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Role of Insulin-like Growth Factor 1 Receptor Signaling in Stem Cell Stemness and Therapeutic Efficacy

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Abstract

Evidence has emerged that stem cells represent a promising therapeutic tool for tissue engineering and regenerative medicine. Thus, identifying functional markers for selecting stem cells capable of superior self-renewal and pluripotency (or multipotency) and maintaining stem cell identity under appropriate culture conditions are critical for guiding the use of stem cells toward clinical applications. Many investigations have implicated the insulin-like growth factor 1 receptor (IGF1R) signaling in maintenance of stem cell characteristics and enhancement of stem cell therapy efficacy. IGF1R-expressing stem cells display robust pluripotent or multipotent properties. In this review, we summarize the essential roles of IGF1R signaling in self-renewal, pluripotency (or multipotency), and therapeutic efficacy of stem cells, including human embryonic stem cells, neural stem cells, cardiac stem cells, bone marrow mesenchymal stem cells, placental mesenchymal stem cells, and dental pulp mesenchymal stem cells. Modifying IGF1R signaling may thus provide potential strategies for maintaining stem cell properties and improving stem-cell-based therapeutic applications.

Keywords

insulin-like growth factor 1 receptor, multipotency, pluripotency, self-renewal, stem cells

Introduction

Stem cells are biological cells that have the capacity to undergo unlimited numbers of either symmetrical or asymmetrical cell divisions to maintain the stem cell population (self-renewal) as well as produce a broad array of differentiated cell types found in the organism[1]. There are two major types of stem cells: pluripotent embryonic stem cells (ESCs), which are derived from blastocyst-stage embryos and can generate all types of differentiated cells found in the embryonic tissues[2]; and multipotent adult stem cells, which are obtained inside different types of tissues and are capable of producing some types of differentiated cells in the organism[3], such as the mesenchymal stem cells (MSCs) that are isolated from the connective tissue surrounding other tissues and organs[4]. Their unique self-renewal ability and multilineage potential make stem cells a promising tool for a wide variety of medical therapies (regenerative medicine) such as bone marrow transplantation, myocardial repair, bone regeneration, and nerve regeneration[5–7]. To guide the use of stem cells toward clinical applications, a key issue to be addressed is the identification and maintenance of stem cells capable of both robust self-renewal and pluripotency (or multipotency) *in vitro* before *in vivo* transplantation.

Insulin-like growth factor 1 receptor (IGF1R) is a cell-surface receptor tyrosine kinase that can bind its cognate ligands IGF1 and IGF2 to activate two principle downstream signaling pathways – the phosphoinositide 3-kinase (PI3 K)/AKT and the RAS/mitogen activated protein kinase (MAPK) pathways – to promote cell proliferation, differentiation, migration, and survival, and inhibit apoptosis[8–10].

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Several studies suggest that IGF1R is highly expressed when stem cells are exposed to conditions favorable for self-renewal and pluripotency (or multipotency); the expression of IGF1R recognizes stem cells with superior self-renewal, pluripotency (or multipotency), and therapeutic potential. Activation of IGF1R signaling by autocrine, paracrine, or inter-receptor cross-talk regulations contributes to maintaining the self-renewal and pluripotent (or multipotent) capacities of stem cells. In this review, we provide a quick insight into the essential roles of IGF1R signaling in maintaining stem cell characteristics, and highlight modification of IGF1R signaling as an applicable strategy for improving stem cell-based therapy for human diseases, including heart failure, neurodegenerative diseases, and bone disorders.

Igf1R Signaling Establishes the Stem Cell Niche for Self-Renewal and Pluripotency of Human Embryonic Stem Cells (hESCs)

Human embryonic stem cells are the cells isolated from the inner cell mass of human embryos that are in the blastocyst stage of development[11]. Although several factors have been identified to play a role in supporting the culture and maintenance of hESCs, including basic fibroblast growth factor (bFGF)[12], transforming growth factor β1[13], activin A[14], neurotrophins[15], Wnt/β-catenin signaling[16], platelet-derived growth factor, and sphingosine-1-phosphate[17], little is known about the cell-surface receptors that are activated under conditions supportive of hESC self-renewal.

