

Review Article

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

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To cite this article:

Qing Wu, Yulei Xie, Yinxu Wang, Xin Chen. HIF-1 α Related Signaling Pathway and Its Role in Common Gastrointestinal Tumors. *American Journal of Biomedical and Life Sciences*. Vol. 10, No. 4, 2022, pp. 125-130. doi: 10.11648/j.ajbls.20221004.15

Received: February 16, 2022; **Accepted:** July 8, 2022; **Published:** August 5, 2022

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-1 α , by the fine regulation of O₂ 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-1 α 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-1 α 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-1 β subunit (also called as the aromatic hydrocarbon receptor nuclear transporter) and an oxygen-sensitive HIF-1 α [3]. Their relative molecular weights are 91-94 and 120kd, respectively. Both HIF-1 α and HIF-1 β are memberships of the BHLH-PAS superfamily and contain basic Helix-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 1 α 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-1 α stability, while C-TAD participates in the regulation of HIF-1 α transcriptional activation under hypoxia [5]. HIF-1 β , also known as aromatic 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-1 α , and the expression level and protein stability are regulated by oxygen

content. Oxygen regulates the stability and activity of HIF-1 α through the hydroxylation of proline and asparagine residues. Under normal oxygen partial pressure, two proline residues (P⁴⁰² and P⁵⁶⁴) in the HIF-1 α 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-1 α , 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-1 α [10]. Therefore, it is difficult to detect HIF-1 α 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-1 α protein and increased interaction with its co-activator. Therefore, in anoxic cells, a large number of HIF-1 α aggregates and combines with HIF-1 β 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-1 α Related Hypoxia Stress Signaling Pathways

HIF-1 α was initially considered to be a crucial factor for cells to adapt to hypoxia. It is now fine acknowledged that HIF-1 α normalizes an assortment of physiological processes [12]. The physiological process in which HIF-1 α 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-1 α 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-1 α , as described below:

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

2.1.1. pVHL Dependent Pathways

Under normoxia, the expression of HIF-1 α 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 (P⁴⁰²/P⁵⁶⁴) are located in the LXXLAP amino acid sequence of HIF-1 α , 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, K⁵³²) can be

acetylated by acetyltransferase [15]. Therefore, the adapted HIF-1 α subunit with hydroxylated P⁴⁰²/P⁵⁶⁴ and acetylated K⁵³² 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-1 α proline and lysine residues are neither hydroxylated nor acetylated under anoxic conditions, ensuing in the structural stability of HIF-1 α .

2.1.2. pVHL Independent Pathways

Additional major oxygen-dependent instrument of negative regulation of HIF-1 α pathway under normoxia conditions is by monitoring the transcriptional activation of HIF-1 α . This pathway characterizes another post-translational modification level of HIF-1 α transcriptional activation region, but does not involve pVHL protein. The transcriptional activation of HIF-1 α target gene is originated by the synergistic binding of C-TAD and coactivator CBP/p300 in HIF-1 α . Under normoxia conditions, the oxygen-dependent hydroxylation of asparagine residue (N⁸⁰³) in HIF-1 α blocks the interaction between the two domains by preventing HIF-1 (FIH-1), thus canceling HIF-1 α -mediated gene transcription [17, 18]. In addition, hypoxia promotes this interaction by inhibiting the oxygen-dependent hydroxylation of N⁸⁰³, leading to transcriptional activation of target genes [19].

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

2.2. PHD/HIF-1 α /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-1 α [20]. The HIF-1 α 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-1 α 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-1 α is degraded rapidly [21]. At the same time, HIF-1 inhibitors can inhibit HIF-1 α 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-1 α to pVHL, resulting in the inhibition of HIF-1 α degradation, and then transferred to the nucleus to bind to HIF-1 β 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-1 α [23].

2.3. PI3K/Akt/ HIF-1 α 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-1 α and then initiate the transcription of HIF-1 α -related target genes, which enhances the ability of cell proliferation and weakens the ability of apoptosis [24]. Former studies have exposed that HIF-1 α is regulated by PI3K/Akt/mTOR signal pathway [25]. Hypoxia increased the protein levels of p-Akt and HIF-1 α in human bone marrow mesenchymal stem cells [26]. The expression of p-Akt was earlier than that of HIF-1 α . Interestingly, both PI3K inhibitor LY294002 and dual PI3K/mTOR inhibitor NVP-BEZ235 could inhibit hypoxia-induced p-Akt activation and HIF-1 α expression [27, 28]. Akt inhibitor wortmannin can only inhibit the expression of HIF-1 α 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-1 α activation. Based on previous studies, PI3K/Akt signaling pathway may regulate post-transcriptional protein level of HIF-1 α 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-1 α and PTEN needs to be further studied.

