Kermanshah University of Medical Sciences

Journal of Kermanshah University of Medical Science

Journal homepage: Htpp://journals.kums.ac.ir/ojs/index.php/jkums

Role of hypoxia and hypoxia inducible factor in physiological and pathological conditions

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Review Article

Article Info

Keywords: Hypoxia, HIF-1, cancer

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Received: 10 July, 2017
Accepted: 14 November, 2017

J Kermanshah Univ Med Sci. 2017; 21(3): 126-132

Abstract

Introduction: Organisms are exposed to oxygen deprivation (Hypoxia) in various physiological and pathological conditions. There are different conserve evolutionary responses to counterview with this stress that primary transcriptional response to stress related to hypoxia is interceded by hypoxia-inducible factor (HIF-1) in mammals. This factor can regulate different genes that have essential roles in adaptation to this condition. In this review, the role of this factor in physiological and pathological conditions under hypoxic condition has been evaluated after examining structural features and regulation characteristics of HIF-1.

Methods: First, articles related to the keywords of hypoxia and HIF-1 (from 1991-2016) were searched from valid databases such as Springer Link, Google Scholar, PubMed and Science direct. Then, the articles correlated with hypoxia, HIF-1 and their roles in physiological and pathological conditions (120 articles) were searched and just 64 articles were selected for this study.

Result: According to studies, there are different genes in cells and organs that can be regulated by HIF-1. Activation of genes expression by this protein occurs through its linkage to cis-acting of 50 base pair hypoxia response element (HRE) region located in their promotor and enhancer. Depending on circumstances, activation of these genes can be beneficial or harmful.

Conclusion: Activation of different genes in hypoxia by HIF-1 has different effects on physiological and pathological conditions. Therefore, HIF-1, as a hypoxia-inducible factor in hypoxic conditions, plays an essential role in the adaptation of cells and organs to changes related to the presence of oxygen.

Introduction

Aerobic organisms need oxygen to produce their energy. Hence, the reduction in available oxygen leads to severe and destructive stress in living cells (1). Hypoxia (available oxygen deficiency) is a critical condition in physiological and pathological conditions that occur due to an imbalance between supply and demand of oxygen and can have a supportive or pathogenic role (2, 3). When oxygen levels are low, a number of responses related to the adaptation to these conditions are activated by the cells to adapt the amount of oxygen available to the metabolic and bioavailable needs, such that the cell cycle is ceased temporarily, its energy consumption is reduced, and angiogenic factors associated with cell survival are secreted (4). In fact, hypoxia is one of the factors involved in the onset of the process of angiogenesis in tissues and cells. Angiogenesis means the formation of new vessels from pre-existing vessels involved in various pathological conditions such as tumor growth and metastasis, rheumatoid arthritis, as well as in physiological processes such as organ development, wound healing and reproduction. It is the most important process of providing oxygen to hypoxic tissues (5). Regulation and coordination of all events cited are done by various cellular pathways, including the Mechanistic target of rapamycin (mTOR) signaling pathway and factors such as HIF-1. In addition to the adaptive role of HIF-1 in response to cellular stress, the important role of this factor in the physiological and pathological processes has been revealed in recent studies (6, 7). Therefore, the present review study examined the role of this factor in regulating the expression of the genes involved in such processes after expressing its structural characteristics.

Methods

First, articles related to the keywords of hypoxia were searched for in valid databases (Science Direct, PubMed, google scholar, Link Springer, etc.) using the keywords of Hypoxia and HIF-1. Then articles on hypoxia and factors involved in adaptation to these conditions (120 articles), in particular, articles related to hypoxia and HIF-1 were investigated. In order to select the documentation used, the obtained titles through search engines were first examined in terms of subject relevance, then those that were more complete (64 articles) were selected as the reference.

Findings

According to studies, hypoxia has a strong impact on cell biology and the physiology of mammals by activating HIF-1 as one of the important factors involved in this pathway and the effect of this factor on gene expression in them. Therefore, in order to better understand the role of HIF-1, first, its structural and regulatory features were examined.