A report by Wang et al. revealed that when cultured in mouse embryonic fibroblast-conditioned media that support the propagation of undifferentiated hESCs, hESCs displayed prominent tyrosine phosphorylation of IGF1R[18]. Selective disruption of IGF1R signaling by IGF1R-blocking monoclonal antibody or IGF1R-targeted shRNA severely inhibited hESC proliferation and promoted apoptosis, indicating that IGF1R signaling is required for the self-renewal of pluripotent hESCs[18]. Furthermore, Bendall et al. clarified that the activation of IGF1R signaling in hESCs depends on a dynamic interplay between hESCs and hESCs-derived fibroblast-like cells[19]. The hESC-derived fibroblast-like cells were produced by hESCs themselves and acted as a supportive niche via production of IGF2 through a bFGF-dependent autocrine regulation loop[19]. As a ligand binding to IGF1R, IGF2 has a direct role in sustaining self-renewal and pluripotent properties of hESCs via activation of IGF1R signaling[19]. Taken together, these reports demonstrate that IGF1R signaling is essential for the acquisition and maintenance of stemness properties of hESCs.

In addition, IGF1R signaling has been implicated in regulating pluripotent ability of hESCs. Magner et al. reported that the expression of both IGF1 and IGF2 and the phosphorylation of IGF1R increased during hepatocyte differentiation from hESCs[20]. Selective inhibition of IGF1R signaling by small-molecule IGF1R kinase inhibitor or IGF1R-targeted shRNA substantially impaired hepatocyte differentiation, supporting that IGF1R signaling plays an important role in hepatocyte differentiation from hESCs[20]. Activation of the PI3K/AKT pathway, but not the RAS/MAPK pathway, by IGF1R signaling enhanced the expression of hepatocyte nuclear factor 1 (HNF1) and HNF4 to regulate hepatocyte differentiation from hESCs[20]. Furthermore, McDevitt et al. reported that IGF1R signaling induced proliferation of cardiomyocytes derived from hESCs[21]. Blocking of IGF1R by monoclonal antibody attenuated cardiomyocyte proliferation, while addition of IGF1 or IGF2 recombinant protein promoted cardiomyocyte proliferation in a dose-dependent manner[21]. The proliferation of cardiomyocytes was mediated primarily through the PI3K/AKT pathway downstream of IGF1R signaling[21].

Igf1R Signaling Contributes to Human Neural Stem Cell (hNSC)-Mediated Neuroprotection for Amyotrophic Lateral Sclerosis (ALS)

ALS is a lethal neurodegenerative disease that results in loss of motor neurons, leading to rapidly progressive muscular paralysis[22]. To date, there are no effective treatments for ALS. hNSCs are adult stem cells that are isolated from the human brain and are capable of neural differentiation[23]. Several clinical trials have supported the use of hNSCs as a promising approach for treating ALS[24–27]. Enhancing hNSC function may thus increase the benefit of hNSCs-mediated ALS therapy.

Mechanistic investigations of hNSC-mediated neuroprotection revealed that hNSCs produced several neuroprotective growth factors, including vascular endothelial growth factor, brain-derived neurotrophic factor, and IGF1, following intraspinal transplantation in rat and mouse models of ALS, contributing to motor neuron generation, delayed clinical onset, and prolonged life spans[28,29]. Of these growth factors, IGF1 is the most abundantly expressed.

Reports by Lunn et al. demonstrated that exogenous treatment of IGF1 in hNSC cultures enhanced hNSC neural differentiation and promoted neurite outgrowth in both neurite number and length; the IGF1-stimulated hNSC neurite outgrowth could be abolished by IGF1R inhibitor treatment[30]. Higher levels of autocrine IGF1 expression in hNSCs consistently increased potential of hNSC migration, stimulated production of glial-derived neurotrophic factors, and induced neural differentiation from hNSCs[31]. Furthermore, either exogenous treatment or autocrine production of IGF1 augmented the neuroprotective potential of hNSCs and increased motor neuron survival after glutamate exposure in a model of excitotoxic cell death; the IGF1-conferred neuroprotective effect of hNSCs could be abrogated by IGF1R inhibitor treatment[30,31]. Collectively, these reports support that IGF1R signaling plays an important role in

hNSC-mediated neuroprotection and may contribute to the therapeutic benefit of hNSCs for ALS.

Igf1R Signaling Recognized Human Cardiac Stem Cells (hCSCs) with Superior Therapeutic Efficacy for Myocardial Regeneration

Human cardiac stem cells are adult stem cells that are obtained from the human heart and have a tendency to differentiate into cardiac myocytes and vessels[32]. Considering that age and coronary artery disease may have adverse effects on the function of hCSCs[33,34], it is important for tissue regeneration therapy to identify hCSCs with high self-renewal capacity and ability to form myocytes and vessels within the failing heart.

