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Review Article

HIF-1α Related Signaling Pathway and Its Role in Common Gastrointestinal Tumors

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Abstract: Esophageal cancer, gastric cancer and liver cancer are common digestive tract tumors. at present, radical surgery, radiotherapy and chemotherapy and traditional chinese medicine are the main clinical treatments for digestive tract tumors, but the morbidity and mortality of patients are still high. Therefore, it is very important to strengthen the research on the pathogenesis of digestive tract tumors. Therefore, it is very important to strengthen the research on the pathogenesis of digestive tract tumors in order to find the biomarkers and therapeutic targets for the early diagnosis of digestive tract tumors. Hypoxia-inducible factor-1 (Hypoxia-inducible factor-1, HIF-1), as an important regulator in hypoxia environment, is a heterodimer composed of subunits α and β. Its role is mainly determined by HIF-1α, by the fine regulation of O_2 content in the microenvironment, and participates in the regulation of a variety of tumor signal pathways. There is a strong correlation between high expression of HIF-1α and tumor metastasis, angiogenesis, poor prognosis and drug resistance treatment. This article reviews the research progress on the structure, function, expression regulation, action mechanism and role of HIF-1α in common digestive tract tumors, in order to provide theoretical basis for clinical treatment of digestive tract tumors.

Keywords: Hypoxia Inducible Factor-1, Cell Signaling Pathway, Gastrointestinal Tumors

1. Introduction

1.1. The Structure of HIF-1

Hypoxia inducible factor-1, also known as HIF-1, is a heterodimer transcription factor associated with hypoxia stress response discovered by Semenza team in 1992 in the study of erythropoietin gene expression [1, 2]. HIF-1 is composed of a structurally expressed HIF-1β subunit (also called as the aromatic hydrocarbon receptor nuclear transporter) and an oxygen-sensitive HIF-1α [3]. Their relative molecular weights are 91-94 and 120kd, respectively. Both HIF-1α and HIF-1β are memberships of the BHLH-PAS superfamily and contain basic Helic-Loop-Helix (bHLH) and Per-Arnt-Sim (PAS) domains that are obligatory for dimerization and binding to their consistent DNA sequences in the target gene promoter region [4]. Hypoxia-inducing-factor 1α exists in the cytoplasm and has two autonomous trans-activation domains at its COOH incurable, amino-terminal trans-activation domain (N-TAD) and COOH-terminal trans-activation domain (C-TAD). N-TAD establishes a dilapidation box and participates in the regulation of HIF-1α stability, while C-TAD participates in the regulation of HIF-1α transcriptional activation under hypoxia [5]. HIF-1β, also known as aromatics transporter, is steady in cytoplasm or cytoplasm and acting an organizational role. Its protein expression is not affected by oxygen concentration. Heterodimerization with different bHLH-PAS proteins [6].

1.2. The Instruction of HIF-1 Expression

The transcriptional movement of HIF-1 is mainly strongminded by the expression level of HIF-1α, and the expression level and protein stability are regulated by oxygen

content. Oxygen regulates the stability and activity of HIF-1α through the hydroxylation of proline and asparagine residues. Under normal oxygen partial pressure, two proline residues (P^{402} and P^{564}) in the HIF-1α domain are hydroxylated by proline hydroxylase domain protein (PHD), which interacts with von Hippel-Lindau (VHL) protein. VHL can recruit E3 ubiquitin ligase to catalyze the polyubiquitin of HIF-1α, which in turn leads to protease degradation [7-9]. The HIF inhibitor (factor inhibiting HIF-1, FIH), that is, asparagine hydroxylase, can be hydroxylated on the aspartic acid residue, thus inhibiting the transcriptional activity of HIF-1α [10]. Therefore, it is difficult to detect HIF-1α when the partial pressure of oxygen is normal. Under anoxic condition, the hydroxylation of proline and asparagine was inhibited, which led to the stabilization of HIF-1α protein and increased interaction with its co-activator. Therefore, in anoxic cells, a large number of HIF-1α aggregates and combines with HIF-1β to form an activated heterodimer HIF-1. The activated deficient HIF-1 binds to the common a sequence 5 in hypoxia response element (HRE), and activates its transcription, which participates in the expression of genes in different signal pathways [11].

