

The Clinical Applications of Hypoxia-Inducible Factor-1Alpha (HIF-1 α)

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Abstract. Hypoxia is a microenvironment that occurs when the oxygen supply is insufficient to perform physiological functions. HIF-1 is a transcriptional factor that mediates metabolisms and cellular responses under hypoxic conditions, which protects the cell's viability. Harness of the HIF-1 α pathway gives control over cellular response and cells' differentiation directions. In this review article, the degradation process of HIF-1 α will be firstly be discussed. It has been proved that the activation and suppression of HIF-1 α pathway can stimulate many cellular responses in human body, for instance, chondrogenesis and angiogenesis. Three clinical applications of HIF-1 α will be analyzed in this article, which are cartilage repairments, recovery of anemia and the cancer treatment. The upregulation of HIF-1 α activates the transcription of many genes responsible for cell proliferation, and this can be achieved by small biomaterial. This method is more controllable in terms of its mechanism, and more commercially available compared with gene therapy approaches and recombinant tissues.

Keywords: HIF, Cartilage Repair, Anemia, Cancer.

1. Introduction

The hypoxia-inducible factor, abbreviated as HIF is a group of post-transcriptional proteins, which guides for metabolic cellular responses to different oxygen levels. HIFs are transcriptional proteins that consist of two similar but different subunits (heterodimeric): an oxygen-controlled HIF- α monomer (HIF-1 α , HIF-2 α , and HIF-3 α) and a non-oxygen-regulated HIF- β monomer [1]. HIF-1 α is continually being made and degraded by the oxygen-dependent proteolysis reactions at physiological levels of oxygen. The oxygen-dependent degradation domain (ODDD) regulates this degradation process. A particular enzyme known as HIF prolyl hydroxylases hydroxylates (PHDs) a proline residue as the initial stage of degradation. Von Hippel-Lindau protein (pVHL), a tumour suppressor protein, is then attached after that. The von Hippel Lindau protein associates with a ubiquitin ligase complex that causes the attachment of ubiquitin to HIF-1 α . Ubiquitination causes in proteolysis and degradation of HIF-1 α [2]. However, under hypoxic conditions, PHDs are inactivated due to reduced activity of PHD.

There may be numerous clinical applications for HIF-1 activation. For instance, vascular endothelial growth factor (VEGF), which is crucial for angiogenesis and fracture repair, was controlled by the transcriptional factor HIF-1. A significant clinical challenge is the repair and management of articular cartilage damage. The pain of people who have suffered a cartilage injury is currently simply relieved; there is no cure. The articular cartilage is avascular and frequently subjected to strain and friction, making cartilage abnormalities difficult to identify early on. A highly anticipated remedy for osteochondral problems is osteochondral tissue engineering. The differentiation of human mesenchymal stem cells and the maturation of articular cartilage tissues would be impacted by HIF-1 and the cells that it is mediated through.

The causes of anemia are diverse. Any functional hemoglobin deficiency and RBC quality decline may lead to anemia. When tissue oxygen supply is impaired, anemia and incidence rate and mortality will increase accordingly [3]. Anemia can harm human health in two ways. The first is to weaken the ability of blood to carry oxygen, which will lead to insufficient oxygen supply to tissues, and then lead to digestive system diseases, listlessness and other hazards. The second aspect is the decrease of blood viscosity, which leads to the increase of blood flowing back to the heart, which in turn leads to dizziness and accelerated heartbeat after slight exercise, and even heart failure.

This article summarizes that anemia can be improved by compensatory HIF-1 modulation. Hypoxia conditions prevent the cytoplasmic HIF-1 from being degraded, allowing it to build up, dimerize, and go into the nucleus, facilitating the transcription of a variety of hypoxic molecules. Consequently, HIF-1 is crucial to the development of anemia. It targets anemia-induced brain damage in perioperative patients. This type of brain injury can be repaired thanks to HIF-1, the overall balance of erythropoietin and vascular endothelial growth factor, and other factors. HIF-1, cancer therapies that cause anemia It is connected to HB, which offers a fresh approach to treating anemia.

The importance of developing effective treatments for cancer is underscored by the fact that it accounts for a sizable share of global mortality and that its effects are still expanding. The more established treatments, such radiation and chemotherapy, have evolved into more individualized forms of care. Biotechnological techniques are developing with the aim of enhancing specialized patient care [4]. A fresh viewpoint may be provided by the role of HIF-1 regulation in the development of cancer.