A report by D'Amario et al. showed that the expression of IGF1R in hCSCs identified a pool of hCSCs that exhibited longer telomere length, stronger telomerase activity, enhanced cell proliferation, and decreased apoptosis, whereas absence of IGF1R led to increased apoptosis[35]. IGF1R-expressing hCSCs produced both IGF1 and IGF2, which supported stem cell proliferation and promoted myocyte differentiation[35]. Furthermore, IGF1R-positive hCSCs improved cardiomyogenesis and vasculogenesis in a rat model of myocardial infarction; stimulation of IGF1R-positive hCSCs with IGF2 resulted in the development of more mature cardiomyocytes and superior regeneration of ventricular structure[35]. These results indicate that an IGF1R-positive hCSC subset is an ideal candidate cell for the treatment of human heart failure.

In addition, IGF1 has been known to be a key cardioprotective cytokine that through binding to IGF1R activates IGF1R downstream prosurvival pathways and improves postischemic cardiac function[36]. Jackson et al. reported that genetically enhancing the paracrine production of IGF1 by transplanted hCSCs promoted hCSCs and cardiomyocyte survival and improved hCSC-mediated myocardial repair in an immunodeficient mouse model of myocardial ischemia, supporting an important role of IGF1R signaling in hCSCs function[37].

Igf1R Signaling Promotes Human Bone Marrow Mesenchymal Stem Cell (hBMMSC)-Mediated Myocardial Repair and Bone Formation

Human bone marrow mesenchymal stem cells are MSCs isolated from human bone marrow and are capable of differentiating into several cell types, including cardiomyocytes and vascular endothelial cells[38,39]. In addition to the application of hCSCs in myocardial regeneration, mentioned above, transplantation of hBMMSCs is also shown to be an attractive approach for myocardial repair. The transplanted hBMMSCs can improve angiogenesis and cardiac function in rat models of heart failure through their ability not only to differentiate into cardiomyocytes and vascular endothelial cells, but also to supply large amounts of angiogenic, anti-apoptotic, and mitogenic factors[40–42].

IGF1 has been shown to enhance the migratory response of MSCs to the stromal cell-derived factor-1α (SDF-1α), a potent chemoattractant of stem cells, through activation of the IGF1R downstream PI3K/AKT signaling to increase the expression levels of the SDF-1α receptor, C-X-C motif chemokine receptor 4 (CXCR4)[43]. Additionally, SDF-1α plays a significant role in modulating stem cell functions via activating molecular pathways of cell growth, proliferation, and survival[44]. A report by Haider et al. revealed that hBMMSCs, which were transgenically overexpressed with IGF1, showed increased CXCR4 expression with a concomitant increase in SDF-1α production[45]. After transplantation in a rat model of permanent coronary artery occlusion, the IGF1-overexpressing hBMMSCs accelerated hBMMSC mobilization and retention into the infarcted heart via paracrine activation of SDF-1α/CXCR4 signaling to promote myocardial repair[45].

In addition, hBMMSCs can differentiate into chondrocytes and osteoblasts. Longobardi et al. reported that IGF1 is a key factor to promote differentiation of hBMMSCs into chondrocytes by stimulating proliferation, regulating apoptosis, and inducing expression of chondrocyte markers[46]. The effect of IGF1 on hBMMSC chondrogenesis was mediated by IGF1R downstream MAPK signaling[46]. Furthermore, IGF1 is the most abundant growth factor in the bone matrix[47]. A report by Xian et al. showed that IGF1 plays a crucial role in maintaining bone mass through stimulating osteoblastic differentiation of hBMMSCs during bone remodeling, which is mediated by activation of the PI3K/AKT signaling downstream of IGF1R[48].

Igf1R Signaling Maintains Self-Renewal and Multipotent Properties of Human Placental Mesenchymal Stem Cells (hPMSCs)

Different parts of the human placenta (including chorionic villi, membranes, umbilical cord, chorioallantois, and amniotic fluid) have been shown as a readily available source of MSCs, termed hPMSCs[49]. hPMSCs are multipotent and can differentiate into a variety of cell types, including cartilage, bone, endothelial, adipose, muscle, or neuronal lineages[50–52]. Because studies have shown that hPMSCs have significantly less or no allo- or xenogeneic immune responses[53,54], hPMSCs offer great promise for regenerative therapy and tissue engineering. For this purpose, hPMSCs need to be maintained in culture conditions that support their self-renewal and multipotent properties.

