

REVIEW ARTICLE

The role of hypoxia in stem cell regulation of the central nervous system: From embryonic development to adult proliferation

Gaifen Li^{1,2} | Jia Liu¹  | Yuying Guan^{1,2} | Xunming Ji^{1,2}

¹Laboratory of Brain Disorders, Ministry of Science and Technology, Collaborative Innovation Center for Brain Disorders, Beijing Institute of Brain Disorders, Capital Medical University, Beijing, China

²Department of Neurosurgery, Xuanwu Hospital, Capital Medical University, Beijing, China

Correspondence

Xunming Ji, Beijing Institute of Brain Disorders, Capital Medical University, 10 Xi Tou Tiao, You Anmen, Beijing 100069, China.

Email: robertjixm@hotmail.com

Funding information

Beijing Hundred Thousand and Ten Thousand Talent Project, Grant/Award Number: 2019A36; Beijing Municipal Health Commission, Grant/Award Number: 303-01-005-0019; National Key R&D Program of China, Grant/Award Number: 2016YFC1301502

Abstract

Hypoxia is involved in the regulation of various cell functions in the body, including the regulation of stem cells. The hypoxic microenvironment is indispensable from embryonic development to the regeneration and repair of adult cells. In addition to embryonic stem cells, which need to maintain their self-renewal properties and pluripotency in a hypoxic environment, adult stem cells, including neural stem cells (NSCs), also exist in a hypoxic microenvironment. The subventricular zone (SVZ) and hippocampal dentate gyrus (DG) are the main sites of adult neurogenesis in the brain. Hypoxia can promote the proliferation, migration, and maturation of NSCs in these regions. Also, because most neurons in the brain are non-regenerative, stem cell transplantation is considered as a promising strategy for treating central nervous system (CNS) diseases. Hypoxic treatment also increases the effectiveness of stem cell therapy. In this review, we firstly describe the role of hypoxia in different stem cells, such as embryonic stem cells, NSCs, and induced pluripotent stem cells, and discuss the role of hypoxia-treated stem cells in CNS diseases treatment. Furthermore, we highlight the role and mechanisms of hypoxia in regulating adult neurogenesis in the SVZ and DG and adult proliferation of other cells in the CNS.

KEYWORDS

dentate gyrus, hypoxia, neurogenesis, stem cell, subventricular zone

1 | INTRODUCTION

Oxygen is a fundamental element for all living organisms and provides energy by taking part in metabolism.¹ Hypoxia refers to oxygen levels lower than the normal value in the body or environment, which causes a series of different physiological and pathological reactions.² The brain is the most sensitive organ to oxygen fluctuation. In particular, severe hypoxia usually causes acute and chronic brain

damage; however, moderate hypoxia, such as levels used in intermittent hypoxia (IH) treatment, shows neuroprotective effects in various central nervous system (CNS) disease models.^{3,4} Therefore, targeting hypoxia may be a potential therapeutic strategy for neurological diseases.^{5,6} In this review, we focus on the roles and mechanisms of hypoxia in stem cells related to CNS, including embryonic stem cells (ESCs) and neuronal stem cells (NSCs), and also discuss the research progress of hypoxia in stem cell therapy of CNS diseases.

Gaifen Li and Jia Liu are contributed equally to this work.

This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

© 2021 The Authors. *CNS Neuroscience & Therapeutics* Published by John Wiley & Sons Ltd.

2 | HYPOXIA RESPONSE

The body can respond to oxygen fluctuations through a series of molecular mechanisms, of which hypoxia-inducing factors (HIFs) play a key role.⁷ HIF-1, composed of HIF-1 α subunit and HIF-1 β subunit, is the most important transcription factor in response to hypoxia in the brain. Under normoxic conditions, the HIF-1 α subunit can be hydroxylated by proline hydroxylase, after which it binds with Von Hippel–Lindau complex to be ubiquitinated and degraded through proteasomes. Under hypoxia conditions, however, HIF-1 α cannot be degraded, but combines with HIF-1 β and translocates to the nucleus, promoting the transcriptional activation of multiple downstream hypoxia-related genes, including vascular endothelial growth factor (VEGF), erythropoietin (EPO), glucose transporter 1, and more than 100 other genes.⁸

3 | HYPOXIA AND STEM CELLS

Stem cells possess self-renewal activities and multipotency, characteristics that tend to be maintained under hypoxic microenvironments.⁹ HIF signaling is a primary modulator for cellular metabolism in stem cells to maintain their undifferentiated status and pluripotent potential.¹⁰ In particular, stem cell niches usually exist in a hypoxic environment; for example, the oxygen level of the ESC niche is 2%–8%, and that of neural stem cells is 1%–8%.¹¹ Hypoxia also maintains stem cell pluripotency and improves survival.¹² In brief, hypoxia determines the fate of both embryonic and adult stem cells, as well as induced pluripotent stem cells (iPSCs) *in vitro*.¹³

3.1 | Hypoxia and ESCs

Physiological hypoxia plays an important role in embryonic development and is involved in angiogenesis and blood flow regulation neural development, among others.¹⁴ Therefore, hypoxia treatment is thought to be beneficial to the culture of ESCs. *In vitro* experiments have shown that a hypoxic environment promotes stem cell survival; for example, 4% O₂ maintains self-renewal characteristics and limits the spontaneous differentiation of human ESCs (hESCs).¹⁵ Furthermore, 2%–5% O₂ was shown to increase the total cell number approximately twofold compared with 20% O₂ in mouse ESC cultures.¹⁶ Hypoxia was also found to facilitate the differentiation of ESCs into nerve cells. Under physiological hypoxic conditions, mouse ESCs were induced to differentiate into neural progenitor cells (NPCs), which were similar to mouse brain-derived NSCs in terms of proliferation and self-renewal ability, gene expression profile, and pluripotency.¹⁷ In addition, hypoxia stimulation promoted ESCs to differentiate into nerve cells but did not change the cell fate; early passaged ESCs tended to give rise to neurons, whereas late-passaged ESCs tended to give rise to glial cells.¹⁸

Critical signaling molecules are involved in the regulation of ESCs under hypoxic conditions. Specifically, hypoxia was shown to

promote pluripotency of hESCs and maintain their self-renewal characters by promoting Notch activation.¹⁹ Hypoxia was also shown to regulate self-renewal of hESCs through HIF-2 α and glycolytic sensors C-terminal binding proteins.²⁰ Hypoxic preconditioning enhanced hESC neural differentiation and cell survival by upregulation of HIF-1 α and HIF-2 α signaling.²¹ In addition to HIF-mediated signaling, hypoxia also modulates ESCs via mitogen-activated protein kinase (MAPK)/extracellular regulated protein kinase signaling.²² Taken together, these findings suggest that hypoxia is necessary to maintain the pluripotency and self-renewal capacity of hESCs.

3.2 | Hypoxia and NSCs and NPCs

Similar to ESCs, oxygen concentration is also involved in the regulation of NSCs and NPCs. NSCs and NPCs can self-renew and generate terminally differentiated nerve cells that integrate into the neural circuitry and further contribute to the regulation of neurological function throughout life.²³ During early cortical development, the presence of HIF-1 α prevents NSCs from producing differentiated progeny.^{24,25} Furthermore, during embryonic neural development, the effects of hypoxia on NSCs are temporally regulated. Specifically, hypoxia inhibits NSC differentiation and maintains their undifferentiated state during early development, whereas it induces neural differentiation at later stages.²⁶ Recently, NSC-based treatment was shown to be a promising therapeutic strategy in hypoxic-ischemic brain injury, which is an important cause of morbidity and mortality in adults and newborns. The above data indicate that hypoxia promotes the differentiation and development of iPSCs, which may have a promising therapeutic outcome in CNS diseases.

Multiple signaling pathways are involved in the regulation of NSCs by hypoxia. Hypoxia was shown to increase the proliferation of NSCs by upregulating HIF-1 α expression and activating the Wnt/ β -catenin pathway.²⁷ Similarly, hypoxia-induced HIF-1 α expression prevented NSCs from premature neuronal differentiation by activating neural repressor Hes1, which is independent of Notch signaling.²⁸ Hypoxia also upregulated the expression of several HIF-1 α downstream proteins, including VEGF.²⁹ In addition, hypoxia promoted cell proliferation by increasing miR-21 expression in NSCs; an action possibly mediated by phosphatidylinositol 3-kinase (PI3K) signaling pathway activation.³⁰ Finally, hypoxic exposure was found to promote proliferation of NPCs via PI3K/protein kinase B (AKT)-dependent glycogen synthase kinase-3 β signaling.³¹

Hypoxia and ischemia triggered NPC proliferation by upregulating complex 1-chromobox7 through HIF-1 α activation.³² Ischemia and hypoxia by unilateral carotid occlusion also promoted migration and proliferation of NPCs through chemokine upregulation.³³ RNA-binding protein RBM3 was found to be highly upregulated in response to hypoxia, which in turn increased proliferation of primary NSCs.³⁴ In addition, gene set enrichment analysis identified the calcium-regulated transcription factor NFATc4, which is significantly upregulated in NSCs after hypoxia treatment, as a potential candidate in the regulation of hypoxic NSC functions.³⁵ Therefore,

hypoxia plays an important role in the development and differentiation of NSCs and NPCs and suggests that understanding the molecular mechanism of hypoxia-mediated behavioral changes in NSCs and NPCs is helpful to optimize stem cell therapies for neurological diseases.^{36,37}

3.3 | Hypoxia and iPSCs

Advances in human iPSC technology have resulted in the development of new drug candidates for many CNS diseases by capturing patient heterogeneity. Hypoxia may enhance iPSC generation and maintenance. Specifically, iPSC generation has been shown to be poor under normoxic conditions; however, under mildly hypoxic conditions (5% O₂), iPSC generation and reprogramming efficiency increased.³⁸ The pluripotency of iPSCs is a prerequisite for their differentiation and expansion, and hypoxic conditions help to maintain the pluripotency of iPSCs.³⁹ In addition, hypoxia was shown to promote iPSCs to differentiate into specific cell types, such as endothelial cells (ECs),^{40,41} neurons,^{42,43} and cardiomyocytes.⁴⁴ HIF-1 α signaling is critical for iPSC pluripotency and lineage differentiation.⁴⁵ In addition, FGFR1-induced activation of PI3K/AKT and MAPK signaling was also involved in mild hypoxia-mediated maintenance of iPSC pluripotency.⁴⁶

