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Research Progress of HIF- 1α and its Intervention Factors in Osteogenic Synthesis of Blood Vessels in Bone Marrow Mesenchymal Stem Cells

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Abstract: *Objective to review the development and applications and intervention factors of hypoxia-inducible factor 1α (HIF-1α) in the strategy of tissue engineered angiogenesis and osteogenesis. Methods the literature about HIF-1α in tissue engineering technology was reviewed, analyzed, and summarized. Results HIF-1α and its intervention factors plays a key role in angiogenicosteogenic coupling, and as an upstream regulator.*

Keywords: *Tissue engineering, Hypoxia-inducible factor 1α, DFO, DMOG, Cocl2*

1. Introduction

In recent years, the repair and reconstruction of bone tissue defects through tissue engineering technology has become one of the research hotspots in this field. According to previous studies, the osteogenic and angiogenic ability of bone marrow mesenchymal stem cells can be mediated by some specific factors, such as bone morphogenetic protin (BMP), vascular endothelial growth factor (VEGF), hepatocytic growth factor (HGF). On the other hand, these growth factors can only enhance the osteogenic or angiogenic ability of mesenchymal stem cells. Previous studies have found that a nuclear protein with transcriptional activity, namely hypoxia induced factor 1 α (HIF-1 α), is directly or indirectly involved in the whole process of angiogenesis and osteogenesis [1-4]. In recent years, it has been found that hypoxia mimics can inhibit the degradation of HIF-1 α by PhD through competitive inhibition of endogenous iron ions or oxidative glutaric acid, stabilize and up regulate the level of HIF-1 α, thus promoting angiogenesis and bone regeneration. This article reviews the role of HIF-1 α and hypoxia mimics in angiogenesis and bone regeneration [5].

2. HIF-1α

Cell life needs oxygen. After hypoxia, the afferent input from carotid body is sent to the respiratory center of brain stem to increase ventilation, thus improving the delivery of O2 to blood. After long-term chronic persistent hypoxia, cells need longer adaptation to maintain the steady state of oxygen, which is mediated by hypoxia-inducible factors [6]. The factor includes three subtypes, namely HIF-1, HIF-2 and HIF-3. At present, the main research is on HIF-1, which is a heterodimer composed of HIF-1α and HIF-1β, but the HIF function is mainly regulated by HIF-1α protein [7]. Under normal oxygen partial pressure, HIF-1α subunit is degraded because of the action of prolyl hydroxylase. Under hypoxia, the activity of prolyl hydroxylase was inhibited, and HIF-1a shifted to the nucleus, forming a complex with HIF-1β stably expressed in the nucleus. They act on DNA together and regulate downstream genes such as VEGF, PDK1, PDK4 and VEGF, so as to make cells survive [8].

2.1. The role of HIF-1 α in angiogenesis

HIF-1 α has been proved to be a key transcription regulator for gene expression in hypoxia response, which regulates the expression of many genes, including genes of angiogenic factors, such as VEGF, PDGF and ang [1-3]. Moreover, HIF-1 α transfected MSCs can enhance angiogenesis [9]. HIF-1 α participates in the process of angiogenesis through two stages [10, 11]. The formation stage works with

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VEGF, angiopoietin 2 and integrin to promote the synthesis of vascular network by vascular kiss. The vascular wall structure was completed by PDGF and Ang-1 in the shaping and reconstruction stages. There are more than 60 downstream genes regulated by HIF-1 α. The most important downstream gene is vascula endostatic growth factor (VEGF). However, single VEGF can not obtain mature and stable vascular network [12]. Zelzer et al. [13] studies found that VEGF 164 and vegf188 are two subtypes of vegf-164 and vegf188, which may be the vascular endothelial growth factor that can be specifically mediated by the angiogenesis of cartilage tissue. Sun et al. [14] infected MSc by HIF-1 α overexpression vector, and the mRNA and secretion of angiogenic factor were determined by RT-qPCR and ELISA. The results showed that the mRNA and protein expression of angiogenic factors in vitro and in vivo were increased after overexpression of HIF-1 α in exocrine.

2.2. Effect of HIF-1 α on osteogenesis

HIF-1α plays a key role in the development of articular cartilage. It also plays an important role in the differentiation of bone marrow mesenchymal stem cells/stromal cells and cartilage precursor cells into cells capable of producing cartilage-like extracellular matrix [15, 16]. Yu et al. [17] studied whether HIF-1α is involved in the differentiation of bone marrow mesenchymal stem cells into osteoblasts induced by periodic tensile stress, and detected the expression of HIF-1α mRNA and protein by reverse transcription quantitative polymerase chain reaction and Western blot. All experiments showed that the expression of HIF-1mRNA and protein in bone marrow mesenchymal stem cells increased significantly after stretching treatment. Therefore, HIF-1 alpha may be involved in the regulation of bone metabolism in bone marrow mesenchymal stem cells during cyclic stretching and hypoxic microenvironment. Through experimental studies, Zhan et al. [18] confirmed that HIF-1 α plays an important role in the expression of VEGF, angiogenesis and fracture repair induced by umsc exos. Many human experimental studies have confirmed that hypoxia can activate HIF **-** 1 α, significantly enhance the osteogenic ability of osteoblasts, and jointly act on cartilage defects to promote defect repair [19, 20].