2.4. MAPK/HIF-1 α Signaling Pathways

ERK/MAPK pathway is the furthestmost 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-1 α [31]. Under the stimulation of hypoxia, intracellular ERK is phosphorylated, and the expression level of HIF-1 α 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-1 α . At the same time, some studies have found that MAPK and PI3K/Akt signal pathways can jointly regulate the expression of HIF-1 α ,

thus affecting cell proliferation and apoptosis [32].

2.5. Other HIF-1 α -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-1 α also mediates other signal pathways. It has been found that the deletion of p53 tumor suppressor gene is related to the increase of HIF-1 α level in some tumors [33]. This can be explained by the fact that under normoxia, HIF-1 α binds to p53 and permits Mdm2 (mouse double minute 2 homologue) to mediate HIF-1 α ubiquitination and proteasome degradation [34]. In hypoxia tumors, deletions or mutations in tumor suppressor genes reduce any chance of Mdm2-mediated HIF-1 α 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-1 α under hypoxia, prevent the ubiquitin degradation of HIF-1 α , promote the expression of HIF-1 α , 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-1 α levels regardless of the presence of oxygen [36]. In addition, studies have found that there is an interaction between Myc and HIF-1 α , which is related to tumorigenesis and development. When hypoxia occurs, the expression level of HIF-1 α 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-1 α and other signal pathways also interact with each other in the regulation of hypoxia.

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

3.1. HIF-1 α 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-1 α is exceedingly expressed in esophageal cancer, which can bind to the HIF-1 α 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-1 α and VEGF is poor [39]. In addition, some studies have shown that under hypoxia, the high expression of HIF-1 α 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-1 α in

esophageal cancer are more likely to have tumor metastasis [42]. On the one hand, HIF-1 α can promote lymph node metastasis of esophageal cancer by promoting the expression of VEGF-C [43]. On the other hand, HIF-1 α 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-1 α 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-1 α plays an important role in promoting proliferation, metastasis and inhibiting apoptosis of gastric cancer cells. Zhang [46] et al found that HIF-1 α 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-1 α can also be regulated by PVT1/miR-186 [47] and linc-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-1 α 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-1 α 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-1 α in hepatocellular carcinoma is higher than that in paracancerous tissues, and the high expression of HIF-1 α is related to poor tumor grade and intrahepatic metastatic capsule infiltration [55]. It has been found that HIF-1 α can promote tumor cell proliferation and angiogenesis by mediating a variety of growth factors, such as VEGF, EGF, TGF- α , 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-1 α 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 β 2 (ADRB2) can promote the proliferation of hepatocellular carcinoma cells by stabilizing HIF-1 α 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-1 α [57]. Studies have shown that necrotic fragments of liver cancer cells under hypoxia can promote the release of IL-1 β from M2 macrophages, which can bind to cyclooxygenase-2 and up-regulate HIF-1 α , thus promoting the EMT process of liver cancer cells [58]. In addition, HIF-1 α 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-1 α 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-1 α is associated with poor prognosis of patients. However, the specific role of HIF-1 α in the pathogenesis of digestive tract tumors needs to be further studied. Therefore, in-depth study of HIF-1 α 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-1 α inhibitors by better understanding the molecular structure of the domains that mediate the key functions of HIF-1 α . This study summarizes the research of HIF-1 α in common digestive tract tumors, in order to provide new ideas and treatment strategies for the diagnosis and treatment of digestive tract tumors.

Acknowledgements

This research was supported by the Research and Development Project of Affiliated Hospital of North Sichuan Medical College (grant number: 2021ZD014), the Medical Research Project of Sichuan (grant number: S20048) and the Development of Scientific Research Plan of North Sichuan Medical College (grant number: CBY20-ZD-05 and CBY20-QA-Y14).

References

- [1] Ke Q and Costa M. Hypoxia-inducible factor-1 (HIF-1). *Mol Pharmacol*, 2006, 70 (5): 1469-1480.
- [2] Semenza GL and Wang GL. A nuclear factor induced by hypoxia via de novo protein synthesis binds to the human erythropoietin gene enhancer at a site required for transcriptional activation. *Mol Cell Biol*, 1992, 12 (12): 5447-5454.
- [3] Befani C and Liakos P. The role of hypoxia-inducible factor-2 alpha in angiogenesis. *J Cell Physiol*, 2018, 233 (12): 9087-9098.