3.4 | Hypoxia and stem cell treatment

Due to the poor regeneration capacity of the nervous system, stem cell transplantation therapy is a promising strategy for CNS disease treatment.⁴⁷ Mesenchymal stromal cells (MSCs) are a group of cell types commonly used in stem cell therapy.^{48,49} These cells are distributed in various tissues, such as bone marrow, umbilical cord, nasal mucosa, and fat; furthermore, their pluripotency is largely regulated by hypoxia.⁵⁰ Hypoxia has regulatory effects on cell vitality and repair effects on cell function. MSCs cultured under hypoxic conditions upregulated several stem cell markers and promoted cell proliferation.^{51,52} Exosomes derived from hypoxia-treated MSCs promoted functional behavioral recovery in a spinal cord injury mouse model by shifting microglial polarization from the M1 to M2 phenotype.⁵³

Bone MSCs (BMSCs) are commonly used stem cells, as they have been shown to develop into neurons and glia *in vitro*. Hypoxic preconditioning of BMSCs enhanced generation of NPCs⁵⁴ and the secretion of bioactive factors.⁵⁵ Interestingly, a combination of hypoxia and modest inflammatory stimuli promoted the migration of BMSCs.⁵⁶ Mechanically, hypoxia preconditioning enhanced BMSC survival and reinforced their regenerative properties by upregulating HIF-1 α and various trophic/growth factors, including brain-derived neurotrophic factor (BDNF), VEGF, and EPO. Hypoxia also promoted the proliferation and migration of umbilical cord blood-derived human MSCs via the HIF-1 α /FASN/mTORC1 axis.⁵⁷ Hypoxia preconditioning enhanced BMSC survival after transplantation by

activating HIF-1 α in a spinal cord injury model. Transplantation of these hypoxia pretreated BMSCs enhanced neurogenesis and angiogenesis in cerebral ischemia rats.⁵⁸ In addition, hypoxic conditions were also shown to affect other types of stem cells, for example, the proliferation of MSCs in adipose tissue of livestock and their differentiation and transformation into pluripotent stem cells.⁵⁹ Furthermore, treatment with human amnion epithelial cells could alleviate hypoxic-ischemic injury in the perinatal brain.⁶⁰ Hypoxic preconditioning increased grafted-cell survival of NSCs and improved therapeutic effects of NSC transplantation in a hemorrhagic stroke mouse model.⁶¹ Finally, hypoxia-preconditioned olfactory mucosa MSCs were shown to inhibit the death of microglia after cerebral ischemia/reperfusion insult via HIF-1 α activation.⁶²

3.5 | Hypoxia and adult neurogenesis

Neural stem cells exist not only in the developing mammalian nervous system but also in the adult nervous system. Among them, the lateral ventricle subventricular zone (SVZ) and hippocampal dentate gyrus (DG) are recognized as the most concentrated regions of NSCs in the adult brain.⁶³ Under certain conditions, NSCs can differentiate into neurons to participate in the repair process of nerve function, which is called neurogenesis.⁶⁴ The biggest difference between the two regions is that DG NSCs cannot be transported over a long distance, whereas those of the SVZ can; therefore, SVZ NSCs are a better model for studying neural cell value-added migration and differentiation.⁶⁵ Similar to embryonic neurodevelopment, in adult mammals, moderate hypoxia can also promote neurogenesis both in the SVZ and DG.⁶⁶

3.6 | Hypoxia and SVZ neurogenesis

Hypoxia is involved in SVZ neurogenesis throughout life (Figure 1). In fact, most of the neuroblasts produced from SVZ NSCs migrate a long distance to the olfactory bulb where they differentiate into local neurons.⁶⁷ Hypoxia and hypoxic preconditioning were shown to enhance the regenerative capacity of neural progenitors in the perinatal SVZ region.^{68,69} Furthermore, perinatal asphyxia promoted cell proliferation and neurogenesis in the SVZ, delayed cell death and affected the neural circuits of the basal ganglia and hippocampus, although the mechanism remains to be elucidated.⁷⁰ Neonatal hypoxic-ischemic injury also promoted SVZ neurogenesis.⁷¹ IH enhanced expansion and differentiation of NPCs in the SVZ.⁷² Creating an endogenous hypoxic environment, such as during intense exercise, restored the normal cell cycle length and quiescent phase of stem cells and neuroblasts by promoting the proliferation of adult SVZ stem cells of mice.⁶³

At the molecular level, HIF-1 α signaling is necessary for the maintenance of NSCs and vascular stability in the SVZ. In particular, genetic inactivation of HIF-1 α results in gradual loss of NSCs in the adult SVZ.⁷³ As hypoxia has been shown to upregulate the expression of HIF-1 α and VEGF and to promote the regulation of cell

FIGURE 1 Hypoxia involves subventricular zone (SVZ) neurogenesis. Neural stem cell (NSC) in lateral ventricle (LV) SVZ could migrate a long distance to the olfactory bulb (OB) through rostral migratory stream (RMS). Hypoxia promotes SVZ neurogenesis in several stages, including proliferation, migration, and differentiation

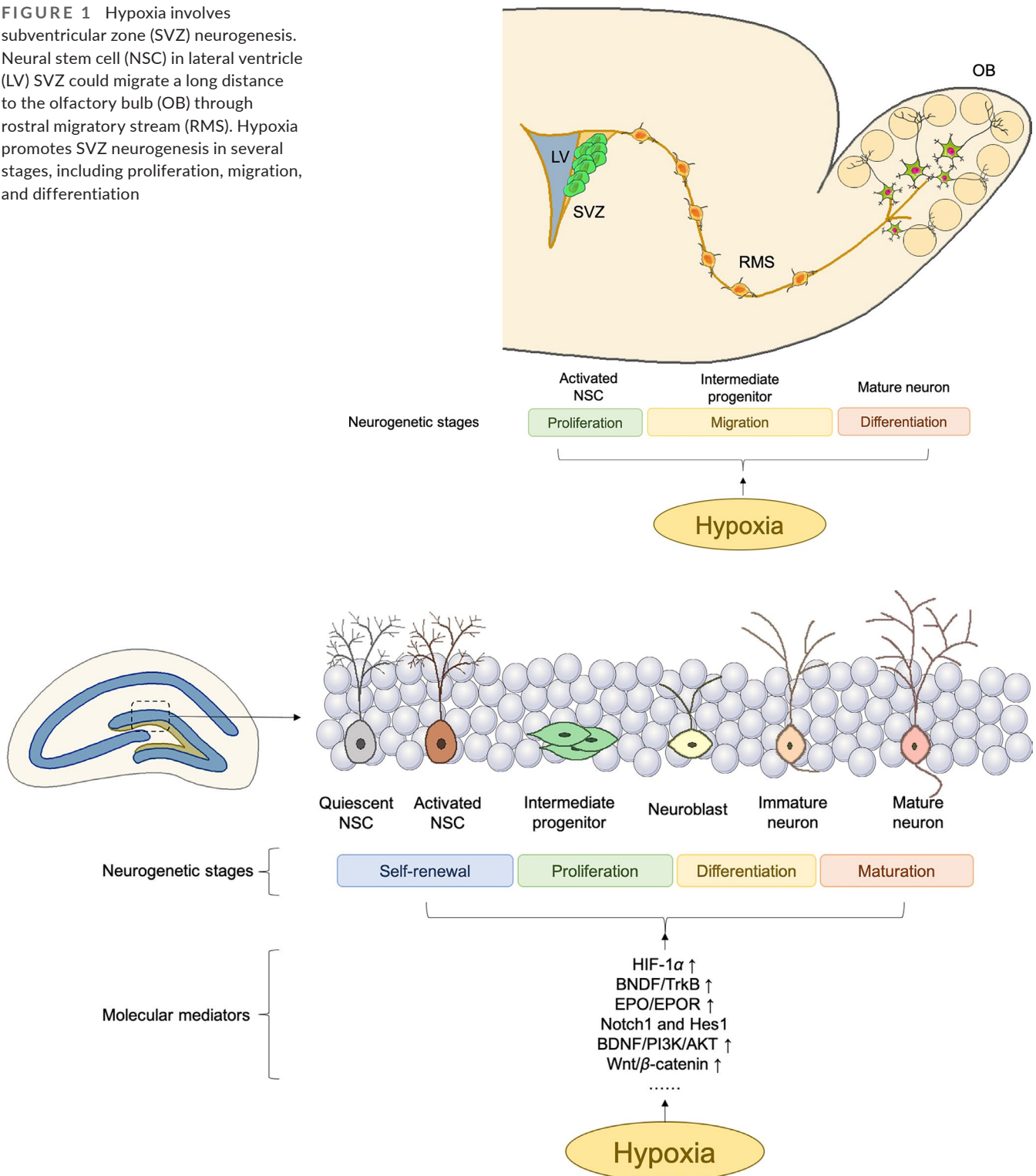


FIGURE 2 Hypoxia involves hippocampal neurogenesis. Hypoxia promotes hippocampal neurogenesis in various stages, including self-renewal, proliferation, differentiation, and maturation. Several mediators or pathways are involved in these processes, such as HIF-1 α , brain-derived neurotrophic factor (BDNF)/tryrosine receptor kinase B (TrkB), erythropoietin (EPO)/EPO receptor (EPOR), and so on. AKT, protein kinase B; PI3K, phosphatidylinositol 3-kinase

division in the SVZ,⁷⁴ it may also improve the prognosis of newborns after ischemia and hypoxia.⁷⁵ H19, a long noncoding RNA, was significantly upregulated during the hypoxic response of SVZ NSCs in a focal cerebral ischemia rat model.⁷⁶