HIF-1 structure

HIF-1 is a heterodimer protein consisting of HIF-1α and HIF-1β subunits that become active under hypoxic conditions and activate the expression of many related genes in these conditions (8). Both subunits of this protein belong to the protein family of basic helix-loop-helix PER-ARNT-SIM nuclear translocator (bHLH-PAS) (9). Depite the constant expression of HIF-1β in the cell, HIF-1α, which has an effect on erythropoietin, glucose transporters, glycolytic enzymes and an epithelium-derived growth factor that plays an important role in angiogenesis, has a role in adaptive cellular and systemic responses to hypoxia and is only expressed under these conditions (10). HIF-1α is a protein with 826 amino acids and its gene, located on chromosome 14 (14q21-q24), consists of 15 exons and 14 introns (Fig. 1). There are bHLH (amino acids 17-71) and PAS (amino acids 58-298) domains at the amino acid end of this protein, which is involved in dimerizing this protein with HIF-1β and binding to the HRE region (5'-RCGTG-3') in DNA. The PAS domain is divided into two sub-domains of PAS-A (amino acids 58-158) and PAS-B (amino acids 228-298) (9). There are transactivation domains (TAD) at the carboxylic end of this protein consisting N-TAD (amino acids 531-575) and C-TAD (amino acids 786-826) that are separated from each other by an inhibitor domain (11, 12). Additionally, at its amino end (amino acids 17-17) and in the carboxyl region (amino acids 718-721), there are nuclear localization signals (NLSs). The NLS motif plays an important role in the carboxyl region in the entrance of the protein into the nucleus, while the motif in the amino region plays a weak role (13). HIF-1α is highly unstable under normoxic conditions and its decomposition is controlled by the oxygen-dependent degradation domain (ODDD) (amino acids 603-401) in its structure [14]. Variable factors play a role in regulating the expression and stability of HIF-1α, including the prolyl hydroxylase domain (PHD) enzyme which, by hydroxylation of ODDD in the structure of this factor, leads to its identification by the ubiquitination complex and ultimately, its degradation by proteasome (15); glycolytic pyruvate kinase isoenzyme M2, which is the dominant form of pyruvate kinase in a tumor, resulting in an increase in the expression of HIF-1α, and activating in response to its transcription by this factor (16); and, finally, the runt-related transcription factors (RUNX), each of which can have a different effect on the stability of HIF-1α (17).

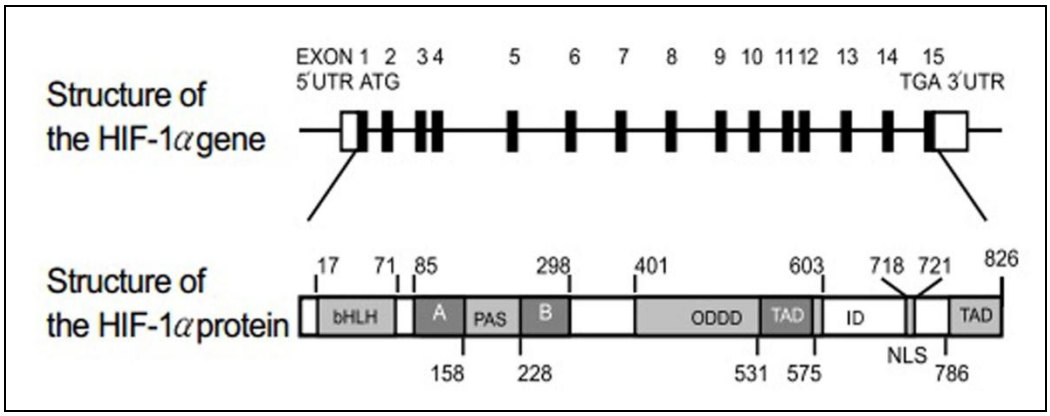

Figure 1. Gene and protein structure of HIF-1α: The HIF-1 gene located on chromosome 14, consists of 15 exons and 14 introns. The protein associated with this gene includes different domains of bHLH, PAS, TAD, ID, and ODDD (10).

