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MODERN CONCEPTS OF HYPOXIA-INDUCIBLE FACTOR -1 (HIF-1) AS AN IMPORTANT PATHOPHYSIOLOGICAL MECHANISM FOR THE DEVELOPMENT OF ISCHEMIA.

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Abstract:

Hypoxia-inducible factor (HIF)-1, is a dimeric protein complex that plays an important role in the body's response to low oxygen concentrations or hypoxia. HIF-1 is one of the main genes involved in the homeostatic process, which can increase vascularization in hypoxic areas such as localized ischemia and tumors. It is a transcription factor for dozens of target genes; HIF-1 is also important for immunological responses and is an important physiological regulator of homeostasis, vascularization, and anaerobic metabolism. In addition, HIF-1 is increasingly being studied due to its purported therapeutic potential. Because it induces angiogenesis, upregulation of this gene in patients with ischemia may promote vascular proliferation required for oxygenation. On the contrary, since HIF-1 promotes the survival and proliferation of cancer cells due to its angiogenic properties, inhibition could potentially prevent the spread of cancer. With the growing understanding of the HIF-1 pathway, inhibition and stimulation of its transcriptional activity by small molecules is currently an attractive target. Gene therapy to achieve both vascular proliferation and tumor regression has been demonstrated in animal studies but needs significant improvement and modification before it is commercially available. This review examines the potential of the HIF-1 pathway in a therapeutic intervention for diseases such as cancer and ischemia.

Keywords: hypoxia; ischemia; hypoxia-inducible factor; homeostasis; anaerobic glycolysis; Krebs cycle.

RELEVANCE. Many pathogenetic aspects of pathogenetic disorders in chronic liver diseases remain unexplored [1-4]. One of the most common causes of chronic hepatitis and liver cirrhosis is infection with hepatitis B and C [5-9]. At the same time, more than 180 hepatotoxic drugs have been identified, of which 6 groups seriously injure the liver. At the same time, 50% of drugs are hepatotoxic, especially in women this effect is more pronounced. Medicines cause hepatocellular damage, even liver necrosis, which is clinically manifested mainly by jaundice, fever, and increased liver enzymes [10].

Oxygen is required by the cells of most organisms to produce enough ATP for metabolic activity. Hypoxia, or oxygen starvation, occurs in human tissues and cells due to a variety of conditions, including heart and lung disease, anemia, and circulatory problems. Depending on the severity, irreversible damage to tissues and cells can occur [11].

However, hypoxia can also play an important and beneficial role in human physiology and development. It is an essential part of proper embryonic development. Although the exact mechanisms are not known, oxygen tension is associated with neural tube closure, mediation of apoptosis, and proper morphological development during pregnancy. Such data show that in addition to genetic signals, environmental conditions such as hypoxia serve as signals in embryonic development [12,13,14]

Many organisms have developed mechanisms for adaptation to hypoxic conditions. Changes in oxygen levels can lead to the activation or repression of certain homeostatic regulatory genes, allowing tissues and cells to survive despite fluctuations in environmental conditions. Genes such as HIF-1, which are activated under hypoxic conditions, can interact with enzymes and other transcription factors to control vascularization and tissue growth. While the microenvironment surrounding cancerous tumors is extremely hypoxic, the spread of such masses is often made possible by the activation of HIF-1, which leads to an increase in angiogenesis and thus an increase in oxygen supply to this area [15, 16].

Given its important function, manipulation of HIF-1 activity in areas of ischemia and tumor masses has become a major focus of efforts to develop non-invasive, pharmaceutical treatment options for patients with cancer and heart disease. Although no such human protein has been successfully regulated by scientific methods, control of HIF-1 activity is becoming increasingly feasible as the details of its structure, function, and genetic pathway are elucidated.