3.7 | Hypoxia and hippocampal DG neurogenesis

The hippocampus is characterized by the presence of lifelong neurogenesis (Figure 2).^{77,78} Specifically, newborn neurons in the

hippocampus are mainly generated by dentate granule cells, which then integrate into the neural circuit and maintain hippocampal function.⁷⁹ Many adult newborn cells die during early differentiation in the hippocampus, with oxidative damage being a critical factor.⁸⁰ Similar to SVZ NSCs, hypoxia also determines the survival and proliferation of newborn cells derived from the DG.^{81,82}

Adult hippocampal neurogenesis is critical for cognitive function, especially during aging or after brain injury, such as ischemia.⁸³ Newborn hippocampal neurons contribute to memory performance by establishing functional synapses with target cells.⁸⁴ Hippocampal neurogenesis in DG improve cognitive and emotional remodeling in chronic unpredictable mild stress-induced rats.⁸⁵ A moderate hypoxic treatment was shown to enhance adult hippocampal neurogenesis both *in vitro* and *in vivo*.^{4,86} Furthermore, mild hypoxic conditions increased NSCs proliferation, promoted newborn neuron survival and migration, and contributed to the maturation of hippocampal neurons.^{81,87} Therefore, activation of neurogenesis by hypoxic treatment may be a potential therapeutical strategy for various CNS diseases.⁸⁸

Chronic hypoxia (10% O₂) treatment was shown to stimulate hippocampal neurogenesis by activating the Wnt/ β -catenin signaling pathway in an Alzheimer's disease mouse model.⁸⁹ Chronic intermittent hypobaric hypoxia also rescued spatial and object memory deficits by promoting hippocampal neurogenesis and synaptic plasticity via the Wnt/ β -catenin pathway in pilocarpine-treated epileptic rats.⁹⁰ IH, a type of mild hypoxia strategy, is thought to have neuroprotective effects in many types of CNS diseases.⁹¹ A study showed that IH rescued spatial learning and prevented memory impairment by inducing hippocampal neurogenesis.⁹² IH was also found to alleviate long-term memory impairment induced by ischemic injury by increasing hippocampal neurogenesis and synaptogenesis via BDNF/PI3K/AKT signaling.⁹² IH enhanced NSC proliferation, newborn neurons survival, and dendritic spine morphogenesis in the DG by activating Notch1, whereas Notch1 deficiency inhibited hippocampal neurogenesis induced by IH.⁸⁷ HIF-1 α -Notch signaling is also involved in increased neurogenesis in epilepsy rats.⁹³ Consecutive mild hypoxia exposure for 28 days was shown to contribute to hippocampal neurogenesis and rescue cognitive deficits by activating Notch1 and Hes1 signaling in epileptic rats.⁹⁴

Brain-derived neurotrophic factor is a neurotrophic factor involved in neurogenesis and neuroplasticity.^{95,96} Severe hypoxia was shown to inhibit synaptic plasticity, which contributed to cell death and impaired neurogenesis.⁹⁷ However, modest episodes of hypoxia were found to exert neuroprotective effects by triggering adaptation of cells.^{98,99} Enhancement of BDNF expression is regarded as a recognized protective mechanism of hypoxia-related treatment, such as IH. Specifically, IH improved cognitive function and depressed anxiety by enhancing BDNF expression in the hippocampus of mice.⁴ Furthermore, IH was found to produce antidepressant-like effects by targeting BDNF-tyrosine receptor kinase B signaling in rats.⁸¹ In addition, IH promoted serotonin-dependent BDNF synthesis and improved synaptic plasticity.¹⁰⁰ Post-ischemia IH intervention increased synaptogenesis via upregulation of BDNF in neurons⁹² and protected vulnerable neurons

from hypoxia/ischemia-induced injury.¹⁰¹ Meanwhile, enhancing BDNF secretion from brain ECs into the cerebral microvasculature has also been considered as a potential therapeutic target of IH treatment.¹⁰² IH training combined with physical exercise promoted the proliferation of endogenous neural progenitors and further enhanced BDNF expression in the adult hippocampus, eventually leading to an increased number of newborn neurons.¹⁰³ Taken together, these results suggest that moderate IH treatment exerts neuroprotective effects by promoting BDNF expression and secretion.

4 | HYPOXIA AND NON-NEURONAL CELL PROLIFERATION IN THE CNS

Hypoxic responses in the CNS are not limited to stem cell proliferation; other cells also undergo changes in this hypoxic environment,¹⁰⁴ such as vascular ECs¹⁰⁵ and glial cells,¹⁰⁶ among others. Hypoxia-induced changes can promote metabolism, which is conducive to energy production and waste excretion in the body.¹⁰⁷ At the same time, hypoxic conditions can provide energy for signal transmission, such as neurogenesis and stem cell proliferation, which are significant for CNS subordinate feedback loops that help to adjust the subordinate to initiate corresponding strategies through the integration of information; the CNS in turn sends signals to instruct the subordinate to initiate the corresponding changes.¹⁰⁸ Glial cells are significant components of the CNS and, as they do not conduct electrical impulses like neurons, have long been considered to play a supporting role. It is only in recent years that scientists have begun to realize the regulatory role of glial cells in the brain.¹⁰⁹ In the following sections, we discuss the effects of hypoxia on glial cells and ECs from the perspective of cell proliferation.

4.1 | Hypoxia and astrocytes

Astrocytes are the most widely distributed type of cells in the mammalian brain and are also the largest type of glial cells.¹¹⁰ They are star-shaped with many long and branched protrusions from the cell body, which stretch and fill the space between neuronal cell bodies and their projections, helping to support and separate neurons.¹¹¹ In particular, because astrocytes are involved in the structural and functional interface of cerebral circulation and neuronal networks, they play an important role in the resistance to hypoxia-induced brain damage.¹¹²

Hypoxia can stimulate astrocytes to activate and proliferate to help maintain neuronal networks and cerebral microcirculation.¹¹³ Astrocytes are able to regulate cerebral blood flow to maintain constant PO₂; furthermore, local astrocytes are also involved in the protective effect of hypoxia-induced ischemic nerve injury.¹¹² Hypoxia can induce the proliferation of astrocytes via various pathways, such as HIF¹¹⁴ and Notch.¹¹⁵ Hypoxia-induced astrocyte proliferation is involved in the formation of glial scarring following ischemic hypoxic brain injury.^{116,117} Hypoxic preconditioning can upregulate glucose transporter levels and activity in astrocytes during acute hypoxia,

increasing glucose uptake and promoting cell glycolysis and lactic acid production, which provide energy for neuronal activity.¹¹⁸⁻¹²⁰

4.2 | Hypoxia and microglia

Microglia are considered to be the largest population of local immune cells in the CNS and are involved in the removal of damaged neurons, plaques, and infectious substances.^{121,122} However, microglia play a “double-edged sword” role in CNS diseases, as studies have shown that abnormal microglial activation is involved in the pathogenesis of neurodegenerative diseases, such as Parkinson's disease, multiple sclerosis, and Alzheimer's disease.¹²³⁻¹²⁵

Different degrees of hypoxic treatment have different effects on residential microglia or repopulated microglia; the underlying mechanisms remain obscure. In general, mild and short-term hypoxic stimulation activates resident microglia first,¹²⁶⁻¹²⁸ whereas stronger continuous hypoxia induces microglia proliferation. Microglia are considered to be the final product of neural differentiation, a special support cell that is very different from neurons, whereas recent studies suggested that some glial cells may act as primary progenitors or NSCs.¹²⁹ These glial cells could differentiate and proliferate under hypoxia stimulation and exert neuroprotective effects.^{104,130} Specifically, hypoxia treatment produced mildly stressed microglia, which activated a feedback loop to regulate the increase in antiinflammatory factors, thus exerting a protective effect. Therefore, hypoxia treatment not only causes mild stress in microglia to modulate inflammatory responses but also stimulates the differentiation and proliferation of certain microglia to promote CNS recovery following an insult.

4.3 | Hypoxia and oligodendrocytes

Oligodendrocytes, which are smaller than astrocytes, are widely distributed in the CNS. Their main function is to surround axons to form

an insulating myelin structure and to further assist in the efficient transmission of bioelectrical signals.¹³¹

Oligodendrocyte progenitor cells (OPCs) are the main proliferative cells in the adult brain, which differentiate into myelinated oligodendrocytes during the CNS development.¹³² When the nervous system is damaged, especially myelin-related damage, OPCs differentiate and proliferate to aide in repair.^{133,134} Hypoxia and HIF signaling play an important role in stimulating OPCs differentiation.¹³⁵ HIF signaling activated-patient-derived iPSCs transplanted into the brain during the subacute phase of white matter stroke induced the proliferation and remyelination of endogenous oligodendrocyte precursors and promoted axonal budding and, thus, cognitive recovery effects.¹³⁶ HIF-1 α -induced oligodendrocyte lineage gene-1 expression promotes the growth of oligodendrocytes and triggers the repair of hypoxic-induced neuronal myelin damage.¹³⁷

4.4 | Hypoxia and vascular ECs

Vascular proliferation refers to the formation of new blood vessels by sprouting or intussusception from preexisting blood vessels through the proliferation and migration of ECs.¹³⁸ This process is critical for the transportation of oxygen and nutrients to cells through the blood, which in turn promotes tissue regeneration, development, and repair.¹³⁹ Recent evidence suggests that there may be an interaction or dependence between stroke-induced neurogenesis and angiogenesis. Ischemic stroke promotes neurogenesis through growth factors such as VEGF and improves the recovery of neurological function after stroke.¹⁴⁰ VEGF increases the proliferation of NSCs through the VEGF receptor 2 signaling pathway, promotes the migration of new cells, actively participates in the initial stage of neurogenesis, and reduces cognitive impairment after epilepsy.¹⁴¹ Vascular ECs play a significant role in regulating blood pressure and the balance of coagulation and anticoagulation, so as to maintain the normal flow of blood and the long-term patency of