Studies have suggested both IGF1 concentration and low-oxygen tension as important regulators for hPMSC physiology *in vivo*[55,56]. Reports by Youssef et al. revealed that exogenous treatment of IGF1 in hPMSC cultures promoted

hPMSC proliferation in a dose-dependent manner; the IGF1-mediated hPMSC proliferation was further increased by low-oxygen tension[57,58]. Furthermore, hPMSC multipotency was also maintained by IGF1 and low-oxygen tension, as shown by increased expression of the ESC marker OCT4 in hPMSCs[57,58]. Both the proliferation and multipotency of hPMSCs mediated by IGF1 and low-oxygen tension were dependent on IGF1R signaling because inhibition of IGF1R signaling by IGF1R neutralizing antibody or IGF1R-targeted siRNA diminished the proliferation and multipotency of hPMSC in the presence of IGF1 and low-oxygen tension[57,58]. Overall, these reports indicate that culturing hPMSCs in conditions with IGF1 under low-oxygen tension is critical to maintaining hPMSC multipotency prior to preparation for regenerative therapies.

Igf1R Signaling Enhances Human Dental Pulp Mesenchymal Stem Cell (hDPSC)-Mediated Neuroprotection for Cerebral Hypoxia-Ischemia

Compared with isolation from other sources of MSCs, human dental pulp is regarded as a readily accessible source for MSCs, termed hDPSCs[59]. hDPSCs could be noninvasively isolated from teeth routinely extracted in the clinic and discarded as medical waste. Moreover, hPDSCs show multipotent capability to differentiate into osteoblasts, odontoblasts, adipocytes, and neural cells[60], supporting hPDSCs as a useful source for stem-cell-based therapies.

For the therapeutic applications of MSCs, it is important to identify multipotent markers for selecting MSCs that retain potent self-renewal and multipotent abilities and to maintain the selected MSCs under appropriate culture conditions before *in vivo* transplantation. Reports by Lee et al. and Chiu et al. revealed that an IGF1R-expressing subpopulation in hDPSCs exhibited both self-renewal and multipotent properties[61,62]. Importantly, IGF1R expression could be optimally maintained in hPDSCs when they were cultured in 2% human umbilical cord blood serum (hUCBS) in contrast to that in 10% fetal calf serum (FCS)[61]. Human umbilical cord blood serum contained higher amount of IGF1 compared to FCS, hence triggering a sustained activation of IGF1R signaling[61]. Also, hDPSC-secreted IGF1 interacted with IGF1R through an autocrine signaling pathway to maintain hDPSC self-renewal[62]. Furthermore, IGF1 increased expression of CXCR4, a receptor for SDF-1α. Bidirectional cross-talk between IGF1R/IGF1 and CXCR4/SDF-1α signaling synergistically strengthened the activation of IGF1R signaling, contributing to the maintenance of hDPSC stemness[61].

In rats with neonatal hypoxia-ischemia, IGF1R-positive hDPSC transplantation to the brain promoted neurite regeneration and improved neurological function through enhancing glucose metabolic activity, inducing angiogenesis and anti-inflammatory effects, increasing anti-apoptotic protein expression, and facilitating cerebral blood flow[61,62]. In summary, these reports suggest that transplantation of IGF1R-positive hDPSCs is a feasible therapeutic strategy for neurodegenerative diseases.

Conclusion

Although clinical application of stem cells raises some ethical and safety concerns[63], results of completed and ongoing clinical trials suggest that stem cells hold great promise in the treatment of a number of human diseases, including degenerative, autoimmune, and genetic disorders[64,65]. For the purpose of achieving better applications of stem cells in tissue regeneration therapy, it is necessary to isolate highly enriched pluripotent stem cells and maintain their stemness properties *in vitro* before *in vivo* transplantation. This review emphasizes that IGF1R signaling is an ideal functional marker for identifying stem cells with superior self-renewal and pluripotent capacities. Moreover, modulating IGF1R signaling activity is a promising strategy to maintain stem cell identity and improve stem cell therapy efficacy. Considering the concern that IGF1R signaling is also implicated in cancer stemness and chemoresistance[66,67], the stem cells whose IGF1R signaling activity was modified should be appropriately and adequately differentiated into the tissue-specific cell types *in vitro* before *in vivo* transplantation, minimizing the potential side effects of tissue regeneration therapy.

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