HIF-1 is a heterodimeric transcription factor consisting of a constitutively expressed β-subunit and an oxygen-regulated α-subunit. The HIF-1α and HIF-1β proteins both contain basic helix-loop-helix motifs that bind DNA and induce subunit dimerization [17, 18, 19]. Both subunits also have a Per-ARNT-Sim (PAS) domain with similar functions. The α-subunit has an oxygen-dependent degradation domain (ODD), which is hydroxylated by proline hydroxylase-2 (PHD-2), making the α-subunit vulnerable to proteasomal degradation under normoxic cellular conditions [20].

PURPOSE OF THE STUDY. Determine the significance of hypoxia-inducible factor-1 in the development of ischemia.

The HIF-1α subunit also contains two transactivation domains (TADs) that regulate HIF-1 target genes. CREB-binding protein (CBP) and p300, two HIF-1 transcription coactivators, interact with the carboxy-terminal transactivation domain (C-TAD) of HIF-1α.

Both activators are required for HIF-1 transcription and therefore are targets for the regulation of HIF-1 expression; inhibition of HIF-1α C-TAD interactions by proline hydroxylation suppresses HIF-1 gene expression, preventing normal transcription and translation [11]. HIF-1β contains only one such analogous region, which is not needed for the complex function of HIF-1 [7,10,12]. Recent reports indicate that HIF-1β is identical to a previously discovered vertebrate protein, the aryl hydrocarbon receptor nuclear translocator (ARNT).

HIF-1 is the main regulator of oxygen homeostasis in cells. As a transcription factor, it influences and regulates the expression of dozens of genes involved in maintaining homeostasis when the oxygen concentration changes [13]. HIF-1 further mediates cellular responses to hypoxia by regulating glucose uptake and anaerobic respiration in oxygen-depleted environments [5,2].)

One important function of HIF-1 is to promote angiogenesis; HIF-1 directs the migration of mature endothelial cells to a hypoxic environment [2,5]. This is done through HIF-1 regulation of vascular endothelial growth factor (VEGF) transcription. VEGF is the main regulator of angiogenesis, which promotes the migration of endothelial cells towards the hypoxic region. During hypoxia, HIF-1 binds the regulatory region of the VEGF gene, inducing its transcription and initiating its expression [12,15,16]. These endothelial cells eventually help form new blood vessels, supplying the area with oxygenated blood [14].

HIF-1 regulates transition to anaerobic metabolism

HIF-1 can also regulate anaerobic metabolism. When oxygen is available, most cells produce ATP through oxidative phosphorylation. However, in a hypoxic environment, there is a shift towards anaerobic metabolism for cellular energy production. HIF-1 is one of the main genes coordinating this shift by inducing various glycolytic enzymes and glucose transporters, such as aldolase A and pyruvate kinase M, which help cells efficiently generate energy in a hypoxic environment [5,16]. In addition to increasing the expression of these enzymes, HIF-1 reduces mitochondrial oxygen consumption by activating pyruvate dehydrogenase kinase I and stopping the citric acid cycle [17].

The environment surrounding metastasizing tumor masses is often hypoxic. HIF-1 is the most important protein in such masses; it enables tumor progression by inducing alternative metabolic pathways in cancer cells, as discussed above in the context of physiological hypoxia.

Due to its role in hypoxia, HIF-1 plays a critical role in tumor proliferation [18]. As the tumor develops and grows, a hypoxic environment is created due to the extreme energy needs of numerous rapidly dividing cells. Such cell masses often induce angiogenesis to meet demands for increased oxygen, energy, and blood supply [5,16]. Simultaneously, HIF-1 promotes the transition to anaerobic metabolism. The importance of this transcription factor in tumor cell survival is reflected in the finding that HIF-1α levels in glioma tumor cells increase in proportion to tumor grade [19].

The mechanisms of tumor survival mediated by HIF-1 are partly disclosed by Semenza et al. on VHL-deficient renal carcinoma cells. HIF-1 has been found to reduce oxygen consumption in these cells by inhibiting C-MYC, a transcription factor that regulates mitochondrial mass and oxygen consumption and is known to be downregulated in various human cancers. Semenza et al. report that HIF-1 reduces C-MYC levels by increasing the transcription of MXI1, a C-MYC repressor, and by increasing the rate of proteasomal degradation of the C-MYC protein. It has been found that reduced levels of C-MYC in these cancer cells ultimately lead to increased glycolysis and reduced mitochondrial respiration, critical characteristics of cancer cells that survive and proliferate in the hypoxic conditions of the tumor microenvironment [30].