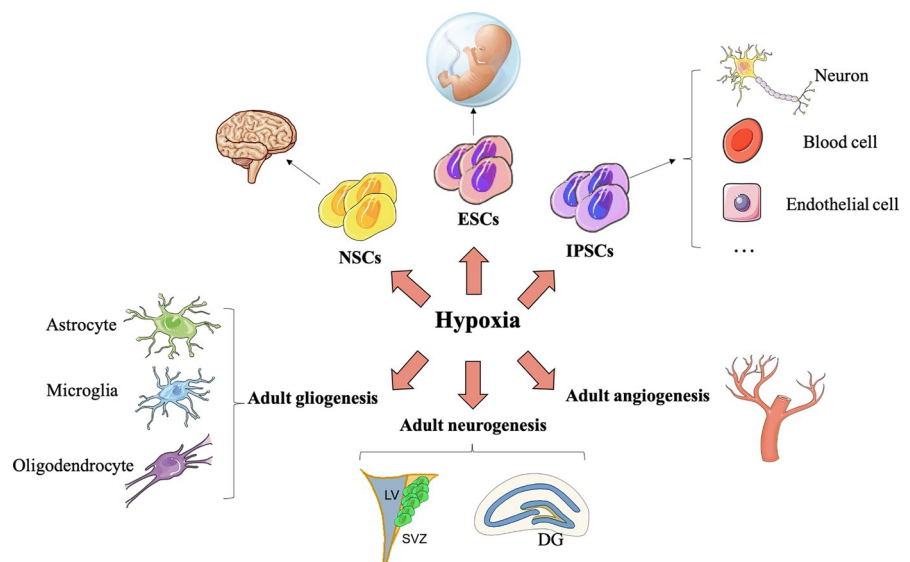


FIGURE 3 Hypoxia promotes stem cell proliferation, differentiation, and survival. Hypoxia promotes the pluripotency, proliferation, and directed differentiation of embryonic stem cells (ESCs) and neural stem cells (NSCs) and helps induced pluripotent stem cells (iPSCs) to develop into different types of cells in vitro. Hypoxia is also involved in adult neurogenesis, angiogenesis, and gliogenesis. DG, dentate gyrus; LV, lateral ventricle; SVZ, subventricular zone

blood vessels.¹⁴² VEGF is highly specific to vascular ECs and has important biological functions such as promoting the proliferation of ECs. VEGF is a downstream gene of HIF, and its expression is upregulated by hypoxic stimulation.¹⁴³ In the developing brain, neurons expressing VEGF-A are closely linked to blood vessels, and miR-9 directly targets the transcription factors TLX and ONECUTs to regulate VEGF expression. Due to the dual role of miR-9 in the proliferation and angiogenesis of neural stem cells, the regulation of VEGF expression by miR-9 is of great research significance for the treatment of stem cell regeneration.¹⁴⁴ Neurovascular unit (NVU) is a special cerebrovascular structure composed of ECs, neurons, pericytes, glial cells, and other cells; it plays an important role in maintaining brain function.¹⁴⁵ At present, there are few studies on the relationship between hypoxia and NVU; in-depth and systematic researches on this field are of great significance for us to understand the role of hypoxia-induced neurogenesis and angiogenesis in treatment of CNS diseases.

5 | PERSPECTIVES AND CONCLUSION

Hypoxia plays a significant role in the construction of the microenvironment and differentiation of NSCs and in the protection of neurons after CNS injury. NSCs have the characteristics of self-renewal and the ability to differentiate into multiple cells and, as such, have broad application prospects in cell transplantation therapy.¹⁴⁶ Hypoxia was shown to enhance the directional differentiation of stem cells. Furthermore, hypoxia promoted ion human iPSCs to differentiate into NSCs by regulating the Wnt/ β -catenin pathway. Together, these findings have important implications for potential therapeutic strategies for CNS diseases.¹⁴⁷ At present, NSC transplantation is a hot topic in the treatment of stroke,¹⁴⁸ spinal cord injury,¹⁴⁹ traumatic brain injury,¹⁵⁰ and other CNS diseases. Indeed, NSCs were shown to induce the release of Mir-133b in BMSCs to promote the survival of neurons, thus further improving the therapeutic effect of NSC transplantation on cardiac arrest-induced brain injury.¹⁵¹ In recent years, hypoxia has been proven to induce stem cell differentiation, which indicates that hypoxia combined with stem cell therapy is not only a therapeutic target for ischemic stroke but also shows great potential for multiple therapeutic strategies in other CNS diseases treatment. However, further studies are needed to understand the molecular mechanisms of hypoxia in the treatment of CNS diseases.¹⁵²

In addition to CNS diseases, hypoxia combined with stem cell therapy can be applied to a variety of other diseases. Hypoxia promoted human iPSCs to differentiate into neural crest cells, which produced functional EPO and induced hematopoietic progenitor cells differentiate into erythrocytes, thus exerting therapeutic effects in renal and nonrenal anemia.¹⁵³ In addition, hypoxia may have a role in delaying senescence, and a previous study showed that the life span of mammalian primary cells increased under hypoxia conditions.¹⁵⁴ It has also been shown that hypoxia can induce MSCs to

differentiate into tendon, which indicates that hypoxia combined with stem cell therapy could also be applicable to tendon injury intervention.¹⁵⁵ Taken together, the results indicate that hypoxic treatment combined with stem cell therapy can be applied to combat anemia, aging, tendon injury, and so on. However, the molecular mechanisms associated with this combined therapeutic approach are still unclear, which limits the application of these therapies.

In conclusion, hypoxia can induce many types of stem cells to proliferate, differentiate, and develop into specific cell types, such as neurons. Although its specific molecular mechanisms are not entirely clear yet, hypoxic treatment has great therapeutic promise for the treatment of CNS diseases. Therefore, it is important to further investigate the molecular mechanisms of hypoxia-induced stem cell maintenance and optimize and promote the use of hypoxia in stem cell therapy associated with CNS diseases (Figure 3).

ACKNOWLEDGEMENTS

This review was supported by the Beijing Hundred Thousand and Ten Thousand Talent Project (grant number: 2019A36), the National Key R&D Program of China (grant number: 2016YFC1301502), and the Beijing Municipal Health Commission (grant number: 303-01-005-0019).

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

Data sharing does not apply in this article because no new data were created or analyzed in this study.

ORCID

Jia Liu  <https://orcid.org/0000-0001-6711-3841>

REFERENCES

1. Lunt SY, Vander Heiden MG. Aerobic glycolysis: meeting the metabolic requirements of cell proliferation. *Annu Rev Cell Dev Biol.* 2011;27:441-464. <https://doi.org/10.1146/annurev-cellbio-092910-154237>
2. Fajersztajn L, Veras MM. Hypoxia: from placental development to fetal programming. *Birth Defects Res.* 2017;109(17):1377-1385. <https://doi.org/10.1002/bdr2.1142>
3. Carissimi A, Martinez D, Kim LJ, et al. Intermittent hypoxia, brain glyoxalase-1 and glutathione reductase-1, and anxiety-like behavior in mice. *Braz J Psychiatry.* 2018;40(4):376-381. <https://doi.org/10.1590/1516-4446-2017-2310>
4. Meng SX, Wang B, Li WT. Intermittent hypoxia improves cognition and reduces anxiety-related behavior in APP/PS1 mice. *Brain Behav.* 2020;10(2):e01513. <https://doi.org/10.1002/brb3.1513>
5. Corcoran A, O'Connor JJ. Hypoxia-inducible factor signalling mechanisms in the central nervous system. *Acta Physiol (Oxf).* 2013;208(4):298-310. <https://doi.org/10.1111/apha.12117>
6. Baillieux S, Chacaroun S, Doutreleau S, Detante O, Pepin JL, Verges S. Hypoxic conditioning and the central nervous system: a new therapeutic opportunity for brain and spinal cord injuries? *Exp Biol Med (Maywood).* 2017;242(11):1198-1206. <https://doi.org/10.1177/1535370217712691>

