COMMENTARY

Hypoxia-based Stem/Progenitor Cell Therapy: Focus on CXCR4/SDF-1 Axis

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ABSTRACT

Cell therapy is becoming a promising approach to treat degenerative diseases. Homing of the transplanted cells is one of the continuous challenges being faced by the stem cell biologists. Chemokine receptors are one of the highly studied factors which are known to be crucial in controlling the cell/stem cell migration and targeted homing to the damaged tissues. The expression of chemokine receptors is dependent on a number of transcription factors and HIF-1α has been considered the crucial molecules controlling cellular migration and homing. Several studies have revealed that hypoxia conditions stabilize the HIF-1α which upregulate the CXCR4/SDF-1 expression and help in the improvement of tissue regeneration. Here, we review pivotal roles of HIF-1α /CXCR4/SDF-1 pathway in homing of progenitor/Stem cell which were affected by physical hypoxia as well as various hypoxia-mimicking agents.

Keywords: Cell therapy, HIF-1α, CXCR4/SDF-1 Axis, Hypoxia-mimicking agents, Therapeutic strategy, Regenerative medicine.

Introduction

Repairing of damaged or injured tissues is raising a major health concern and is one of the current challenges being faced by clinical practitioners. Stem/progenitor cells have been considered as an appropriate therapy for clinical purposes to repair irreversible tissue injuries and enhance tissue regeneration (1). Recently, appealing knowledge of stem cell therapy has been highly regarded in preclinical and clinical studies. It has been known that throughout the lifespan of individuals, stem cells maintaining their differentiation and proliferative capacity, repair the damaged tissues. For stem cell based regenerative therapies, mesenchymal stem cells (MSCs) are considered as

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an interesting source of stem cells because of its immunosuppressive property, multilineage potential, differentiation, proliferative and self-renewal capacity (2). Studies have shown that tissue hypoxia may be an essential mechanism governing progenitor and stem cell survival and recruitment to the damaged tissues (3). Hopefully, increasing trend of stem cell therapy in clinic is offering a promising therapy for many patients suffering from degenerative diseases and further strategies to improve the efficacy of stem cell therapy will assure the patients and clinicians trust on cell-based therapeutic approaches. In this commentary, we have focused hypoxia based treatment approaches to enhance the stem cell therapeutic efficacy for improved regeneration.

HIF-1 and its Pivotal Role in Stem Cells Functioning

Oxygen plays a crucial role in the maintenance of stem cell appreciation in terms of cell proliferation and differentiation. It has been determined that hypoxia inducible factor-1 (HIF-1) expression is regulated by oxygen which is responsible to control the expression of various stem cell characteristics genes. Oxygen is required as a necessary condition for culturing of stem cells in laboratory at a concentration of 20% but cellular niche usually required only 2 and 9% for their normal function (4). MSCs maintain their niches and themselves in low O_2 concentration by generating high levels of hypoxia inducible factors (HIFs). HIFs are activated when O_2 concentration falls below 5% and their amount increase in parallel with reduction in oxygenation (3). HIFs is a transcriptional factor that are necessary for cell functions and adaptation in hypoxia condition. HIFs activated when their subunits HIF-α (HIF-1α, HIF-2α, and HIF-3α) interacts with HIF-β subunits (HIF-1β and HIF-2β). HIF-1α subunit has been better known in the activation of some target genes and their mechanisms (5). It has been determined that under normal O_2 concentration, at least there are three different HIF prolyl hydroxylases (PHDs) that hydroxylat the prolyl residues in the HIF-1α oxygen-dependent degradation domain (ODD) and cause HIF-1 degradation; thereby regulating HIF-1 triggered signalling pathway (6). PHDs exist in three isoforms and catalyzed the degradation by an enzyme is named FIH (factor inhibiting HIF) having asparagine hydroxylase activity. These enzymes are dioxygenases and start their activity when bind with oxygen or 2-oxoglutarate as their substrates. So, in the hypoxic conditions, there is not enough oxygen and these enzymes (PHDs and FIH) don't find their substrates thus remain inactive. Their inactivity stabilizes and translocates HIFα to nucleus and then it interacts with HIFβ and a heterodimer develops. This heterodimer binds to the hypoxia response elements in the regulatory regions on DNA and regulate expression of relevant genes (7). It also has been studied that hypoxia-inducible factor1a (HIF1a) is ubiquitinated by an E3-ligase complex to control proteasomal degradation (8).