HIF-1 regulation

Although HIF regulation has primarily been thought to be subject to the amount and pressure of oxygen, several studies have now shown that this protein can be regulated under oxygen-independent conditions. Oxygen-dependent degradation of the HIF-1α subunit is mediated by PHDs, Von Hippel-Lindau (VHL), the ElonginC/ElonginB E3 ubiquitin-ligase complex and the proteasome, while its oxygen-independent degradation is mediated by the Receptor for Activated C Kinase 1 (RACK1) protein. RACK1 connection in PAS-A area to HIF-1α induces the use of ElonginC, ubiquitination, and ultimately the oxygen/PHD/VHL-independent proteasomal degradation of HIF-1α. However, the interaction between RACK1 and HIF-1α can be inhibited by the heat shock protein 90 (HSP90), which competes with it for binding to HIF-1α. Therefore, HSP90 inhibition results in instability of HIF-1α and ultimately its degradation. The activated protein kinase receptor is, in fact, a protein that has the ability to interact with HIF-1α, which is competing with HSP90 to bind to this factor, and it is necessary for the oxygen-independent and HSP90 inhibitor-induced degradation (18). Another factor involved in oxygen-independent regulation of HIF-1α is a hypoxia-associated factor (HAF). This factor, which is a novel E3 ubiquitin ligase, leads to proteasomal degradation of HIF-1α irrespective of the amount of oxygen available to the cell. HAF and HIF-1α interact in vitro and in vivo through binding of HAF residues 654–800 to HIF-1α residues 296–400. The HIF-1α residues 296–400 are oxygen-independent and do not require proline hydroxylation to decompose this protein (19). Therefore, HAF is capable of negatively regulating HIF-1α levels under conditions in

which the pVHL-E3 ligase complex is inactive, like hypoxia.

HIF-1 target genes

Due to the need of different cells and organs to adapt to changes in the oxygen tension, there are various genes in these cells and organs that are regulated by HIF-1. Today, more than 100 genes with different functions are identified at the gene downstream associated with HIF-1 (Fig. 2), that activates their expression by binding to the cis-acting region, has 50 bp HRE located in the augmentation portion and the promoter of these genes (20). Here are some of the genes whose expressions are affected by HIF-1, along with their role in the cell.

The role of HIF-1 in the expression of genes involved in hematopoietic metabolism/iron

Increasing the production of red blood cells is one of the ways to respond to hypoxia in the body, with HIF-1 playing an important role in these conditions. According to studies, HIF-1 regulates the expression of various genes and thus increases the production of erythropoietin in the liver and kidneys, increases the absorption and consumption of iron, and ultimately increases the reproduction and maturity of erythroid precursors in the bone marrow. In these conditions, the number of red blood cells increases by increasing the expression of the genes involved in Hematopoiesis and iron metabolism, which also increases the delivery of oxygen to the tissues (20). Regarding the genes involved in iron metabolism, the increased expression of transferrin, which transmits Fe^{3+} to the cell; expression of transferrin receptor that binds to transferrin and causes it to be absorbed by the cell (21); and ultimately expression of the ceruloplasmin gene which is involved in the oxidation of ferrous Fe^{2+} to ferric Fe^{3+} by HIF-1 were observed (22). Increased expression of these genes supports the supply of iron required for erythroid tissues (23).

The role of HIF-1 in angiogenesis

A large number of genes involved in various stages of angiogenesis are induced by hypoxia and also by HIF-1α, among which Vascular endothelial growth factor (VEGF) is the most powerful endothelial-specific mitogen that directly engages in angiogenesis by employing endothelial cells in the region lacking the vessels with hypoxic conditions and stimulates their proliferation (24). Therefore, induction of VEGF expression and other pro-angiogenic factors leads to an increase in capillary density and, consequently, a decrease in the oxygen diffusion distance. Additionally, HIF-1 regulates the expression of genes such as nitric oxide synthase (NOS) (25), heme oxygenase 1 (26), endothelin 1 (ET1) (27), and adrenomedullin (ADM) (28) that are involved in the control of vasoconstriction tone.

The role of HIF-1 in glucose metabolism

When the amount of oxygen available to cells is very lower than their need, cells change their pathway of glucose metabolism from the oxygen-dependent Krebs cycle to the glycolysis process, which is independent of oxygen (29). Although the number of ATP molecules produced in the glycolysis is very lower than that of the Krebs cycle (2 vs. 38), hypoxia-qualified cells provide the ATP they need by increasing the expression of genes related to the glycolytic enzymes and glucose transporters and thus increase glucose absorption. Under hypoxic conditions and increased HIF-1 levels, all glycolytic enzymes, as well as glucose transporters 1 and 3 (GLUT1, GLUT3), are increased (30). In addition, metabolic products of glycolysis, including lactate and pyruvate, under hypoxic conditions, cause accumulation of HIF-1α and regulation of the expression of hypoxia-inducible genes, thereby creating a positive feedback loop (31).