- [4] Wang GL, Jiang BH, Rue EA, et al. Hypoxia-inducible factor 1 is a basic-helix-loop-helix-PAS heterodimer regulated by cellular O₂ tension. *Proc Natl Acad Sci U S A*, 1995, 92 (12): 5510-5514.
- [5] Loboda A, Jozkowicz A and Dulak J. HIF-1 and HIF-2 transcription factors--similar but not identical. *Mol Cells*, 2010, 29 (5): 435-442.
- [6] Semenza GL. A compendium of proteins that interact with HIF-1 α . *Exp Cell Res*, 2017, 356 (2): 128-135.
- [7] Bruick RK and McKnight SL. A conserved family of prolyl-4-hydroxylases that modify HIF. *Science*, 2001, 294 (5545): 1337-1340.
- [8] Iwai K, Yamanaka K, Kamura T, et al. Identification of the von Hippel-Lindau tumor-suppressor protein as part of an active E3 ubiquitin ligase complex. *Proc Natl Acad Sci U S A*, 1999, 96 (22): 12436-12441.
- [9] Epstein AC, Gleadle JM, McNeill LA, et al. C. elegans EGL-9 and mammalian homologs define a family of dioxygenases that regulate HIF by prolyl hydroxylation. *Cell*, 2001, 107 (1): 43-54.
- [10] Block KM, Wang H, Szabó LZ, et al. Direct inhibition of hypoxia-inducible transcription factor complex with designed dimeric epidithiodiketopiperazine. *J Am Chem Soc*, 2009, 131 (50): 18078-18088.
- [11] Masoud GN and Li W. HIF-1 α pathway: role, regulation and intervention for cancer therapy. *Acta Pharm Sin B*, 2015, 5 (5): 378-389.
- [12] Hirai K, Furusho H, Hirota K, et al. Activation of hypoxia-inducible factor 1 attenuates periapical inflammation and bone loss. *Int J Oral Sci*, 2018, 10 (2): 12.
- [13] McGarry T, Biniecka M, Veale DJ, et al. Hypoxia, oxidative stress and inflammation. *Free Radic Biol Med*, 2018, 125: 15-24.
- [14] Semenza GL. Targeting HIF-1 for cancer therapy. *Nat Rev Cancer*, 2003, 3 (10): 721-732.
- [15] Jeong JW, Bae MK, Ahn MY, et al. Regulation and destabilization of HIF-1 α by ARD1-mediated acetylation. *Cell*, 2002, 111 (5): 709-720.
- [16] Maxwell PH, Wiesener MS, Chang GW, et al. The tumour suppressor protein VHL targets hypoxia-inducible factors for oxygen-dependent proteolysis. *Nature*, 1999, 399 (6733): 271-275.
- [17] Dann CE, 3rd, Bruick RK and Deisenhofer J. Structure of factor-inhibiting hypoxia-inducible factor 1: An asparaginyl hydroxylase involved in the hypoxic response pathway. *Proc Natl Acad Sci U S A*, 2002, 99 (24): 15351-15356.
- [18] Lando D, Peet DJ, Gorman JJ, et al. FIH-1 is an asparaginyl hydroxylase enzyme that regulates the transcriptional activity of hypoxia-inducible factor. *Genes Dev*, 2002, 16 (12): 1466-1471.
- [19] McNeill LA, Hewitson KS, Claridge TD, et al. Hypoxia-inducible factor asparaginyl hydroxylase (FIH-1) catalyses hydroxylation at the beta-carbon of asparagine-803. *Biochem J*, 2002, 367 (Pt 3): 571-575.
- [20] Kaelin WG. Proline hydroxylation and gene expression. *Annu Rev Biochem*, 2005, 74: 115-128.