2. HIF-1a Related Hypoxia Stress Signaling Pathways

HIF-1α was initially considered to be a crucial factor for cells to adapt to hypoxia. It is now fine acknowledged that HIF-1α normalizes an assortment of physiological processes [12]. The physiological process in which HIF-1α participates in regulation is inseparable from the stimulation of hypoxia. The body and cells can explicitly regulate the expression of genes and proteins through oxygen receptors and signal pathways, thus forming a tedious oxidative stress response system to maintain the stability of their own internal environment [13]. In recent years, more and more attention has been paid to the involvement of HIF-1α in the regulation of gene transcription during hypoxia. Many hypoxia signal pathways, including hydroxylation, acetylation, ubiquitin and phosphorylation, have been shown to control the stability and transcriptional activity of HIF-1α, as described below:

2.1. Oxygen-dependent Regulation of HIF-1α Pathways

2.1.1. pVHL Dependent Pathways

Under normoxia, the expression of HIF-1α is negatively controlled by proteasome degradation and ubiquitin, which involves a tumor suppressor protein pVHL, which is also a constituent of E3 ubiquitin ligase [8]. Two proline residues (P^{402}/P^{564}) are located in the LXXLAP amino acid sequence of HIF-1α, which provides a good substrate for the activity of prolyl-4 hydroxylase (PHDs) or proline hydroxylase (HPH) [7, 9]. It is a 2-OG-dependent dioxygenase that needs oxygen for hydroxylation and the synthesis of other cofactors such as iron and ascorbic acid. Therefore, PHD hydroxylation of proline residues happens only when oxygen is satisfactory [14]. In addition, another ODDD residue (lysine, K^{532}) can be acetylized by acetyltransferase [15]. Therefore, the adapted HIF-1α subunit with hydroxylated P^{402}/P^{564} and acetylated K^{532} portions is known by pVHL in priority and is labeled for ubiquitination and proteasome degradation [16]. Because the hydroxylation of PHD requires the presence of oxygen, HIF-1α proline and lysine residues are neither hydroxylated nor acetylized under anoxic conditions, ensuing in the structural stability of HIF-1α.

2.1.2. pVHL Independent Pathways

Additional major oxygen-dependent instrument of negative regulation of HIF-1α pathway under normoxia conditions is by monitoring the transcriptional activation of HIF-1α. This pathway characterizes another post-translational modification level of HIF-1α transcriptional activation region, but does not involve pVHL protein. The transcriptional activation of HIF-1α target gene is originated by the synergistic binding of C-TAD and coactivator CBP/p300 in HIF-1α. Under normoxia conditions, the oxygen-dependent hydroxylation of asparagine residue (N^{803}) in HIF-1α blocks the interaction between the two domains by preventing HIF-1 (FIH-1), thus canceling HIF-1α-mediated gene transcription [17, 18]. In addition, hypoxia promotes this interaction by inhibiting the oxygen-dependent hydroxylation of N^{803}, leading to transcriptional activation of target genes [19].

To sum up, the oxygen-dependent regulation of HIF-1α pathway encompasses a series of post-translational modifications. pVHL is involved in regulating the stability of HIF-1α, but not VHL in regulating the transcriptional activation of HIF-1α.

2.2. PHD/HIF-1α/pVHL Signaling Pathways

PHD is an oxygen-dependent hydroxylase and an intracellular oxygen sensor. Its activity varies with intracellular oxygen concentration and dramas an important role in regulating the stability of HIF-1α [20]. The HIF-1α structure contains an oxygen-dependent domain ODDD. When the oxygen partial pressure is normal, the proline residue in this domain is easily hydroxylated by PHD, and the hydroxylated HIF-1α quickly binds to the tumor suppressor protein pVHL. Then, a variety of ubiquitin proteins are recruited to form a ubiquitin protease complex, thus the HIF-1a is degraded rapidly [21]. At the same time, HIF-1 inhibitors can inhibit HIF-1a transcription by catalyzing HIF transcriptional domain (TAnC) and interfering with the binding of transcriptional cofactor p300/CBP to TAnC [15]. On the contrary, under hypoxia, the hydroxylation of PHD is repressed, which hinders the binding of HIF-1a to pVHL, resulting in the inhibition of HIF-1α degradation, and then transferred to the nucleus to bind to HIF-1β to form a HIF-1 complex, which binds to the hypoxia response element HRE and regulates the transcriptional activation of downstream genes such as erythropoietin (EPO), metalloproteinases (MMPs) and vascular endothelial growth factor (VEGF) [22]. At the same time, hypoxia can also inhibit the activity of FIH-1, promote the binding of p300/CBP and TAnC, and improve the transcriptional activity of HIF-1α [23].