The role of HIF-1 in cell proliferation and survival

Hypoxia and the increased expression of HIF-1 as one of its results, lead to the expression of some of the growth factors whose production and binding to their receptor activate the signaling pathways involved in cell survival and proliferation, also increase the expression of HIF-1α itself. Such factors include insulin-like growth factor 2 (IGF2) and transforming growth factor alpha (TGF-α) (32). Cytokines and growth factors in some types of cells are capable of activating the Mitogen-activated protein kinases (MAPK) and Phosphatidylinositol-3 kinase (PI3K) signaling pathways, which in turn contribute to the proliferation and survival of the cell as well as the HIF-1 function. The activation of these signaling pathways can lead to cancer progression by increasing the transcriptional activity of HIF-1 at the site of target genes including the genes related to the IGF2 and TGF-α, and thus activating the autocrine signaling pathways in pathological cases such as cancer (33).

The role of HIF-1 in programmed cell death (apoptosis)

The adaptation of the cells to hypoxic conditions not only plays a role in the survival and proliferation of cells but in some cases leads to cell death. Studies using embryonic stem cells have shown that the removal of HIF-1α gene in hypoxic conditions reduces apoptosis compared to when its wild type is present in the cell (34). In addition, with regard to the dual role of hypoxia in cell survival, the activation of caspase-3 and Apaf-1 mediated by caspase-9, and release of cytochrome c has been reported in several cell types under these conditions (35). The association between the expression of HIF-1α and HIF-1β with apoptosis and pro-apoptotic agents such as caspase-3, Fas, and Fas ligands has been proven, too. It has been shown that a number of genes involved in controlling the cell cycle, such as p53 and p21 depend on HIF. P53 induces genes involved in apoptosis such as *Bax*, *NOXA*, *PUMA*, and *PERP* to regulate hypoxia-induced apoptosis (36).

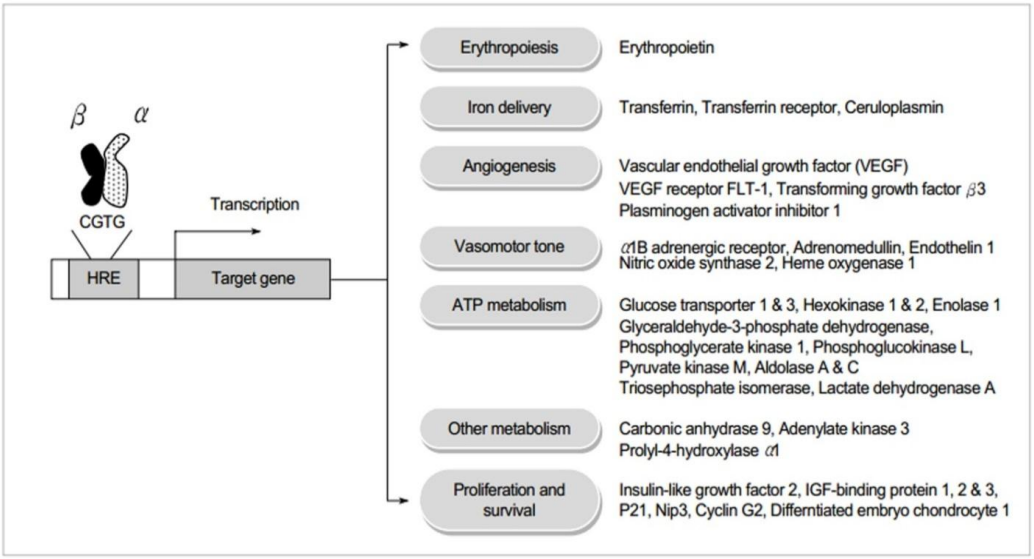

Figure 2. List of target genes of HIF-1α and their role in the cell: α, β HIF1β, HIF-1α, and HRE hypoxia response cis-element (10).

The role of HIF-1 in physiological and pathological conditions

Hypoxia and the HIF-1 signaling pathway play an important role in the physiological and pathological conditions of many human diseases, the most important of which is their role in the development of the fetus and in cancer and ischemic diseases. Regarding the growth of tumors, the role of these two factors has been demonstrated to increase the amount of oxygen delivered to the cell through angiogenesis and activation of glycolysis. Therefore, due to the importance of HIF-1 in activating the necessary genes to advance these processes, the existence of HIF-1α and HIF-2α for the development of cancer is not unanticipated.