Currently, there are many studies on the role of HIF-1 in hypoxia-induced apoptosis of various cell types. For example, Krick et al.recently reported that overexpression of HIF-1 in alveolar epithelial cells leads to increased apoptosis [21]. Although the exact pathways and mechanisms involved in this process remain unclear, evidence suggests that the p53 tumor suppressor is activated under hypoxic conditions. Through interaction with the HIF-1 protein, p53 stabilizes and starts to activate genes such as p21, which in turn cause cell death [5,21].

HIF-1 Supports Inflammatory Responses and Hypoxic Recovery

In addition to other roles in adaptation to hypoxia, HIF-1 has been shown to play a role in inflammation. Kramer et al demonstrated that HIF-1 is required for metabolism in myeloid cells [22]. Overexpression of HIF-1 in vivo resulted in increased localized inflammation, while loss of the HIF-1 gene reduced the ability of myeloid cells to aggregate, migrate, and stimulate bactericidal responses. This dependence of myeloid cells on HIF-1 may be related to their dependence on anaerobic respiration as a means of energy production. Myeloid cells lacking this gene cannot

efficiently produce ATP, migrate effectively to damaged tissues, or destroy foreign invaders [22]. In addition, HIF-1α expression plays a role in the differentiation of myeloid cells into monocytes and macrophages [23].

In contrast, HIF-1 may prevent tissue and heart damage caused by ischemia, which can lead to many long-term heart problems. Overexpression of HIF-1 in such tissues can induce angiogenesis and thus increase oxygenation of the area [24,25]. This serves as the basis for current efforts to find pharmaceutical and other non-invasive treatments for ischemia and related diseases.

Under normoxic conditions, HIF-1α is cleaved by proteasomes. The HIF-1α subunit is "tagged" for such degradation by proline hydroxylase-2 (PHD-2) and von-Hippel-Lindau (VHL)-ubiquitin ligase complexes. Therefore, HIF-1 does not function in the presence of sufficient oxygen [10,26]. Also, HIF-1 inactivation under normoxic conditions is promoted by the HIF-1 inhibitory factor (FIH) protein, which hydroxylates HIF-1, preventing the interaction of this subunit with p300 and CBP coactivators. Expression and stabilization of the HIF-1 complex are regulated through feedback inhibition, since PHD-2 itself is activated by HIF-1 [12].

However, under hypoxic conditions, the HIF-1 protein is stable and active, since hydroxylases, VHL and FIH proteins are inhibited by a lack of oxygen. HIF-1 can then interact with its coactivators and can dimerize with its constitutively expressed β subunit. After stabilization, the HIF-1 protein can bind to the regulatory regions of its target genes, causing their expression [7,10,27].

Various HIF-1 stimuli operate independently of oxygen concentration. These stimuli are primarily proteins that regulate HIF-1 translation, in stark contrast to the hypoxic stimuli of this gene that act on the already expressed α-subunit. Protein kinase C (PKC) increases the rate of HIF-1α transcription and functions in conjunction with the phosphatidylinositol 3-kinase pathway (PI3K), which also enhances HIF-1α translation. The PKC pathway activates the expression of the S6 ribosomal protein, which specifically recognizes mRNA transcripts such as HIF-1α. Through phosphorylation of the S6 protein under normoxic conditions, the translation rate of HIF-1α mRNA can be significantly increased, effectively counteracting the effects of proteasomal degradation of this subunit and increasing levels of the HIF-1 complex in the cell. The PI3K pathway has been identified as the primary means by which various mediators, such as lipopolysaccharides, influence HIF-1α activation in vascular smooth muscle cells and macrophages [12,27].