2.3. PI3K/Akt/ HIF-1α Signaling Pathways

PI3K/Akt pathway is an important signal pathway in the process of cell cycle, which is faithfully related to cell proliferation and apoptosis. It has been found that under hypoxia, PI3K can be activated and bind to its downstream Akt to phosphorylate Akt. Phosphorylated Akt can enhance the transcriptional activity of HIF-1α and then initiate the transcription of HIF-1α-related target genes, which enhances the ability of cell proliferation and weakens the ability of apoptosis [24]. Former studies have exposed that HIF-1a is regulated by PI3K/Akt/mTOR signal pathway [25]. Hypoxia increased the protein levels of p-Akt and HIF-1a in human bone marrow mesenchymal stem cells [26]. The expression of p-Akt was earlier than that of HIF-1α. Interestingly, both PI3K inhibitor LY294002 and dual PI3K/mTOR inhibitor NVP-BEZ235 could inhibit hypoxia-induced p-Akt activation and HIF-1a expression [27, 28]. Akt inhibitor wortmannin can only inhibit the expression of HIF-1α at the protein level [29]. mTOR is a kind of hypoxia/oxygen-rich receptor, which is the downstream target of Akt involved in cell cycle regulation, glucose metabolism and protein synthesis. In addition, mTOR is also considered to be an upstream regulator of HIF-1α activation. Based on previous studies, PI3K/Akt signaling pathway may regulate post-transcriptional protein level of HIF-1α through mTOR. Some studies have shown that in some tumors, the activation of PI3K/AKt pathway is mainly caused by the mutation of tumor suppressor gene PTEN. Phosphatase produced by PTEN gene can be used to degrade PI3K products. The loss of PTEN function enhances the phosphorylation and activity of Akt, which leads to the increase of cell proliferation signal and the decrease of apoptosis signal [25]. The regulation mechanism between HIF-1α and PTEN needs to be further studied.

2.4. MAPK/HIF-1α Signaling Pathways

ERK/MAPK pathway is the furthermost classical signal pathway, which dramas an important role in controlling cell proliferation, differentiation, metastasis and other physiological processes [30]. The signal transduction step follows the MAPK three-stage enzyme cascade, which is composed of upstream activation sequence, MAP3K, MAP2K and MAPK. The extracellular signal is transmitted to the intracellular regulatory target, and the target is activated to produce biological functions closely related to the occurrence and development of tumor. In the ERK pathway, Ras is the upstream activating protein, Raf is the MAP3K, MAPK/ERK kinase (MEK) is MAPKK, ERK is MAPK, forming the Ras-Raf-MEK-ERK pathway. Some studies have publicized that the MAPK pathway can regulate the expression of HIF-1α [31]. Under the stimulation of hypoxia, intracellular ERK is phosphorylated, and the expression level of HIF-1α is significantly increased [31]. In addition, some specific growth factors can also activate the MAPK pathway by activating RAS, thus increasing the production rate of HIF-1a. At the same time, some studies have found that MAPK and PI3K/Akt signal pathways can jointly regulate the expression of HIF-1α, thus affecting cell proliferation and apoptosis [32].

2.5. Other HIF-1α-related Signaling Pathways

In addition to the above-mentioned signal pathways, some studies have found that the hypoxia adaptive signal pathway participated in by HIF-1α also mediates other signal pathways. It has been found that the deletion of p53 tumor suppressor gene is related to the increase of HIF-1α level in some tumors [33]. This can be explained by the fact that under normoxia, HIF-1a binds to p53 and permits Mdm2 (mouse double minute 2 homologue) to mediate HIF-1α ubiquitination and proteasome degradation [34]. In hypoxia tumors, deletions or mutations in tumor suppressor genes reduce any chance of Mdm2-mediated HIF-1α degradation. Some studies have also found that heat shock protein 90 (Heat shock proteins 90, Hsp90) can bind to the bHLH-PAS domain of HIF-1α under hypoxia, prevent the ubiquitin degradation of HIF-1α, promote the expression of HIF-1α, and then regulate downstream target genes [35]. At the same time, it has been reported that Hsp90 inhibitors such as GA can down-regulate HIF-1α levels regardless of the presence of oxygen [36]. In addition, studies have found that there is an interaction between Myc and HIF-1α, which is related to tumorigenesis and development. When hypoxia occurs, the expression level of HIF-1α is up-regulated and suppresses the expression of Myc target genes, and then down-regulates the expression level of genes related to cell cycle and DNA repair, thus affecting cell growth [37]. These results recommend that HIF-1α and other signal pathways also interact with each other in the regulation of hypoxia.

3. Common Digestive Tract Tumors Associated with HIF-1α

3.1. HIF-1α and Esophageal Cancer

Esophageal cancer is the most common intestinal tract tumor, which is separated into esophageal squamous cell carcinoma and esophageal adenocarcinoma. China is one of the countries with high frequency of esophageal cancer, and more than 90% of esophageal cancer is esophageal squamous cell carcinoma [38]. It has been found that HIF-1a is exceedingly expressed in esophageal cancer, which can bind to the HIF-1α binding site of the regulatory region of VEGF gene and promote the expression of VEGF [39]. High expression of VEGF can promote tumor angiogenesis and vascular permeability, thus promoting tumor proliferation and metastasis [40]. Therefore, the prognosis of esophageal cancer patients with high expression of HIF-1α and VEGF is poor [39]. In addition, some studies have shown that under hypoxia, the high expression of HIF-1α in esophageal cancer can promote the expression of a variety of key glycolysis enzymes, and then promote glycolysis of esophageal cancer cells, provide sufficient energy for cell growth and proliferation, but also increase its tolerance under hypoxia [41]. Other studies have shown that patients with high expression of HIF-1α in

