HIF-1α [93]. Additionally, hypoxia was reported to promote the self-renewal capacity of CD133-positive human GSCs, which involved the activation of HIF-1α and inhibition of GSC differentiation [12]. There were also evidences showing that hypoxia led to an enrichment of stem cell markers, e.g., CD133 in glioma cells [11, 13, 14, 17].

Similarly, it was found that the forced expression of HIF-2α induced GSC marker expression and augmented the tumorigenic potential of the non-stem population, which implied a specific role of HIF-2α in promoting glioma tumorigenesis [9]. Knockdown of HIF-2α in neuroblastoma and GSCs led to reduced levels of VEGF and poorly vascularized, highly necrotic tumors [94]. HIF-2α

and multiple HIF-regulated genes were preferentially expressed in GSCs in comparison to non-stem tumor cells and normal neural progenitors [10]. Moreover, the stem cell regulator Oct4 as a specific HIF-2α target gene directly linked HIF2α to stem cell biology [95]. Similar result was reported by Heddleston et al. [9] that HIF-2α increased the percentage of CD133-positive cells in a sorted population of CD133-negative cells maintained even in serum containing medium and this HIF-2α expression also resulted in concomitant increases in the mRNA levels of the stem-cell associated genes c-Myc, Nanog and Oct.

Notably and interestingly, there are different opinions about the roles of HIF-1α and HIF-2α [96, 97]. Gordan et al. [98] demonstrated that HIF-2α enhanced the transcriptional activity of another stem cell related gene, c-Myc, whereas HIF-1α destabilized c-Myc complexes. Seidel et al. [14] showed that HIF-2α, but not HIF-1α knockdown, abrogated the hypoxia-dependent induction of the GSC phenotypes. Furthermore, HIF-2α induced a dramatic upregulation of a panel of genes for side population signature, while HIF-1α expression had no effect on the levels of tumor stem cell related genes.

In addition, hypoxia enhanced the expression of ATP-binding cassette transporters such as multidrug resistance-1 or ATP-binding cassette G2 (ABCG2) that conferred multidrug resistance on a variety of cancer cells including gliomas [8, 21, 99]. Together, these data linked HIFs to glioma invasion, angiogenesis and GSC biology, which underscore the promising approach of targeting HIFs in GSCs for glioma therapies.

Future Directions

Hypoxia-inducible factors (HIFs) may play an important role in the migration of NSCs to GSCs. Meanwhile, HIFs are highly involved in the growth, migration, self-renewal and differentiation process of both NSCs and GSCs. Since hypoxia represents a typical component of glioma microenvironment, it would be interesting to know how the induced HIFs in gliomas affect the migration of adjacent NSCs, and how the HIFs subunits differentially regulate the "stemness" phenotypes of both the migrated NSCs and the targeted GSCs, especially given the sophisticated signal pathways existent in GSC niche. Taking into account that GSCs might be derived from NSCs, it is illusive to predict the final fate of the NSCs that have migrated to the hypoxic tumor niche. Could the NSCs exert a repressive effect on the glioma cells and/or GSCs, or exactly the opposite, undergo aberrant changes and recruited into glioma propagating cells? And what roles do the HIFs have in the two-way regulation on the normal NSCs and aberrant GSCs in the in vivo hypoxic niche? Further work is needed to answer these questions.

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