2. HIF-1 α and osteochondral defects repairment

Due of cartilage's low capacity for self-repair, healing it remains a significant clinical issue. In addition to causing discomfort, the loss of joint function may also result in other osteochondral abnormalities (e.g., osteoarthritis). Natural, healthy cartilage's main job is to protect bones from impact and maintain the smooth motion of articular joints. Proper oxygen pressure keeps the subchondral bones and cartilage in place. The underlying bones are made of collagen type I and osteocytes, whereas cartilage is mostly made of a collagen type II-rich matrix embedded with chondrocytes. Making artificial tissues to replace those that are damaged in human bodies is the goal of the field of study known as tissue engineering. The level of oxygen is higher in the bones than that in the cartilage, and the oxygen level will affect the differentiation direction of human mesenchymal stem cells, either from chondrocytes to chondroblasts or osteocytes to osteoblasts. Oxygen level is often associated with different HIF pathways, so it might be feasible to harness the cellular response to oxygen level by creating scaffolds [5].

By controlling the oxygen level in the osteochondral tissues locally, the chondrogenesis and osteogenesis process can be controlled. For example, by incorporating oxygen-releasing molecules into the scaffold. These molecules include hemoglobin and manganese dioxide nanoparticles, and the oxygen level will be enhanced locally by these biomaterials [6,7]. In addition, the local oxygen level can be reduced by incorporating oxygen-absorbing biomaterials or just simply preventing oxygen diffusion locally. This can stimulate the chondrogenesis process and thus the formation of articular cartilage.

Nevertheless, hypoxia may have detrimental effects on cell metabolism and viability, thus hampering tissue formation. Thus, understanding the network and pathway of HIF may be helpful to control the chondrogenic differentiation of progenitor cells. There are many ways to activate the HIF-1 α pathway. First is by applying PHD inhibitors, some of the common inhibitors including desferrioxamine and dimethyloxallyglycine, the inactivation of PHD can prevent the degradation of HIF-1 α [8]. Second, by applying mechanical stress, the expression of HIF-1 α is enhanced [2]. The enhanced expression of HIF-1 α activates the transcription of many genes coding for angiogenesis and cell proliferation.

3. HIF-1 α and anemia

Anemia refers to the reduction of the total amount of red blood cells in the circulating blood of the whole body below the normal value. Erythrocyte production is affected by the regulatory factor erythropoietin (EPO) and the interaction between stromal cells and erythroid progenitor cells. Recent clinical experiments have found that anemia in HIF-2 α knockout mice is due to impaired expression of VCAM-1 in spleen endothelial cells (ECs), leading to impaired erythrocyte maturation. However, the anemia erythrocyte index observed in HIF-1 α knockout heterozygous mice is significantly improved compared with HIF-2 α knockout mice, because VEGF receptor, FLK-1, FLT-1 in the spleen are highly expressed, and they are regulated by HIF-1 α under hypoxic conditions. This suggests that there is a compensatory modulation involving HIF-1 α that improves anemia [9].

Although there are specific EPO targets to HIF-2 α , HIF-PHD inhibitor (HIF-PHDi) has no selectivity to HIF substrate to a great extent [10]. At the same time, HIF-PHDi can stabilize HIF-1 α and increase EPO, so it has become a new choice for clinical treatment of renal anemia [11]. Under anoxic conditions, cytoplasmic HIF-1 α 's ability to aggregate, dimerize, and transfer to the nucleus is blocked, which encourages the transcription of several hypoxia-related molecules. HIF-1 α is therefore crucial to the development of anemia.

Cerebral oxygen homeostasis may change drastically when acute anemia occurs. Currently, HIF-1 α has the capacity to control how brain cells react in anoxic and normoxic circumstances. HIF-1 α Possibly neurotoxic or neuroprotective.

It targets anemia-induced brain damage in postoperative patients. The enhancement of cerebral oxygen delivery that is dependent on NOS/NO as well as cell protection mechanisms like HIF-1 α , erythropoietin, and vascular endothelial growth factor are examples of potential brain protection processes. Because anemia is conducive to the repair of such brain damage, the overall balance of these activated cellular mechanisms may determine whether their upregulation will result in cell protection or cell damage during anemia [12].