esophageal cancer are more likely to have tumor metastasis [42]. On the one hand, HIF-1α can promote lymph node metastasis of esophageal cancer by promoting the expression of VEGF-C [43]. On the other hand, HIF-1α can promote the separation of β-catenin from E-cadherin/β-catenin complex. The isolated β-catenin enters the nucleus and can be used as a promoter to promote the transcription of genes related to epithelial mesenchymal transformation (epithelia-mesenchymal transition, EMT), thus reducing the adhesion of tumor cells and enhancing their invasive ability [44].

3.2. HIF-1α and Gastric Cancer

Gastric cancer is the fifth largest type of malignant tumor in the world, which originates from gastric mucosal epithelium and has high morbidity and mortality [38]. In recent years, although prodigious progress has been made in the diagnosis and treatment of gastric cancer, the survival rate of patients with gastric cancer is still low [45]. Studies have shown that HIF-1α dramas an important role in promoting proliferation, metastasis and inhibiting apoptosis of gastric cancer cells. Zhang [46] et al found that HIF-1a can enhance the proliferation, metastasis and invasion of gastric cancer by promoting the expression of PI3K/Akt pathway and VEGF. At the same time, HIF-1α can also be regulated by PVT1/miR-186 [47] and linnc-pint [48] as a target gene under hypoxia, or as an activator to promote the expression of miR-421 [49] and GAPLINC [50] in gastric cancer and inhibit apoptosis. In addition, under hypoxia, HIF-1α can promote the transformation of gastric cancer cells from epithelium to stroma by up-regulating the expression of TFF1 [51], KLF8 [52] and Snail [53]; on the other hand, it can also interact with heat shock protein 90 (Hsp90) to inhibit the expression of Caveo-lin-1 (Cav-1), thus promoting the EMT-like changes of gastric cancer cells [54].

3.3. HIF-1α and Liver Cancer

As of 2018, liver cancer is the fourth leading cause of cancer death and the sixth largest cancer in the world, of which hepatocellular carcinoma (Hepatocellular carcinoma, HCC) accounts for 75% of primary liver cancer. According to statistics, the incidence of liver cancer in China ranks fourth among malignant tumors, and its mortality rate is second only to lung cancer [38]. It is reported that the expression level of HIF-1α in hepatocellular carcinoma is higher than that in paracancerous tissues, and the high expression of HIF-1α is related to poor tumor grade and intrahepatic metastatic capsule infiltration [55]. It has been found that HIF-1α can promote tumor cell proliferation and angiogenesis by mediating a variety of growth factors, such as VEGF, EGF, TGF-a, IGF-2 and so on. At the same time, the above cytokines can bind to their corresponding tyrosine kinase receptors, and then promote the production of HIF-1α under hypoxia through Ras/Raf/MEK/ERK or PI3K/Akt signal pathway, form feedback regulation, and accelerate the deterioration of tumor. In addition to growth factors, some studies have shown that adrenergic receptor β2 (ADRB2) can promote the proliferation of hepatocellular carcinoma cells by stabilizing HIF-1a protein in an Akt-dependent manner [56]. In addition, Hsp90 can promote the proliferation and inhibit the apoptosis of hepatocellular carcinoma cells by regulating the expression of HIF-1α [57]. Studies have shown that necrotic fragments of liver cancer cells under hypoxia can promote the release of 1L-1β from M2 macrophages, which can bind to cyclooxygenase-2 and up-regulate HIF-1α, thus promoting the EMT process of liver cancer cells [58]. In addition, HIF-1α under hypoxia can also regulate the transcriptional activities of MMP-2 and MMP-9 and promote the formation of metastatic foci in hepatocellular carcinoma cells [59, 60].

4. Conclusion

To sum up, HIF-1α can be used as a carcinogenic factor in most digestive tract tumors, and can endorse the existence and development of tumors in a variety of ways. High expression of HIF-1α is associated with poor prognosis of patients. However, the specific role of HIF-1α in the pathogenesis of digestive tract tumors needs to be further studied. Therefore, in-depth study of HIF-1α and its upstream and downstream genes will provide new ideas for the prevention and treatment of digestive tract tumors. The future research direction can be to develop more specific HIF-1α inhibitors by better understanding the molecular structure of the domains that mediate the key functions of HIF-1α. This study summarizes the research of HIF-1α in common digestive tract tumors, in order to provide new ideas and treatment strategies for the diagnosis and treatment of digestive tract tumors.

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