HIF-1 Protein and the Expression of CXCR4/SDF-1 Axis

CXCR4/SDF-1 axis has been studied by a number of researchers explaining their role in stem cells and cancer cells homing to a specific tissue (9, 10) and this pathway has been described to be critical for regeneration of various damaged tissues (11). HIF-1 through the induction of SDF-1 expression by endothelial cells attracts stem and progenitor cells to the injured sites of tissue. Due to the hypoxic induced temporary condition in stem cells niche, HIF-1 being stabilize and $CXCR4^+$ cells start migrating toward damaged tissues (12). In contrary, HIF-1 overexpression is a negative signature in many types of human cancers because HIF-1 via CXCR4/SDF-1 axis enhances cancer cell metastasis (13, 14). Therefore reducing the CXCR4 expression or blocking it by several compounds or strategies is a serious concern in targeted cancer therapy (15). However, high expression of CXCR4 due to hypoxic conditions in various cell types such as monocyte-derived macrophages, monocytes, cancer cells, tumor-associated macrophages, endothelial cells and mesenchymal stem cells is important for degenerative diseases (10, 16, 17). Studies discussing the importance of CXCR4/SDF-1 pathway in cell migration are enlisted in Table 1.

Hypoxia as a Therapeutic Strategy in Regenerative Medicine

Hypoxia which stabilizes the HIF-1α protein in the later inflammatory phase is involved in, endogenous cell recruitment wound healing, angiogenesis and tissue repair (6).

Table 1. Stem/progenitor cells homing repairs injured tissue by CXCR4/SDF1 pathway.

Stem Cell Type	Site of injury	Ref
BM-MSCs	Myocardial	(18,21)
Cardiac progenitor cells	Myocardial	(22)
Endothelial progenitor cells (EPCs)	Myocardial	(23)
PBMNCs	Myocardial	(24)
BM-MSCs	Renal	(25, 26)
HSCs	Renal	(27)
renal progenitor cells	Renal	(28)
BM-MSCs	Brain infarction	(29)
Ad-MSCs	Brain infarction	(30)
Neural stem cells (NSCs)	central nervous system (CNS)	(31)
Ad-MSCs	Bone marrow	(32)
HSCs	Hepatic	(33, 34)
Liver oval cells	Hepatic	(35)
Ad-MSCs	Diabetes induced Erectile Dysfunction (DED)	(36)

Interestingly, hypoxia based therapies facilitates the angiogenesis and also modifies the metabolism of hypoxic tissues to potentially retain tissue functions normal against any possible ischemic. It has been found that MSCs inhabit in hypoxic niches in the body that provide a undifferentiated states (3). Several studies have demonstrated that hypoxic induction in MSCs leads to stabilize the HIF-1α and upregulates the CXCR4/SDF-1 which increases angiogenesis and *in vivo* recruitment of MSCs to damaged tissues (37, 38). A number of hypoxia-mimicking agents have been described in Table 2 which are required to stabilize HIF-1α in stem/progenitor cells for enhanced homing.

Conclusion

Hypoxia has been described as an important cell culturing condition which results in the upregulation of CXCR4 by means of explained HIF pathways (HIF-1α). Upregulation of CXCR4 enhanced the cell/stem cells homing towards the injured tissues. Considering this enhanced migration of stem cells, it has been considered that HIF-1α could be a target molecule in stem cell therapy for clinical applications and improved strategies to increase HIF-1α activation are required for this near-to-end translational research.

Table 2. Some hypoxia-mimicking agents that stabilized HIF-1α.

Hypoxia mimicking agent	Mechanism	Stem/progenitor cell	Ref
2,29-dipyridyl	Decreased levels of multiubiquitinated HIF-1a	HEK-293 (human embryonic kidney)	(39)
Desferoxamine (DFX)	Controlling iron availability (inhibiting PHDs)	BM-MSC	(7, 40)
CoCl2	Controlling iron availability (inhibiting PHDs)	BM-MSC	(7, 40)
Dimethyloxalylglycine (DMOG)	Antagonists of 2-oxoglutarate (inhibiting PHDs)	BM-MSC	(7, 41)
Ciclopiroxolamine (CPX)	Induced EPO	Neuroprogenitor cells	(42)
FG-4497	Inhibiting PHDs	Neuroprogenitor cells	(42)
Valproic acid	HIF-1α upregulation	Mouse Embryonic Stem Cells	(43)

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