7. Choudhry H, Harris AL. Advances in hypoxia-inducible factor biology. *Cell Metab*. 2018;27(2):281-298. <https://doi.org/10.1016/j.cmet.2017.10.005>
8. Greer SN, Metcalf JL, Wang Y, Ohh M. The updated biology of hypoxia-inducible factor. *EMBO J*. 2012;31(11):2448-2460. <https://doi.org/10.1038/emboj.2012.125>
9. Semenza GL. Dynamic regulation of stem cell specification and maintenance by hypoxia-inducible factors. *Mol Aspects Med*. 2016;47-48:15-23. <https://doi.org/10.1016/j.mam.2015.09.004>
10. Mohyeldin A, Garzon-Muvdi T, Quinones-Hinojosa A. Oxygen in stem cell biology: a critical component of the stem cell niche. *Cell Stem Cell*. 2010;7(2):150-161. <https://doi.org/10.1016/j.stem.2010.07.007>
11. Huang X, Trinh T, Aljoufi A, Broxmeyer HE. Hypoxia signaling pathway in stem cell regulation: good and evil. *Curr Stem Cell Rep*. 2018;4(2):149-157. <https://doi.org/10.1007/s40778-018-0127-7>
12. Vieira HL, Alves PM, Vercelli A. Modulation of neuronal stem cell differentiation by hypoxia and reactive oxygen species. *Prog Neurobiol*. 2011;93(3):444-455. <https://doi.org/10.1016/j.pneurobio.2011.01.007>
13. Singh RP, Franke K, Wielockx B. Hypoxia-mediated regulation of stem cell fate. *High Alt Med Biol*. 2012;13(3):162-168. <https://doi.org/10.1089/ham.2012.1043>
14. Dunwoodie SL. The role of hypoxia in development of the Mammalian embryo. *Dev Cell*. 2009;17(6):755-773. <https://doi.org/10.1016/j.devcel.2009.11.008>
15. Ezashi T, Das P, Roberts RM. Low O₂ tensions and the prevention of differentiation of hES cells. *Proc Natl Acad Sci USA*. 2005;102(13):4783-4788. <https://doi.org/10.1073/pnas.0501283102>
16. Rodrigues CA, Diogo MM, da Silva CL, Cabral JM. Hypoxia enhances proliferation of mouse embryonic stem cell-derived neural stem cells. *Biotechnol Bioeng*. 2010;106(2):260-270. <https://doi.org/10.1002/bit.22648>
17. Cheng L, Hu W, Qiu B, et al. Generation of neural progenitor cells by chemical cocktails and hypoxia. *Cell Res*. 2014;24(6):665-679. <https://doi.org/10.1038/cr.2014.32>
18. Lukmanto D, Khanh VC, Shirota S, Kato T, Takasaki MM, Ohneda O. Dynamic changes of mouse embryonic stem cell-derived neural stem cells under in vitro prolonged Culture and Hypoxic Conditions. *Stem Cells Dev*. 2019;28(21):1434-1450. <https://doi.org/10.1089/scd.2019.0101>
19. Prasad SM, Czepiel M, Cetinkaya C, et al. Continuous hypoxic culturing maintains activation of Notch and allows long-term propagation of human embryonic stem cells without spontaneous differentiation. *Cell Prolif*. 2009;42(1):63-74. <https://doi.org/10.1111/j.1365-2184.2008.00571.x>
20. Arthur SA, Blydes JP, Houghton FD. Glycolysis regulates human embryonic stem cell self-renewal under hypoxia through HIF-2alpha and the glycolytic sensors CTBPs. *Stem Cell Reports*. 2019;12(4):728-742. <https://doi.org/10.1016/j.stemcr.2019.02.005>
21. Francis KR, Wei L. Human embryonic stem cell neural differentiation and enhanced cell survival promoted by hypoxic preconditioning. *Cell Death Dis*. 2010;1:e22. <https://doi.org/10.1038/cddis.2009.22>
22. Kucera J, Netusilova J, Sladeczek S, et al. Hypoxia downregulates MAPK/ERK but Not STAT3 signaling in ROS-Dependent and HIF-1-Independent manners in mouse embryonic stem cells. *Oxid Med Cell Longev*. 2017;2017:4386947. <https://doi.org/10.1155/2017/4386947>
23. Bobkova NV, Poltavtseva RA, Leonov SV, Sukhikh GT. Neuroregeneration: regulation in neurodegenerative diseases and aging. *Biochemistry (Mosc)*. 2020;85(Suppl 1):S108-S130. <https://doi.org/10.1134/S0006297920140060>
24. Lange C, Turrero Garcia M, Decimo I, et al. Relief of hypoxia by angiogenesis promotes neural stem cell differentiation by targeting glycolysis. *EMBO J*. 2016;35(9):924-941. <https://doi.org/10.15252/emj.201592372>
25. Morante-Redolat JM, Farinas I. Fetal neurogenesis: breathe HIF you can. *EMBO J*. 2016;35(9):901-903. <https://doi.org/10.15252/emj.201694238>
26. Binh NH, Aoki H, Takamatsu M, et al. Time-sensitive effects of hypoxia on differentiation of neural stem cells derived from mouse embryonic stem cells in vitro. *Neural Res*. 2014;36(9):804-813. <https://doi.org/10.1179/1743132814Y.0000000338>
27. Qi C, Zhang J, Chen X, et al. Hypoxia stimulates neural stem cell proliferation by increasing HIF1alpha expression and activating Wnt/beta-catenin signaling. *Cell Mol Biol (Noisy-le-grand)*. 2017;63(7):12-19. <https://doi.org/10.14715/cmb/2017.63.7.2>
28. Vecera J, Prochazkova J, Sumberova V, et al. Hypoxia/Hif1alpha prevents premature neuronal differentiation of neural stem cells through the activation of Hes1. *Stem Cell Res*. 2020;45:101770. <https://doi.org/10.1016/j.scr.2020.101770>
29. Lee HL, Lee HY, Yun Y, et al. Hypoxia-specific, VEGF-expressing neural stem cell therapy for safe and effective treatment of neuropathic pain. *J Control Release*. 2016;226:21-34. <https://doi.org/10.1016/j.jconrel.2016.01.047>
30. Chen R, Liu Y, Su Q, et al. Hypoxia stimulates proliferation of rat neural stem/progenitor cells by regulating mir-21: an in vitro study. *Neurosci Lett*. 2017;661:71-76. <https://doi.org/10.1016/j.neulet.2017.09.037>
31. Kisoh K, Hayashi H, Arai M, Orita M, Yuan B, Takagi N. Possible involvement of PI3-K/Akt-Dependent GSK-3beta signaling in proliferation of neural progenitor cells after hypoxic exposure. *Mol Neurobiol*. 2019;56(3):1946-1956. <https://doi.org/10.1007/s12035-018-1216-4>
32. Chiu HY, Lee HT, Lee KH, Zhao Y, Hsu CY, Shyu WC. Mechanisms of ischaemic neural progenitor proliferation: a regulatory role of the HIF-1alpha-CBX7 pathway. *Neuropathol Appl Neurobiol*. 2020;46(4):391-405. <https://doi.org/10.1111/nan.12585>
33. Wang F, Baba N, Shen Y, et al. CCL11 promotes migration and proliferation of mouse neural progenitor cells. *Stem Cell Res Ther*. 2017;8(1):26. <https://doi.org/10.1186/s13287-017-0474-9>
34. Yan J, Goerne T, Zelmer A, et al. The RNA-binding protein RBM3 promotes neural stem cell (NSC) proliferation under hypoxia. *Front Cell Dev Biol*. 2019;7:288. <https://doi.org/10.3389/fcell.2019.00288>
35. Moreno M, Fernandez V, Monllau JM, Borrell V, Lerin C, de la Iglesia N. Transcriptional profiling of hypoxic neural stem cells identifies calcineurin-NFATc4 signaling as a major regulator of neural stem cell biology. *Stem Cell Reports*. 2015;5(2):157-165. <https://doi.org/10.1016/j.stemcr.2015.06.008>
36. Shi Z, Wei Z, Li J, et al. Identification and verification of candidate genes regulating neural stem cells behavior under hypoxia. *Cell Physiol Biochem*. 2018;47(1):212-222. <https://doi.org/10.1159/000489799>
37. Liu J, Gu Y, Guo M, Ji X. Neuroprotective effects and mechanisms of ischemic/hypoxic preconditioning on neurological diseases. *CNS Neurosci Ther*. 2021;27(8):869-882. <https://doi.org/10.1111/cns.13642>
38. Yoshida Y, Takahashi K, Okita K, Ichisaka T, Yamanaka S. Hypoxia enhances the generation of induced pluripotent stem cells. *Cell Stem Cell*. 2009;5(3):237-241. <https://doi.org/10.1016/j.stem.2009.08.001>
39. Infantes EC, Prados AB, Contreras ID, et al. Nitric oxide and hypoxia response in pluripotent stem cells. *Redox Biol*. 2015;5:417-418. <https://doi.org/10.1016/j.redox.2015.09.024>
40. Podkalicka P, Stepniewski J, Mucha O, Kachamakova-Trojanowska N, Dulak J, Loboda A. Hypoxia as a driving force of pluripotent stem cell reprogramming and differentiation to endothelial cells.