The role of HIF-1 in embryonic development

The development of the heart in the human embryo and other mammals depends on hypoxia and the expression of the genes activated in these conditions. HIF-1 and VEGF are of the most important of these genes (37). Deactivation of either HIF-1α (37), HIF-2α (38) or HIF-1β (39) genes results in abnormal vascular development and death in the mouse embryo. The expression of HIF-1α on embryonic days 8.5 and 9.5 increases in the normal embryo of mice, while embryos deficient in this gene (*HIF-1α*$^{-/-}$) will die by embryonic day 11 as a consequence of lack of blood vessel formation, defective formation of the neural fold, and cardiovascular malformation (37). Additionally, the rate of cell proliferation and expression of hypoxia-inducible genes in defective cells in the HIF-1α gene is decreased compared to those of wild-type cells. Although heterozygous mice carrying a single HIF-1α gene develop normally, they display impaired physiological responses facing chronic hypoxia (40). Regarding the role of HIF-2α in embryonic development, targeted inactivation of HIF-2α (*HIF-2α*$^{-/-}$) results in different and variable phenotypes in mice. Mouse embryos with this defective gene die by embryonic day 16.5 as a result of inadequate blood flow, impaired lung maturation, and slow heart rate because of insufficient catecholamine production (38). Embryos deficient in the gene (HIF-1β$^{-/-}$) die by embryonic day 10.5, and defect in blood vessel formation, defective angiogenesis of the yolk sac and branchial arches, and stunted stopped development is approved (39). Additionally, *HIF-1β*$^{-/-}$ cells cannot activate genes that normally express in response to hypoxia and low glucose concentration (39).

The role of HIF-1 in cancer

Overexpression of HIF-1α and HIF-2α was found in various human cancers as a consequence of hypoxia or genetic alterations (41). The cells in the center of the tumor become hypoxic as its size increases. According to studies, hypoxic conditions within tumors result in increased HIF-1 stability and activity. Immunohistochemical analyses demonstrated detectable levels of HIF-1α protein in benign tumors, elevated levels in primary malignant tumors, and a remarkable amount in tumor metastases (42). Hypoxia and the activated pathway of HIF in tumor cells are important stimuli for the growth of blood vessels and angiogenesis. HIF-1α and HIF-2α themselves regulate the expression of pro-angiogenic genes, including the VEGF, Ang-1, Ang-2 and Tie-2 genes, many of which are used as hypoxia biomarkers. Thus inhibiting this gene and preventing its activity in transcribing other genes, can prevent angiogenesis and, consequently, metastasis of cancer cells. Recently, Testis Specific Gene, A10 (TSGA10) has been shown to inhibit the transcriptional activity of HIF-1α by binding to the C-TAD domain in this factor, and thereby inhibiting tumor angiogenesis and metastasis; and that the increase in expression of Tsga10 is associated with reduced transcriptional activity in HIF-1α (43).

Generally, angiogenesis is a necessary and important process in natural physiology, but when the balance between the angiogenesis inducing and inhibiting factors is lost, conditions are provided for the onset and progression of many diseases, including cancer. This process essentially consists of 10 consecutive steps, one or several stages of which can be targeted by angiogenesis inhibitors or stimulators. Due to its importance in many physiological and pathological processes, angiogenesis has been studied by researchers

in a variety of in vitro models (44, 45), in order to intervene with this process and ultimately to inhibit it by various methods such as gene therapy and therapeutic methods to improve the pathophysiological conditions, especially cancer. So far, many strategies have been defined and presented by scientists to interfere with angiogenesis which has received the attention from researchers and physicians. According to the above, one of the target genes of the HIF-1α is *VEGF*, whose expression and its associated R2 receptor by the HIF-1α in the endothelium, trigger VEGF-associated autocrine signaling pathways which are essential for survival, proliferation, endothelial cells migration and vascular formation by them (46).

Therefore, by inhibiting HIF-1α, VEGF, and even by preventing endothelial cell function, it is possible to prevent the spread of angiogenesis-related diseases. Further explanations will follow regarding HIF inhibition as an important treatment strategy. Due to the dependence of angiogenesis on the activation of endothelial cell proliferation, binding, migration, and maturation, most approaches concerned with modifying angiogenesis focus on the endothelial cell function during angiogenesis. Many studies have been conducted in Iran in about endothelial cell migration and binding including the identification and study of a variety of angiogenesis inhibitors such as anti-angiogenic peptide in shark cartilage (47), anti-plasminogen monoclonal antibody (48), kunitz trypsin inhibitor from soybean (49), the study of the anti-angiogenesis properties and mechanisms of the allium stipitatum (50, 51) and salvia officinalis (52), as well as the study of the anti-angiogenesis effect of green tea (53) and beeswax extract (54).