3. Hypoxia promotes bone angiogenesis

Bone mesenchymal stem cell (BMSCs) is a long-term microenvironment. Previous studies have shown that under physiological conditions, bone marrow cells are exposed to natural hypoxia for a long time, and the oxygen partial pressure is 2% - 7%. BMSCs cultured in normal concentration of oxygen will produce more oxides and damage cells [21]. The microenvironment in the pathological bone defect area will lead to the lack of blood flow and oxygen supply in the bone marrow. Therefore, BMSCs usually repair bone defects through osteogenesis in a more obvious hypoxic microenvironment [22]. Huang Jiao [23] studied the effect of HIF-1 α on MSCs by establishing the cell culture model of mesenchymal stem cell (MSCs). The results showed that when HIF-1 α gene was inhibited in cells, it promoted the expression of osteogenic specific transcription regulatory factors and enhanced the osteogenic effect of MSCs. Zhuo Yi [24] confirmed that hypoxia microenvironment can promote the proliferation of OM MSCs and the cell activity is normal, and this process shows that HIF-1 α signaling pathway is activated.

Many experiments have proved that hypoxic simulators have similar or even more obvious effects on pretreatment of stem cells under hypoxic conditions. Related hypoxia simulants include cobalt chloride, deferoxamine and dimethoxyglycylglycine [25-27].

4. Hypoxia mimics related to HIF-1 α

4.1. Deferoxamine (DFO)

As an iron chelating agent with strong antioxidant activity, DFO can enhance the resistance of cells to stress conditions by inhibiting proline hydroxylase, and enhance the activity of HIF-1α in cells under normal oxygen conditions, thus enabling cells to adapt to hypoxia environment [27]. Wang et al. [28] found that deferoxamine can stimulate angiogenesis, inhibit apoptosis and protect rats after traumatic brain injury by up-regulating the expression of HIF-1α and its downstream target gene VEGF. Choi et al. [29] Immunofluorescence analysis showed that the expression of HIF-1α in animal lung tissue decreased significantly, while DFO could restore the expression of HIF-1α. Taheem et al. [30] cultured Hbm-MSC with different concentrations of deferoxamine. Compared with the control group, the level of HIF-1α protein increased significantly.

4.2. Dimethyloxalylglycine (DMOG)

DMOG is a cell permeable prolyl 4- hydroxylase inhibitor, which can up-regulate the activity of HIF-

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1α, and then increase the transcription and expression of many osteogenic and angiogenic genes in the nucleus, so that it can play its protective role [26]. Taheem et al. [30] through experimental research, compared with cobalt chloride or deferoxamine, 2- oxoglutarate (2-OG) analog dimethylol glycine can induce HIF signal transduction and articular chondrocyte-like expression in human BMSCs, thus reducing the bioavailability of ferrous iron (Fe^{2+}), suggesting that DMOG may be effective in the treatment of cartilage regeneration. Sen et al. [26] studies found that dmog can upregulate HIF-1 α and protect the cells and repair the nerve. Zhou et al. [31] studied the effect of dmog on HIF-1 α signal transduction pathway of bone marrow mesenchymal stem cells, and confirmed that dmog had a significant regulatory effect on HIF-1 α of BMSCs, and could significantly enhance the angiogenesis and osteogenic potential of stem cells.

4.3. Cobalt Chloride (CoCl2)

CoCl2 is the most common chemical hypoxia inducing reagent. Its cobalt ion can replace the iron ion in the oxygen receptor hemoglobin porphyrin ring, making hemoglobin unable to combine with oxygen and maintain the reducing state, inducing a series of similar hypoxia reactions, thus simulating the hypoxia state. At the same time, it can up regulate the expression of HIF-1 α in cells, which is similar to the effect of hypoxia induced by physics [32]. Tripathi et al. [33] studied the cellular and molecular reactions of cells under CoCl2 induced hypoxia, and found that after CoCl2 exposure, the activities of HIF-1, reactive oxygen species and lipid peroxidase increased significantly, while the activities of glutathione and catalase decreased. Dai et al. [34] treated BMSCs with different concentrations of coc12, and detected the related angiogenic factors and HIF-1 α. The results showed that the protein level of HIF-1 α in BMSCs was generally low, and gradually increased after CoCl2 pretreatment. Moreover, exposure to 50 μ m or 100 μ m CoCl2 for 24 hours could increase the expression of VEGF protein.

5. Conclusion

In conclusion, a variety of methods have systematically confirmed that HIF-1 α can promote the osteogenesis and angiogenesis of tissue stem cells under certain conditions. The physical hypoxia microenvironment induced in vitro can enhance the proliferation ability of BMSCs after HIF-1 α gene transfection, reduce apoptosis and increase the expression of HIF-1 α gene. However, we found that it is difficult to develop the hypoxia environment through physical induction in vitro. Therefore, people should be devoted to explore a more effective and simple method to induce hypoxia, so as to promote the ability of stem cells to become bone and blood vessels in tissue engineering, so that the diagnosis and treatment ideas of the regeneration and repair of Stomatology tissue engineering can be expanded.

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