- Biomolecules*. 2020;10(12):1614. <https://doi.org/10.3390/biom10121614>
41. Hou L, Collier J, Natu V, Hastie TJ, Huang NF. Combinatorial extracellular matrix microenvironments promote survival and phenotype of human induced pluripotent stem cell-derived endothelial cells in hypoxia. *Acta Biomater*. 2016;44:188-199. <https://doi.org/10.1016/j.actbio.2016.08.003>
 42. Yasui T, Nakashima K. Hypoxia epigenetically bestows astrocytic differentiation potential on human pluripotent cell-derived neural stem/precursor cells. *Nihon Yakurigaku Zasshi*. 2019;153(2):54-60. <https://doi.org/10.1254/fpj.153.54>
 43. Wei ZZ, Lee JH, Zhang Y, et al. Intracranial transplantation of hypoxia-preconditioned iPSC-derived neural progenitor cells alleviates neuropsychiatric defects after traumatic brain injury in Juvenile rats. *Cell Transplant*. 2016;25(5):797-809. <https://doi.org/10.3727/096368916X690403>
 44. Correia C, Serra M, Espinha N, et al. Combining hypoxia and bioreactor hydrodynamics boosts induced pluripotent stem cell differentiation towards cardiomyocytes. *Stem Cell Rev Rep*. 2014;10(6):786-801. <https://doi.org/10.1007/s12015-014-9533-0>
 45. Cui P, Zhang P, Zhang Y, et al. HIF-1 α /Act16a/H3K9ac axis is critical for pluripotency and lineage differentiation of human induced pluripotent stem cells. *FASEB J*. 2020;34(4):5740-5753. <https://doi.org/10.1096/fj.201902829RR>
 46. Fojtik P, Beckerova D, Holomkova K, Senfluk M, Rotrekl V. Both hypoxia-inducible factor 1 and MAPK signaling pathway attenuate PI3K/AKT via suppression of reactive oxygen species in human pluripotent stem cells. *Front Cell Dev Biol*. 2020;8:607444. <https://doi.org/10.3389/fcell.2020.607444>
 47. Nair S, Rocha-Ferreira E, Fleiss B, et al. Neuroprotection offered by mesenchymal stem cells in perinatal brain injury: role of mitochondria, inflammation, and reactive oxygen species. *J Neurochem*. 2020;158(1):59-73. <https://doi.org/10.1111/jnc.15267>
 48. Sun Z, Gu L, Wu K, et al. VX-765 enhances autophagy of human umbilical cord mesenchymal stem cells against stroke-induced apoptosis and inflammatory responses via AMPK/mTOR signaling pathway. *CNS Neurosci Ther*. 2020;26(9):952-961. <https://doi.org/10.1111/cns.13400>
 49. Bonsack B, Corey S, Shear A, et al. Mesenchymal stem cell therapy alleviates the neuroinflammation associated with acquired brain injury. *CNS Neurosci Ther*. 2020;26(6):603-615. <https://doi.org/10.1111/cns.13378>
 50. Chen W, Zhuo Y, Duan D, Lu M. Effects of hypoxia on differentiation of mesenchymal stem cells. *Curr Stem Cell Res Ther*. 2020;15(4):332-339. <https://doi.org/10.2174/1574888X14666190823144928>
 51. Samal JRK, Rangasami VK, Samanta S, Varghese OP, Oommen OP. Discrepancies on the role of oxygen gradient and culture condition on mesenchymal stem cell fate. *Adv Healthc Mater*. 2021;10(6):e2002058. <https://doi.org/10.1002/adhm.202002058>
 52. Alijani N, Johari B, Moradi M, Kadivar M. A review on transcriptional regulation responses to hypoxia in mesenchymal stem cells. *Cell Biol Int*. 2019;44(1):14-26. <https://doi.org/10.1002/cbin.11211>
 53. Liu W, Rong Y, Wang J, et al. Exosome-shuttled miR-216a-5p from hypoxic preconditioned mesenchymal stem cells repair traumatic spinal cord injury by shifting microglial M1/M2 polarization. *J Neuroinflammation*. 2020;17(1):47. <https://doi.org/10.1186/s12974-020-1726-7>
 54. Mung KL, Tsui YP, Tai EW, Chan YS, Shum DK, Shea GK. Rapid and efficient generation of neural progenitors from adult bone marrow stromal cells by hypoxic preconditioning. *Stem Cell Res Ther*. 2016;7(1):146. <https://doi.org/10.1186/s13287-016-0409-x>
 55. Chang CP, Chio CC, Cheong CU, Chao CM, Cheng BC, Lin MT. Hypoxic preconditioning enhances the therapeutic potential of the secretome from cultured human mesenchymal stem cells in experimental traumatic brain injury. *Clin Sci (Lond)*. 2013;124(3):165-176. <https://doi.org/10.1042/CS20120226>
 56. Yu Y, Yin Y, Wu RX, He XT, Zhang XY, Chen FM. Hypoxia and low-dose inflammatory stimulus synergistically enhance bone marrow mesenchymal stem cell migration. *Cell Prolif*. 2017;50(1):e12309. <https://doi.org/10.1111/cpr.12309>
 57. Lee HJ, Ryu JM, Jung YH, Oh SY, Lee SJ, Han HJ. Novel pathway for hypoxia-induced proliferation and migration in human mesenchymal stem cells: involvement of HIF-1 α , FASN, and mTORC1. *Stem Cells*. 2015;33(7):2182-2195. <https://doi.org/10.1002/stem.2020>
 58. Wei L, Fraser JL, Lu ZY, Hu X, Yu SP. Transplantation of hypoxia preconditioned bone marrow mesenchymal stem cells enhances angiogenesis and neurogenesis after cerebral ischemia in rats. *Neurobiol Dis*. 2012;46(3):635-645. <https://doi.org/10.1016/j.nbd.2012.03.002>
 59. Deng Y, Huang G, Chen F, et al. Hypoxia enhances buffalo adipose-derived mesenchymal stem cells proliferation, stemness, and reprogramming into induced pluripotent stem cells. *J Cell Physiol*. 2019;234(10):17254-17268. <https://doi.org/10.1002/jcp.28342>
 60. Davidson JO, van den Heuvel LG, Fraser M, et al. Window of opportunity for human amnion epithelial stem cells to attenuate astrogliosis after umbilical cord occlusion in preterm fetal sheep. *Stem Cells Transl Med*. 2021;10(3):427-440. <https://doi.org/10.1002/sctm.20-0314>
 61. Wakai T, Narasimhan P, Sakata H, et al. Hypoxic preconditioning enhances neural stem cell transplantation therapy after intracerebral hemorrhage in mice. *J Cereb Blood Flow Metab*. 2016;36(12):2134-2145. <https://doi.org/10.1177/0271678X15613798>
 62. Huang Y, Tan F, Zhuo Y, et al. Hypoxia-preconditioned olfactory mucosa mesenchymal stem cells abolish cerebral ischemia/reperfusion-induced pyroptosis and apoptotic death of microglial cells by activating HIF-1 α . *Aging (Albany NY)*. 2020;12(11):10931-10950. <https://doi.org/10.18632/aging.103307>
 63. Mastroianni V, Scopa C, Sarauilli D, et al. Physical exercise rescues defective neural stem cells and neurogenesis in the adult subventricular zone of Btg1 knockout mice. *Brain Struct Funct*. 2017;222(6):2855-2876. <https://doi.org/10.1007/s00429-017-1376-4>
 64. Katsimpardi L, Lledo PM. Regulation of neurogenesis in the adult and aging brain. *Curr Opin Neurobiol*. 2018;53:131-138. <https://doi.org/10.1016/j.conb.2018.07.006>
 65. Bond AM, Ming GL, Song H. Ontogeny of adult neural stem cells in the mammalian brain. *Curr Top Dev Biol*. 2021;142:67-98. <https://doi.org/10.1016/bs.ctdb.2020.11.002>
 66. Zhu LL, Zhao T, Li HS, et al. Neurogenesis in the adult rat brain after intermittent hypoxia. *Brain Res*. 2005;1055(1-2):1-6. <https://doi.org/10.1016/j.brainres.2005.04.075>
 67. Lim DA, Alvarez-Buylla A. The adult ventricular-subventricular zone (V-SVZ) and olfactory bulb (OB) neurogenesis. *Cold Spring Harb Perspect Biol*. 2016;8(5):a018820. <https://doi.org/10.1101/cshperspect.a018820>
 68. Yang Z, Levison SW. Hypoxia/ischemia expands the regenerative capacity of progenitors in the perinatal subventricular zone. *Neuroscience*. 2006;139(2):555-564. <https://doi.org/10.1016/j.neuroscience.2005.12.059>
 69. Ara J, De Montpellerier S. Hypoxic-preconditioning enhances the regenerative capacity of neural stem/progenitors in subventricular zone of newborn piglet brain. *Stem Cell Res*. 2013;11(2):669-686. <https://doi.org/10.1016/j.scr.2013.04.007>
 70. Tapia-Bustos A, Perez-Lobos R, Vio V, et al. Modulation of postnatal neurogenesis by perinatal asphyxia: effect of D1 and D2