- [21] Berra E, Benizri E, Ginouvès A, et al. HIF prolyl-hydroxylase 2 is the key oxygen sensor setting low steady-state levels of HIF-1 α in normoxia. *Embo j*, 2003, 22 (16): 4082-4090.
- [22] Lee MC, Huang HJ, Chang TH, et al. Genome-wide analysis of HIF-2 α chromatin binding sites under normoxia in human bronchial epithelial cells (BEAS-2B) suggests its diverse functions. *Sci Rep*, 2016, 6: 29311.
- [23] Buckley DL, Van Molle I, Gareiss PC, et al. Targeting the von Hippel-Lindau E3 ubiquitin ligase using small molecules to disrupt the VHL/HIF-1 α interaction. *J Am Chem Soc*, 2012, 134 (10): 4465-4468.
- [24] Chen J, Bai M, Ning C, et al. Gankyrin facilitates follicle-stimulating hormone-driven ovarian cancer cell proliferation through the PI3K/AKT/HIF-1 α /cyclin D1 pathway. *Oncogene*, 2016, 35 (19): 2506-2517.
- [25] Zhong H, Chiles K, Feldser D, et al. Modulation of hypoxia-inducible factor 1 α expression by the epidermal growth factor/phosphatidylinositol 3-kinase/PTEN/AKT/FRAP pathway in human prostate cancer cells: implications for tumor angiogenesis and therapeutics. *Cancer Res*, 2000, 60 (6): 1541-1545.
- [26] Erler JT, Bennewith KL, Cox TR, et al. Hypoxia-induced lysyl oxidase is a critical mediator of bone marrow cell recruitment to form the premetastatic niche. *Cancer Cell*, 2009, 15 (1): 35-44.
- [27] Yang XM, Wang YS, Zhang J, et al. Role of PI3K/Akt and MEK/ERK in mediating hypoxia-induced expression of HIF-1 α and VEGF in laser-induced rat choroidal neovascularization. *Invest Ophthalmol Vis Sci*, 2009, 50 (4): 1873-1879.
- [28] Karar J, Cerniglia GJ, Lindsten T, et al. Dual PI3K/mTOR inhibitor NVP-BEZ235 suppresses hypoxia-inducible factor (HIF)-1 α expression by blocking protein translation and increases cell death under hypoxia. *Cancer Biol Ther*, 2012, 13 (11): 1102-1111.
- [29] Li L, Qu Y, Mao M, et al. The involvement of phosphoinositid 3-kinase/Akt pathway in the activation of hypoxia-inducible factor-1 α in the developing rat brain after hypoxia-ischemia. *Brain Res*, 2008, 1197: 152-158.
- [30] Lei Q, Tan J, Yi S, et al. Mitochondrial acid 5 activates the MAPK-ERK-yap signaling pathways to protect mouse microglial BV-2 cells against TNF α -induced apoptosis via increased Bnip3-related mitophagy. *Cell Mol Biol Lett*, 2018, 23: 14.
- [31] Semenza G. Signal transduction to hypoxia-inducible factor 1. *Biochem Pharmacol*, 2002, 64 (5-6): 993-998.
- [32] Shi YH, Wang YX, Bingle L, et al. In vitro study of HIF-1 activation and VEGF release by bFGF in the T47D breast cancer cell line under normoxic conditions: involvement of PI-3K/Akt and MEK1/ERK pathways. *J Pathol*, 2005, 205 (4): 530-536.
- [33] Bae MK, Ahn MY, Jeong JW, et al. Jab1 interacts directly with HIF-1 α and regulates its stability. *J Biol Chem*, 2002, 277 (1): 9-12.
- [34] Ravi R, Mookerjee B, Bhujwalla ZM, et al. Regulation of tumor angiogenesis by p53-induced degradation of hypoxia-inducible factor 1 α . *Genes Dev*, 2000, 14 (1): 34-44.