At the same time, it is found that anemia may occur during the treatment of various cancers, reducing the level of oxygen in the tumors. For example, when cervical cancer occurs, HIF-1 α is related to Hb. This discovery changes the tumor oxygen for the treatment of anemia and suggests that changing the Hb level may change the molecular response to hypoxia. Anemia may interact with other pathways, or the expression of the hypoxia protein may represent the response of molecular pathways that can be altered by other signal pathways [13].

4. HIF-1 α in cancer

HIF-1 α has long been proven to be closely related to cancer progression, and thus it is widely applied to act as a biomarker assisting the prognosis of cancer and to develop therapies [14].

Numerous studies have shown that the tumor microenvironment includes hypoxia as a important factor. As the tumor grows rapidly, the exceeding need for blood supply results in hypoxia, which induces the HIF-1 α expression [15].

In most cases, HIF-1 α can be implemented as a biomarker. For example, the study of kidney cancer conducted by Li et al suggested that overexpression of HIF-1 α led to a lower survival rate of the patients than those with low expression. While overall HIF-1 α played an inhibitory role in retarding renal cancer cell (RCC) tumor growth [16]. In gastric cancer, HIF-1 α has been found to promote proliferation and angiogenesis, resulting in the growth of gastric cancer cells [17]. Overexpression in breast cancer also contributes to larger tumor size and its correlation with lower survival is confirmed [18]. However, in terms of patients with non-small-cell lung cancer or head and neck cancer, the opposite result appears. More research demonstrates that the type of tumour affects how HIF-1 functions [19]. In general, although it is controversial whether HIF-1 α is a promoter or inhibitor in cancer progression, its expression level is related to tumor size, treatment outcome and survival rate.

A study also discovers that the overexpressed cytoplasmic HIF-1 α (cHIF-1 α) and nuclear HIF-1 α (nHIF-1 α) function differently (the overexpression of cHIF-1 α contributes to a larger tumor, higher

stage and shorter survival, while nHIF-1 α has the contrary result) [20]. It implies that nHIF-1 α upregulation might become an effective cancer progression control. How cHIF-1 α and nHIF-1 α can be regulated respectively is worth practicing.

Cancer therapy combined with HIF-1 α regulation affects efficacy. The Stereotactic Ablative Radiotherapy (SABR) kills tumors by irradiating and promoting anti-tumor immunity. Through this process, vascular damages are induced and block blood circulation, causing hypoxia and HIF-1 α release, which may lead to immune suppression. The experiment indicates that HIF-1 α inhibition is an accessible method to promote anti-tumor immunity [21]. In chemotherapy, the function of drugs can be damaged by HIF-1 α , causing chemo-resistance [17,18]. It is possible that HIF-1 α upregulation impairs cancer therapy and its inhibition can be admitted in new treatment.

In conclusion, HIF-1 α can be applied as a target of cancer treatment and its regulation offers new therapeutic strategies.

5. Discussion

As a result, the proline residues of HIF-1 α are no longer hydroxylated and the α subunits are able to accumulate and be transported to the nucleus where transcription occurs.

HIF-1 α activation may have many applications for clinical treatments. For example, HIF-1 α is an important transcriptional factor that regulated VEGF, which is important for angiogenesis and fracture healing.

The repair and treatment of articular cartilage injury is a huge clinical challenge. The current treatment for cartilage injury only relieves patients' pain but cannot cure them. The articular cartilage is avascular and often under tension and friction, so the detection of cartilage defects is often late. Tissue engineering of osteochondral tissues is a highly expected answer for osteochondral defects. HIF-1 α and its mediated cells would have an effect on the differentiation of human mesenchymal stem cells and the maturation of articular cartilage tissues [22].

The overexpression of HIF-1 α is often caused by intratumoral hypoxia, genetic alteration and decrease of tumor-suppressor genes. HIF-1 α overexpression is associated with increased mortality in cancer treatment [19]. Inhibition of HIF-1 α activity is therefore a important anti-cancer therapies.

6. Conclusion

The development of HIF-1 α application has conquered some previous obstacles in clinical treatment. HIF-1 α regulation can be used to stimulate tissue formation under the situation of impaired osteochondral structure. It has positive effects in coping with anemia by regulating molecular response to hypoxia environment, which is also applied in cancer treatment. However, HIF-1 α has complex bonds with other molecules so its function cannot be determined individually. The adoption of HIF-1 α still has lots of possibilities, and holds a promising future in medicine.

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