- dopamine receptor agonists. *Neurotox Res.* 2017;31(1):109-121. <https://doi.org/10.1007/s12640-016-9669-6>
71. Plane JM, Liu R, Wang TW, Silverstein FS, Parent JM. Neonatal hypoxic-ischemic injury increases forebrain subventricular zone neurogenesis in the mouse. *Neurobiol Dis.* 2004;16(3):585-595. <https://doi.org/10.1016/j.nbd.2004.04.003>
 72. Ross HH, Sandhu MS, Cheung TF, et al. In vivo intermittent hypoxia elicits enhanced expansion and neuronal differentiation in cultured neural progenitors. *Exp Neurol.* 2012;235(1):238-245. <https://doi.org/10.1016/j.expneurol.2012.01.027>
 73. Li L, Candelario KM, Thomas K, et al. Hypoxia inducible factor-1alpha (HIF-1alpha) is required for neural stem cell maintenance and vascular stability in the adult mouse SVZ. *J Neurosci.* 2014;34(50):16713-16719. <https://doi.org/10.1523/JNEUROSCI.4590-13.2014>
 74. Zhang K, Zhou Y, Zhao T, et al. Reduced cerebral oxygen content in the DG and SVZ in situ promotes neurogenesis in the adult rat brain in vivo. *PLoS One.* 2015;10(10):e0140035. <https://doi.org/10.1371/journal.pone.0140035>
 75. Bain JM, Moore L, Ren Z, Simonishvili S, Levison SW. Vascular endothelial growth factors A and C are induced in the SVZ following neonatal hypoxia-ischemia and exert different effects on neonatal glial progenitors. *Transl Stroke Res.* 2013;4(2):158-170. <https://doi.org/10.1007/s12975-012-0213-6>
 76. Fan B, Pan W, Wang X, et al. Long noncoding RNA mediates stroke-induced neurogenesis. *Stem Cells.* 2020;38(8):973-985. <https://doi.org/10.1002/stem.3189>
 77. Tawarayama H, Yamada H, Amin R, et al. Draxin-mediated regulation of granule cell progenitor differentiation in the postnatal hippocampal dentate gyrus. *Neuroscience.* 2020;431:184-192. <https://doi.org/10.1016/j.neuroscience.2020.02.005>
 78. Kozareva DA, Cryan JF, Nolan YM. Born this way: hippocampal neurogenesis across the lifespan. *Aging Cell.* 2019;18(5):e13007. <https://doi.org/10.1111/acel.13007>
 79. Denoth-Lippuner A, Jessberger S. Formation and integration of new neurons in the adult hippocampus. *Nat Rev Neurosci.* 2021;22(4):223-236. <https://doi.org/10.1038/s41583-021-00433-z>
 80. Bettio LEB, Rajendran L, Gil-Mohapel J. The effects of aging in the hippocampus and cognitive decline. *Neurosci Biobehav Rev.* 2017;79:66-86. <https://doi.org/10.1016/j.neubiorev.2017.04.030>
 81. Zhu XH, Yan HC, Zhang J, et al. Intermittent hypoxia promotes hippocampal neurogenesis and produces antidepressant-like effects in adult rats. *J Neurosci.* 2010;30(38):12653-12663. <https://doi.org/10.1523/JNEUROSCI.6414-09.2010>
 82. Chatzi C, Schnell E, Westbrook GL. Localized hypoxia within the subgranular zone determines the early survival of newborn hippocampal granule cells. *Elife.* 2015;4:e08722. <https://doi.org/10.7554/eLife.08722>
 83. Lazarov O, Hollands C. Hippocampal neurogenesis: Learning to remember. *Prog Neurobiol.* 2016;138-140:1-18. <https://doi.org/10.1016/j.pneurobio.2015.12.006>
 84. Toni N, Schinder AF. Maturation and functional integration of new granule cells into the adult hippocampus. *Cold Spring Harb Perspect Biol.* 2016;8(1):a018903. <https://doi.org/10.1101/cshperspect.a018903>
 85. Li G, Zhao M, Cheng X, et al. FG-4592 improves depressive-like behaviors through HIF-1-mediated neurogenesis and synapse plasticity in rats. *Neurotherapeutics.* 2020;17(2):664-675. <https://doi.org/10.1007/s13311-019-00807-3>
 86. Kushwah N, Jain V, Deep S, Prasad D, Singh SB, Khan N. Neuroprotective role of intermittent hypobaric hypoxia in unpredictable chronic mild stress induced depression in rats. *PLoS One.* 2016;11(2):e0149309. <https://doi.org/10.1371/journal.pone.0149309>
 87. Zhang K, Zhao T, Huang X, et al. Notch1 mediates postnatal neurogenesis in hippocampus enhanced by intermittent hypoxia. *Neurobiol Dis.* 2014;64:66-78. <https://doi.org/10.1016/j.nbd.2013.12.010>
 88. Nikolsky I, Serebrovska TV. Role of hypoxia in stem cell development and functioning. *Fiziol Zh.* 2009;55(4):116-130.
 89. Varela-Nallar L, Rojas-Abalos M, Abbott AC, Moya EA, Iturriaga R, Inestrosa NC. Chronic hypoxia induces the activation of the Wnt/beta-catenin signaling pathway and stimulates hippocampal neurogenesis in wild-type and APPswe-PS1DeltaE9 transgenic mice in vivo. *Front Cell Neurosci.* 2014;8:17. <https://doi.org/10.3389/fncel.2014.00017>
 90. Sun C, Fu J, Qu Z, et al. Chronic intermittent hypobaric hypoxia restores hippocampus function and rescues cognitive impairments in chronic epileptic rats via Wnt/beta-catenin signaling. *Front Mol Neurosci.* 2020;13:617143. <https://doi.org/10.3389/fnmol.2020.617143>
 91. Gonzalez-Rothi EJ, Lee KZ, Dale EA, Reier PJ, Mitchell GS, Fuller DD. Intermittent hypoxia and neurorehabilitation. *J Appl Physiol (1985).* 2015;119(12):1455-1465. <https://doi.org/10.1152/jappphysiol.00235.2015>
 92. Tsai YW, Yang YR, Sun SH, Liang KC, Wang RY. Post ischemia intermittent hypoxia induces hippocampal neurogenesis and synaptic alterations and alleviates long-term memory impairment. *J Cereb Blood Flow Metab.* 2013;33(5):764-773. <https://doi.org/10.1038/jcbfm.2013.15>
 93. Li Y, Wu L, Yu M, et al. HIF-1alpha is critical for the activation of notch signaling in neurogenesis during acute epilepsy. *Neuroscience.* 2018;394:206-219. <https://doi.org/10.1016/j.neuroscience.2018.10.037>
 94. Sun C, Fu J, Qu Z, et al. Chronic mild hypoxia promotes hippocampal neurogenesis involving Notch1 signaling in epileptic rats. *Brain Res.* 2019;1714:88-98. <https://doi.org/10.1016/j.brainres.2019.02.011>
 95. Shen Z, Zhu J, Yuan Y, et al. The roles of brain-derived neurotrophic factor (BDNF) and glial cell line-derived neurotrophic factor (GDNF) in predicting treatment remission in a Chinese Han population with generalized anxiety disorder. *Psychiatry Res.* 2019;271:319-324. <https://doi.org/10.1016/j.psychres.2018.08.111>
 96. Lorenzetti V, Costafreda SG, Rimmer RM, Rasenick MM, Marangell LB, Fu CHY. Brain-derived neurotrophic factor association with amygdala response in major depressive disorder. *J Affect Disord.* 2020;267:103-106. <https://doi.org/10.1016/j.jad.2020.01.159>
 97. Khuu MA, Pagan CM, Nallamotheu T, et al. Intermittent hypoxia disrupts adult neurogenesis and synaptic plasticity in the dentate gyrus. *J Neurosci.* 2019;39(7):1320-1331. <https://doi.org/10.1523/JNEUROSCI.1359-18.2018>
 98. Christiansen L, Urbin MA, Mitchell GS, Perez MA. Acute intermittent hypoxia enhances corticospinal synaptic plasticity in humans. *Elife.* 2018;7:e34304. <https://doi.org/10.7554/eLife.34304>
 99. Wakhloo D, Scharkowski F, Curto Y, et al. Functional hypoxia drives neuroplasticity and neurogenesis via brain erythropoietin. *Nat Commun.* 2020;11(1):1313. <https://doi.org/10.1038/s41467-020-15041-1>
 100. Baker-Herman TL, Fuller DD, Bavis RW, et al. BDNF is necessary and sufficient for spinal respiratory plasticity following intermittent hypoxia. *Nat Neurosci.* 2004;7(1):48-55. <https://doi.org/10.1038/nn1166>
 101. Turovskaya MV, Gaidin SG, Vedunova MV, Babaev AA, Turovsky EA. BDNF overexpression enhances the preconditioning effect of brief episodes of hypoxia, promoting survival of GABAergic neurons. *Neurosci Bull.* 2020;36(7):733-760. <https://doi.org/10.1007/s12264-020-00480-z>
 102. Wang H, Ward N, Boswell M, Katz DM. Secretion of brain-derived neurotrophic factor from brain microvascular endothelial cells. *Eur J Neurosci.* 2006;23(6):1665-1670. <https://doi.org/10.1111/j.1460-9568.2006.04682.x>

103. Schega L, Peter B, Torpel A, Mutschler H, Isermann B, Hamacher D. Effects of intermittent hypoxia on cognitive performance and quality of life in elderly adults: a pilot study. *Gerontology*. 2013;59(4):316-323. <https://doi.org/10.1159/000350927>
104. Shivaraju M, Chitta UK, Grange RMH, et al. Airway stem cells sense hypoxia and differentiate into protective solitary neuroendocrine cells. *Science*. 2021;371(6524):52-57. <https://doi.org/10.1126/science.aba0629>
105. Pedrosa AM, Lemes RPG. Gene expression of HIF-1 α and VEGF in response to hypoxia in sickle cell anaemia: influence of hydroxycarbamide. *Br J Haematol*. 2020;190(1):e39-e42. <https://doi.org/10.1111/bjh.16693>
106. Jablonska B, Gierdalski M, Chew LJ, et al. Sirt1 regulates glial progenitor proliferation and regeneration in white matter after neonatal brain injury. *Nat Commun*. 2016;7:13866. <https://doi.org/10.1038/ncomms13866>
107. Schodel J, Ratcliffe PJ. Mechanisms of hypoxia signalling: new implications for nephrology. *Nat Rev Nephrol*. 2019;15(10):641-659. <https://doi.org/10.1038/s41581-019-0182-z>
108. Sobrino V, Gonzalez-Rodriguez P, Annesse V, Lopez-Barneo J, Pardal R. Fast neurogenesis from carotid body quiescent neuroblasts accelerates adaptation to hypoxia. *EMBO Rep*. 2018;19(3):e44598. <https://doi.org/10.15252/embr.201744598>
109. Dimou L, Gotz M. Glial cells as progenitors and stem cells: new roles in the healthy and diseased brain. *Physiol Rev*. 2014;94(3):709-737. <https://doi.org/10.1152/physrev.00036.2013>
110. Zhou B, Zuo YX, Jiang RT. Astrocyte morphology: diversity, plasticity, and role in neurological diseases. *CNS Neurosci Ther*. 2019;25(6):665-673. <https://doi.org/10.1111/cns.13123>
111. Valori CF, Guidotti G, Brambilla L, Rossi D. Astrocytes: emerging therapeutic targets in neurological disorders. *Trends Mol Med*. 2019;25(9):750-759. <https://doi.org/10.1016/j.molmed.2019.04.010>
112. Marina N, Kasymov V, Ackland GL, Kasparov S, Gourine AV. Astrocytes and brain hypoxia. *Adv Exp Med Biol*. 2016;903:201-207. https://doi.org/10.1007/978-1-4899-7678-9_14
113. Perelli RM, O'Sullivan ML, Zarnick S, Kay JN. Environmental oxygen regulates astrocyte proliferation to guide angiogenesis during retinal development. *Development*. 2021;148(9):dev199418. <https://doi.org/10.1242/dev.199418>
114. Pantazopoulou V, Jeannot P, Rosberg R, Berg TJ, Pietras A. Hypoxia-induced reactivity of tumor-associated astrocytes affects glioma cell properties. *Cells*. 2021;10(3):613. <https://doi.org/10.3390/cells10030613>
115. Zhang Y, He K, Wang F, Li X, Liu D. Notch-1 signaling regulates astrocytic proliferation and activation after hypoxia exposure. *Neurosci Lett*. 2015;603:12-18. <https://doi.org/10.1016/j.neulet.2015.07.009>
116. Zhao X, Zhou KS, Li ZH, et al. Knockdown of Ski decreased the reactive astrocytes proliferation in vitro induced by oxygen-glucose deprivation/reoxygenation. *J Cell Biochem*. 2018;119(6):4548-4558. <https://doi.org/10.1002/jcb.26597>
117. Honsa P, Pivonkova H, Harantova L, et al. Increased expression of hyperpolarization-activated cyclic nucleotide-gated (HCN) channels in reactive astrocytes following ischemia. *Glia*. 2014;62(12):2004-2021. <https://doi.org/10.1002/glia.22721>
118. Xiao F, Lv J, Liang YB, et al. The expression of glucose transporters and mitochondrial division and fusion proteins in rats exposed to hypoxic preconditioning to attenuate propofol neurotoxicity. *Int J Neurosci*. 2020;130(2):161-169. <https://doi.org/10.1080/00207454.2019.1667784>
119. Guo M, Ma X, Feng Y, et al. In chronic hypoxia, glucose availability and hypoxic severity dictate the balance between HIF-1 and HIF-2 in astrocytes. *FASEB J*. 2019;33(10):11123-11136. <https://doi.org/10.1096/fj.201900402RR>
120. Yu S, Zhao T, Guo M, et al. Hypoxic preconditioning up-regulates glucose transport activity and glucose transporter (GLUT1 and GLUT3) gene expression after acute anoxic exposure in the cultured rat hippocampal neurons and astrocytes. *Brain Res*. 2008;1211:22-29. <https://doi.org/10.1016/j.brainres.2005.04.029>
121. Miron VE, Priller J. Investigating microglia in health and disease: challenges and opportunities. *Trends Immunol*. 2020;41(9):785-793. <https://doi.org/10.1016/j.it.2020.07.002>
122. Wang K, Li J, Zhang Y, et al. Central nervous system diseases related to pathological microglial phagocytosis. *CNS Neurosci Ther*. 2021;27(5):528-539. <https://doi.org/10.1111/cns.13619>
123. Guo M, Wang J, Zhao Y, et al. Microglial exosomes facilitate alpha-synuclein transmission in Parkinson's disease. *Brain*. 2020;143(5):1476-1497. <https://doi.org/10.1093/brain/awaa090>
124. Schirmer L, Velmeshev D, Holmqvist S, et al. Neuronal vulnerability and multilineage diversity in multiple sclerosis. *Nature*. 2019;573(7772):75-82. <https://doi.org/10.1038/s41586-019-1404-z>
125. Keren-Shaul H, Spinrad A, Weiner A, et al. A unique microglia type associated with restricting development of Alzheimer's disease. *Cell*. 2017;169(7):1276-1290 e17. <https://doi.org/10.1016/j.cell.2017.05.018>
126. Zhang F, Zhong R, Li S, et al. Acute hypoxia induced an imbalanced M1/M2 activation of microglia through NF-kappaB signaling in Alzheimer's disease mice and wild-type littermates. *Front Aging Neurosci*. 2017;9:282. <https://doi.org/10.3389/fnagi.2017.00282>
127. Tadmouri A, Champagnat J, Morin-Surun MP. Activation of microglia and astrocytes in the nucleus tractus solitarius during ventilatory acclimatization to 10% hypoxia in unanesthetized mice. *J Neurosci Res*. 2014;92(5):627-633. <https://doi.org/10.1002/jnr.23336>
128. Halder SK, Milner R. Mild hypoxia triggers transient blood-brain barrier disruption: a fundamental protective role for microglia. *Acta Neuropathol Commun*. 2020;8(1):175. <https://doi.org/10.1186/s40478-020-01051-z>
129. Kriegstein A, Alvarez-Buylla A. The glial nature of embryonic and adult neural stem cells. *Annu Rev Neurosci*. 2009;32:149-184. <https://doi.org/10.1146/annurev.neuro.051508.135600>
130. Muffat J, Li Y, Yuan B, et al. Efficient derivation of microglia-like cells from human pluripotent stem cells. *Nat Med*. 2016;22(11):1358-1367. <https://doi.org/10.1038/nm.4189>
131. Butt AM, Papanikolaou M, Rivera A. Physiology of oligodendroglia. *Adv Exp Med Biol*. 2019;1175:117-128. https://doi.org/10.1007/978-981-13-9913-8_5
132. Spitzer SO, Sitnikov S, Kamen Y, et al. Oligodendrocyte progenitor cells become regionally diverse and heterogeneous with age. *Neuron*. 2019;101(3):459-471 e5. <https://doi.org/10.1016/j.neuron.2018.12.020>
133. Klingseisen A, Ristoiu AM, Kegel L, et al. Oligodendrocyte neurofascin independently regulates both myelin targeting and sheath growth in the CNS. *Dev Cell*. 2019;51(6):730-744 e6. <https://doi.org/10.1016/j.devcel.2019.10.016>
134. Arai K. Can oligodendrocyte precursor cells be a therapeutic target for mitigating cognitive decline in cerebrovascular disease? *J Cereb Blood Flow Metab*. 2020;40(8):1735-1736. <https://doi.org/10.1177/0271678X20929432>
135. Yuen TJ, Silbereis JC, Griveau A, et al. Oligodendrocyte-encoded HIF function couples postnatal myelination and white matter angiogenesis. *Cell*. 2014;158(2):383-396. <https://doi.org/10.1016/j.cell.2014.04.052>
136. Llorente IL, Xie Y, Mazzitelli JA, et al. Patient-derived glial enriched progenitors repair functional deficits due to white matter stroke and vascular dementia in rodents. *Sci Transl Med*. 2021;13(590):eaz6747. <https://doi.org/10.1126/scitranslmed.aaz6747>