In the treatment of ischemia, activation of HIF-1α can stimulate angiogenesis and increase blood flow. Many genes involved in angiogenesis, such as VEGF, matrix metalloproteinase 2 (MMP2), cathepsin D (CATHD), and keratin (KRT), are targets of the HIF-1 transcription complex. It is believed that elevated levels of HIF-1 lead to a proportional increase in these proteins [12,28]. In several recent studies, mice injected with HIF-1α DNA without ODDD showed increased blood flow to injured or ischemic areas, suggesting that increased levels of HIF-1α may help supply blood, oxygen, and nutrients to focal ischemic sites [29, 30].

Introduction of a constitutively stable hybrid HIF-1α into rat cardiomyocytes resulted in a reduction in ischemic injury. This hybrid consisted of DNA-binding and dimerization domains from HIF-1α and a transactivation domain of the HSV VP16 protein [31]. Overexpression of HIF-1α in mouse models of myocardial infarction reduces infarct size, thereby preserving cardiac function [32]. Upregulation of HIF-1 expression may prove to be a successful drug for the treatment of ischemic patients who cannot be operated on.

Direct phosphorylation of the HIF-1α subunit can increase HIF-1 activity, presumably by interfering with proteasome/VHL recognition. Although very little is known about HIF-1α phosphorylation, protein kinases activated by the p42/p44 mitogen phosphorylate this protein in vitro. In vivo, such phosphorylation is required for HIF-1 function. Activation of the p42/p44 pathway leads to an increase in HIF-1α transcription levels. This phosphorylation may be the optimal step in the HIF-1 pathway to induce overexpression [33].

HIF-1 hydroxylases are composed of several related molecules, including HIF inhibitory factor (FIH) proteins and prolyl hydroxylase domain (PHD) proteins. Since VHL mediates the proteasomal degradation of hydroxylated HIF-1α, HIF-1α levels can be increased by suppressing HIF-1alpha-prolyl-4 hydroxylase-2 (PHD2). Inhibition of PHD2 by siRNA also results in a reduction in the size of myocardial infarction in mice. These pathways can be modified using pharmacological approaches [34].

Several small molecules, such as dimethyloxalylglycine, a prolyl hydroxylase inhibitor, activate HIF-1. The hydroxylase activity can be eliminated by mutation of certain regions or by adding cobalt ions to the cell, which presumably compete for iron binding sites [35]. Some prolyl family hydroxylases can be selectively inhibited by adriamycin in vitro [36]. Cobalt(II) and nickel(II) ions increase HIF-1 activity in cells, presumably because such ions displace iron from the active sites of 2OG hydroxylases.

Small molecule therapy can be useful not only for HIF-1 suppression, but also for its activation in the treatment of ischemic diseases [7]. Hormones such as angiotensin II and platelet growth factor stimulate the HIF pathway by increasing HIF-1α protein levels through the production of reactive oxygen species (ROS) in the cell. Although the exact mechanism is unclear, it appears to be completely different from hypoxia pathways. Thrombin and other growth factors enhance angiogenesis through the mechanisms of HIF-1α protein agonists [14,33]. Insulin also activates HIF-1α, activating many protein kinases required for expression and function [37].

In another study of HIF-1 activation, a homozygous deletion of the p53 gene resulted in HIF-1 activation [38]. Therefore, p53, which is responsible for promoting HIF-1αubiquitination, may be another possible target.

Ultimately, gene therapy could be used to increase HIF-1 levels and alleviate the complications of ischemia. For example, delivery of a stabilized recombinant form of HIF-1α via adeno-associated virus (AAV) to overexpress HIF-1 in skeletal muscle resulted in a significant increase in the number of capillaries [38,39].While gene therapy

approaches targeting the process and effects of angiogenesis continue to be developed and studied, higher levels of success in preclinical trials are currently being sought before clinical applications are made. One of the most notable remaining obstacles to gene therapy is the mode of delivery [38]. The search for the most efficient delivery vector continues.

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