The role of HIF-1 in ischemic diseases

The activation of HIF-1 function has been proven in a wide range of physiological responses to ischemic, hypoxic and inflammatory conditions, plus its important role in response to tissue damage and organ damage. For example, high levels of HIF-1α and VEGF have been observed in the myocardium of patients with coronary artery occlusion (55). Proper and effective vascular changes after ischemic injury are dependent on the expression of genes whose expression is activated by HIF. Additionally, induction of HIF-1α, HIF-2α, and their target genes was observed in rheumatoid arthritis, retinal ischemia, heart ischemia, and wound healing (56, 57).

The role of HIF-1 in various pathological and physiopathological processes, as well as its various regulatory aspects, make this factor suitable for therapeutic purposes. Today, inhibition of this factor is one of the key strategies for cancer treatment. The immunohistochemistry analyzes of HIF-1α expression in cancerous tissues have provided important information in diagnosis, according to which it is possible to determine the necessary measures for treating the patient (42). HIF-1 expression in tumor cells causes their resistance to treatment by chemotherapy and radiotherapy. Thus, inhibition of the pre or post transcription level can prevent the progress of cancer. The researchers carried out studies on these genes in mice and showed that the use of the polypeptide corresponding to the C-TAD region related to HIF-1α through competition with CREB binding protein (CBP)/p300 to bind to this region decreased VEGF expression and tumor growth in mice (58). Additionally, many therapeutic compounds have been identified that by targeting the HIF-1α signaling pathways can stop its function and thereby inhibit angiogenesis (42). Recently, it has been shown that some of these compounds act directly or indirectly through the interaction with the mTOR signalling cascade. mTOR is a serine/threonine protein kinas, which acts in protein synthesis regulation, cell growth and survival, and also in a positive and negative feedback cycle with HIF-1α (59). Studies have shown that phosphorylation of mTOR along with the protein binding to p70S6K-BP(4E)4E1 as its downstream factors increased the amount of this protein in the cells through the stimulation of the translation of HIF-1α. Then the binding of HIF-1α to HIF-1β leads to the activation of the transcription of genes related to growth factors and cytokines that activate the receptor pathway of tyrosine kinase -phosphoinositide-3-kinase (PI3K) - protein kinase B (Akt) and finally overactivity of mTOR (60).

It has been also shown that HIF-1α deactivates mTOR indirectly through stabilizing the protein regulated in development and DNA damage response 1 (REDD1), the next binding of the transcript to tuberous sclerosis 2 protein, and activating this protein by it (61).

Contrary to inhibition of HIF-1 activity in cancer treatment, its increased activity can be effective in the treatment of ischemic diseases (56, 57). Ischemic diseases such as stroke and heart attack result from localized hypoxia in the brain and myocardium, respectively. Increased expression of VEGF by HIF-1α and HIF-2α induces the formation of new blood vessels in the target fragments of the brain and the heart followed by an increased blood flow, oxygen and ultimately harm reduction in response to ischemia (62). Researchers have used polypeptides corresponding to the N- and C-terminal of the ODDD domain for direct induction of HIF-1. The polypeptide induces and increases the amount of HIF-1 by preventing the degradation of it by the VHL (63). In addition, the inhibition of proline hydroxylase and asparaginyl are other strategies for increasing the amount and activity of HIF-1 (64).

Discussion and Conclusions

Hypoxia and HIF-1 play an important role in physiological and pathological conditions through effects on gene expression and hence on the cell biology and physiology in mammals. According to studies on the effect of these factors on angiogenesis, overexpression is necessary for physiological conditions like embryonic development or pathological conditions like ischemic diseases. However, this overexpression in cancer, as one of the most important pathological conditions associated with hypoxia, will have adverse health effects (65). Therefore, conducting more accurate surveys and studies in the field of biology regarding HIF-1 pathway as one of the important pathways involved in hypoxia and its role in human diseases, such as cancer, can have important and useful results in the treatment of this disease.

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