137. Cui H, Han W, Yang L, Chang Y. Expression of hypoxia-inducible factor 1 alpha and oligodendrocyte lineage gene-1 in cultured brain slices after oxygen-glucose deprivation. *Neural Regen Res.* 2013;8(4):328-337. <https://doi.org/10.3969/j.issn.1673-5374.2013.04.005>
138. Bogorad MI, DeStefano JG, Linville RM, Wong AD, Searson PC. Cerebrovascular plasticity: processes that lead to changes in the architecture of brain microvessels. *J Cereb Blood Flow Metab.* 2019;39(8):1413-1432. <https://doi.org/10.1177/0271678X19855875>
139. Chrifi I, Louzao-Martinez L, Brandt MM, et al. CMTM4 regulates angiogenesis by promoting cell surface recycling of VE-cadherin to endothelial adherens junctions. *Angiogenesis.* 2019;22(1):75-93. <https://doi.org/10.1007/s10456-018-9638-1>
140. Ruan L, Wang B, ZhuGe Q, Jin K. Coupling of neurogenesis and angiogenesis after ischemic stroke. *Brain Res.* 2015;1623:166-173. <https://doi.org/10.1016/j.brainres.2015.02.042>
141. Han W, Song X, He R, et al. VEGF regulates hippocampal neurogenesis and reverses cognitive deficits in immature rats after status epilepticus through the VEGF R2 signaling pathway. *Epilepsy Behav.* 2017;68:159-167. <https://doi.org/10.1016/j.yebeh.2016.12.007>
142. Kruger-Genge A, Blocki A, Franke RP, Jung F. Vascular endothelial cell biology: an update. *Int J Mol Sci.* 2019;20(18):4411. <https://doi.org/10.3390/ijms20184411>
143. Liu J, Wang W, Wang L, et al. IL-33 initiates vascular remodelling in hypoxic pulmonary hypertension by up-regulating HIF-1alpha and VEGF expression in vascular endothelial cells. *EBioMedicine.* 2018;33:196-210. <https://doi.org/10.1016/j.ebiom.2018.06.003>
144. Madelaine R, Sloan SA, Huber N, et al. MicroRNA-9 couples brain neurogenesis and angiogenesis. *Cell Rep.* 2017;20(7):1533-1542. <https://doi.org/10.1016/j.celrep.2017.07.051>
145. Schaeffer S, Iadecola C. Revisiting the neurovascular unit. *Nat Neurosci.* 2021;24(9):1198-1209. <https://doi.org/10.1038/s41593-021-00904-7>
146. Wang L, Xu B, Sun S, Wang B. Overexpression of long non-coding RNA H19 relieves hypoxia-induced injury by down-regulating microRNA-107 in neural stem cells. *Neurosci Lett.* 2021;753:135855. <https://doi.org/10.1016/j.neulet.2021.135855>
147. Cui P, Zhang P, Yuan L, et al. HIF-1alpha affects the neural stem cell differentiation of human induced pluripotent stem cells via MFN2-mediated Wnt/beta-Catenin signaling. *Front Cell Dev Biol.* 2021;9:671704. <https://doi.org/10.3389/fcell.2021.671704>
148. Cunningham CJ, Redondo-Castro E, Allan SM. The therapeutic potential of the mesenchymal stem cell secretome in ischaemic stroke. *J Cereb Blood Flow Metab.* 2018;38(8):1276-1292. <https://doi.org/10.1177/0271678X18776802>
149. Zhu S, Ying Y, Ye J, et al. AAV2-mediated and hypoxia response element-directed expression of bFGF in neural stem cells showed therapeutic effects on spinal cord injury in rats. *Cell Death Dis.* 2021;12(3):274. <https://doi.org/10.1038/s41419-021-03546-6>
150. Willing AE, Das M, Howell M, Mohapatra SS, Mohapatra S. Potential of mesenchymal stem cells alone, or in combination, to treat traumatic brain injury. *CNS Neurosci Ther.* 2020;26(6):616-627. <https://doi.org/10.1111/cns.13300>
151. Li F, Zhang J, Chen A, et al. Combined transplantation of neural stem cells and bone marrow mesenchymal stem cells promotes neuronal cell survival to alleviate brain damage after cardiac arrest via microRNA-133b incorporated in extracellular vesicles. *Aging (Albany NY).* 2021;13(1):262-278. <https://doi.org/10.18632/aging.103920>
152. Yasuhara T, Kawauchi S, Kin K, et al. Cell therapy for central nervous system disorders: current obstacles to progress. *CNS Neurosci Ther.* 2020;26(6):595-602. <https://doi.org/10.1111/cns.13247>
153. Brizi V, Butto S, Cerullo D, et al. Human iPSC-derived neural crest stem cells can produce EPO and induce erythropoiesis in anemic mice. *Stem Cell Res.* 2021;55:102476. <https://doi.org/10.1016/j.scr.2021.102476>
154. Otero-Albiol D, Carnero A. Cellular senescence or stemness: hypoxia flips the coin. *J Exp Clin Cancer Res.* 2021;40(1):243. <https://doi.org/10.1186/s13046-021-02035-0>
155. Chen G, Fan D, Zhang W, et al. Mxk mediates tenogenic differentiation but incompletely inhibits the proliferation of hypoxic MSCs. *Stem Cell Res Ther.* 2021;12(1):426. <https://doi.org/10.1186/s13287-021-02506-3>

How to cite this article: Li G, Liu J, Guan Y, Ji X. The role of hypoxia in stem cell regulation of the central nervous system: From embryonic development to adult proliferation. *CNS Neurosci Ther.* 2021;27:1446-1457. <https://doi.org/10.1111/cns.13754>