- [35] Liu YV and Semenza GL. RACK1 vs. HSP90: competition for HIF-1 alpha degradation vs. stabilization. *Cell Cycle*, 2007, 6 (6): 656-659.
- [36] Minet E, Michel G, Remacle J, et al. Role of HIF-1 as a transcription factor involved in embryonic development, cancer progression and apoptosis (review). *Int J Mol Med*, 2000, 5 (3): 253-259.
- [37] Adhikary S and Eilers M. Transcriptional regulation and transformation by Myc proteins. *Nat Rev Mol Cell Biol*, 2005, 6 (8): 635-645.
- [38] Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*, 2018, 68 (6): 394-424.
- [39] Shao JB, Li Z, Zhang N, et al. Hypoxia-inducible factor 1 α in combination with vascular endothelial growth factor could predict the prognosis of postoperative patients with oesophageal squamous cell cancer. *Pol J Pathol*, 2019, 70 (2): 84-90.
- [40] Jászai J and Schmidt MHH. Trends and Challenges in Tumor Anti-Angiogenic Therapies. *Cells*, 2019, 8 (9).
- [41] Zeng L, Zhou HY, Tang NN, et al. Wortmannin influences hypoxia-inducible factor-1 alpha expression and glycolysis in esophageal carcinoma cells. *World J Gastroenterol*, 2016, 22 (20): 4868-4880.
- [42] Shao C, Ji C, Wang X, et al. Expression and significance of GRHL2 in esophageal cancer. *Onco Targets Ther*, 2017, 10: 2025-2031.
- [43] Katsuta M, Miyashita M, Makino H, et al. Correlation of hypoxia inducible factor-1alpha with lymphatic metastasis via vascular endothelial growth factor-C in human esophageal cancer. *Exp Mol Pathol*, 2005, 78 (2): 123-130.
- [44] Zhu Y, Tan J, Xie H, et al. HIF-1 α regulates EMT via the Snail and β -catenin pathways in paraquat poisoning-induced early pulmonary fibrosis. *J Cell Mol Med*, 2016, 20 (4): 688-697.
- [45] Zong L, Abe M, Seto Y, et al. The challenge of screening for early gastric cancer in China. *Lancet*, 2016, 388 (10060): 2606.
- [46] Zhang J, Xu J, Dong Y, et al. Down-regulation of HIF-1 α inhibits the proliferation, migration, and invasion of gastric cancer by inhibiting PI3K/AKT pathway and VEGF expression. *Biosci Rep*, 2018, 38 (6).
- [47] Huang T, Liu HW, Chen JQ, et al. The long noncoding RNA PVT1 functions as a competing endogenous RNA by sponging miR-186 in gastric cancer. *Biomed Pharmacother*, 2017, 88: 302-308.
- [48] Hong L, Wang J, Wang H, et al. Linc-pint overexpression inhibits the growth of gastric tumors by downregulating HIF-1 α . *Mol Med Rep*, 2019, 20 (3): 2875-2881.
- [49] Ge X, Liu X, Lin F, et al. MicroRNA-421 regulated by HIF-1 α promotes metastasis, inhibits apoptosis, and induces cisplatin resistance by targeting E-cadherin and caspase-3 in gastric cancer. *Oncotarget*, 2016, 7 (17): 24466-24482.
- [50] Liu L, Zhao X, Zou H, et al. Hypoxia Promotes Gastric Cancer Malignancy Partly through the HIF-1 α Dependent Transcriptional Activation of the Long Non-coding RNA GAPLINC. *Front Physiol*, 2016, 7: 420.
- [51] Romano E, Vllahu M, Bizzarro V, et al. TFF1 Promotes EMT-Like Changes through an Auto-Induction Mechanism. *Int J Mol Sci*, 2018, 19 (7).
- [52] Liu N, Wang Y, Zhou Y, et al. Krüppel-like factor 8 involved in hypoxia promotes the invasion and metastasis of gastric cancer via epithelial to mesenchymal transition. *Oncol Rep*, 2014, 32 (6): 2397-2404.
- [53] Yang SW, Zhang ZG, Hao YX, et al. HIF-1 α induces the epithelial-mesenchymal transition in gastric cancer stem cells through the Snail pathway. *Oncotarget*, 2017, 8 (6): 9535-9545.
- [54] Kannan A, Krishnan A, Ali M, et al. Caveolin-1 promotes gastric cancer progression by up-regulating epithelial to mesenchymal transition by crosstalk of signalling mechanisms under hypoxic condition. *Eur J Cancer*, 2014, 50 (1): 204-215.
- [55] Xiong XX, Qiu XY, Hu DX, et al. Advances in Hypoxia-Mediated Mechanisms in Hepatocellular Carcinoma. *Mol Pharmacol*, 2017, 92 (3): 246-255.
- [56] Wu FQ, Fang T, Yu LX, et al. ADRB2 signaling promotes HCC progression and sorafenib resistance by inhibiting autophagic degradation of HIF1 α . *J Hepatol*, 2016, 65 (2): 314-324.
- [57] Liu X, Chen S, Tu J, et al. HSP90 inhibits apoptosis and promotes growth by regulating HIF-1 α abundance in hepatocellular carcinoma. *Int J Mol Med*, 2016, 37 (3): 825-835.
- [58] Wang Y, Ma J, Shen H, et al. Reactive oxygen species promote ovarian cancer progression via the HIF-1 α /LOX/E-cadherin pathway. *Oncol Rep*, 2014, 32 (5): 2150-2158.
- [59] Wang B, Ding YM, Fan P, et al. Expression and significance of MMP2 and HIF-1 α in hepatocellular carcinoma. *Oncol Lett*, 2014, 8 (2): 539-546.
- [60] Okazaki I and Inagaki Y. Novel strategies for hepatocellular carcinoma based on MMPs science. *Anticancer Agents Med Chem*, 2012, 12 (7): 753-763.