Hypoxia-inducible factors in hepatocellular carcinoma (Review)

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Abstract. Maintenance of an appropriate oxygen concentration is essential for the function of the liver. However, in many pathological conditions, and particularly in the tumor microenvironment, cells and tissues are frequently in a hypoxic state. In the presence of hypoxia, the cells adapt to the low oxygen levels through the hypoxia-inducible factor (HIF) pathway. Overgrowth of tumor cells restricts the diffusion of oxygen in tumors, leading to insufficient blood supply and the creation of a hypoxic microenvironment, and, as a consequence, activation of the expression of HIFs. HIFs possess a wide range of target genes, which function to control a variety of signaling pathways; thus, HIFs modulate cellular metabolism, immune escape, angiogenesis, metastasis, extracellular matrix remodeling, cancer stem cells and other properties of the tumor. Given their crucial role in the occurrence and development of tumors, HIFs are expected to become new targets of precise treatment of hepatocellular carcinoma.

Contents

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1. Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignant tumors of the digestive system. In 2015,466,100 patients were newly diagnosed with HCC in China, and the number of deaths caused by HCC deaths was ~422,100 (1). In China, HCC is one of the four major causes of cancer-related deaths. HCC is a hypermetabolic tumor that consumes more oxygen than the surrounding normal tissues. However, the uncontrolled proliferation of HCC cells leads to an insufficient oxygen supply and the rapidly growing tumor not only quickly consumes oxygen but also lacks adequate vascularization, subsequently generating a hypoxic microenvironment. Hypoxia-inducible factors (HIFs) are recognized as crucial transcriptional regulators that are activated under hypoxia (2). A number of recent studies have documented the involvement of HIFs in HCC cell proliferation, angiogenesis, invasion and metastasis (3,4). In addition, progress has been made in the development of HCC therapies involving the targeting HIFs (5). Currently, the research on HIFs is focused on two aspects, the mechanism of transcriptional regulation of HIFs and cancer therapy targeting HIFs. Therefore, the present review examined the processes of regulation and activation of HIFs in HCC, and focused on the progress of research on the function of HIFs in HCC.

2. Structure and function of HIFs

The rapid proliferation of cancer cells leads to the rapid consumption of tissue oxygen. When the rate of oxygen consumption exceeds the rate of oxygen supply by the

circulation, hypoxia develops (2). A hypoxic state activates a series of adaptive responses of cells, which are primarily mediated by HIFs. The human genome encodes three different HIF subtypes: HIF-1α, HIF-2α and HIF-3α (Fig. 1). HIFs are heterodimers composed of a functional α subunit and a stably expressed β subunit (6). The N-terminus of HIFs has a basic helix-loop-helix (bHLH) domain and a Per-ARNT-Sim (PAS) domain that participate in the heterodimerization of the α and β subunits. These domains also mediate HIF binding to the hypoxia response element (HRE) in a target gene promoter. The C-terminus of HIF proteins includes two transactivation domains (TAD), an N-terminal (N)-TAD and a C-terminal (C)-TAD. The N-TAD domain serves an essential function in activating HIF-1α or HIF-2α target genes; N-TAD is the major transactivation domain responsible for HIF-1α or HIF-2α target gene specificity; as a transcriptional activation domain, N-TAD may serve as an important cofactor for interaction sites. Transcriptional cooperation between HIF-1α and certain factors (such as SMAD3/4 and ETS-1) can induce activation of multiple HIF target genes under hypoxic conditions (7). The C-TAD acts to recruit p300/CREB-binding protein (CBP) and other auxiliary transcription factors. In addition, the structure of HIFs includes an oxygen-dependent degradation domain (ODDD), which overlaps with N-TAD, but its function is different from N-TAD. The ODDD serves as the recognition site of the von Hippel-Lindau tumor suppressor protein (pVHL) and is involved in the stabilization of proteins and the regulation of intracellular oxygen concentration. The β subunit is constitutively expressed, it is not regulated by intracellular oxygen concentration, and does not have transcriptional activity alone; only a heterodimer of HIF-α and HIF-β subunits is active. The ODDD contains two proline residues that can be hydroxylated by the prolyl hydroxylase domain (PHD) enzymes. Hydroxylated HIF subtypes are recognized by pVHL, which is ubiquitinated by pVHL-related elongin BC-Cul2 ubiquitin ligase complex. Hydroxylated HIF-1α binds to pVHL, which recruits elongin B, elongin C, cullin-2 and loop cassette 1 to form the E3 ubiquitin ligase complex. Unlike the targeted proteasomal degradation, HIF-1α forms the E3 ubiquitin ligase complex, which ubiquitinates HIF-1α and is ultimately mediated by the 26S proteasome (8-10), whereas HIF-2α is ubiquitinated by the of E2 ubiquitin-binding enzyme; but, both HIF-1α and HIF-2α are subsequently degraded by 26S proteasome (8).

PHDs are key enzymes of this degradation process, which uses oxygen and 2-ketoglutarate as substrates, and Fe^{2+} and ascorbate as co-factors of dioxygenase (Fig. 2). The activity of HIFs can also be suppressed by the HIF-1 inhibitor, such as factor inhibiting HIF-1α (FIH-1). The catalytic effect of FIH-1 is similar to that of PHD, which also requires oxygen and 2-ketoglutarate as substrates. Factor inhibiting HIF-1α (FIH) is an asparaginyl hydroxylase that catalyzes the hydroxylation of asparagine 803 (Asn803) on C-TAD, preventing HIF-1α from interacting with p300/CBP and inhibiting its transcriptional activity. However, both PHDs and HIFs are oxygen-dependent and, therefore, are inactive under hypoxic conditions, forming stable aggregates of HIF subtypes in the cytoplasm (11,12). Additionally, PHD activity can be inhibited by numerous important metabolites, including reactive oxygen species (ROS), nitric oxide (NO), succinate and fumarate (13). By contrast, cysteine may enhance PHD2 activity by inhibiting autoxidation (14).

HIF expression can also be regulated by other factors, including growth factors such as platelet-derived growth factor (PDGF), insulin-like growth factor 1 (IGF-1), insulin and heregulin (Fig. 2). The Akt/HIF-1a/PDGF-BB autocrine signaling loop is formed under hypoxic conditions to increase the chemosensitivity of liver cancer cells (15). Previous studies have shown that IGF-1 affects HIF-1α and HIF-2α protein synthesis (16,17). Insulin regulates HIF-1α by a ROS-sensitive activation of Sp1 in 3T3-L1 preadipocytes (18); this is a novel transcriptional mechanism by which insulin is involved in Sp1. Heregulin stimulates HIF-1α synthesis via a rapamycin-dependent manner (19). Acetyltransferases can acetylate the lysine residue at position 532 of HIF-1α, enhancing the binding ability of pVHL to HIF-1α and, ultimately, promoting its degradation (20). Receptor for activated protein C kinase 1 (RACK1) and heat shock protein 90 (Hsp90) compete to bind to the PAS region of HIF-1α; RACK1 enhances the binding of HIF-1α to E3 ligase and promotes degradation, whereas Hsp90 stabilizes HIF-1α and prevents its degradation (Fig. 2) (21).

The expression and activity of HIF-2α are also regulated by certain non-oxygen-dependent pathways, such as small ubiquitin-related modifier (SUMO) modification. SUMO modification is the main mechanism of HIF-2α degradation under hypoxia, which can negatively regulate the expression of HIF-2α. HIF-2α binds covalently to SUMO-2 via Lys394, resulting in its modification by SUMO. SUMO-modified HIF-2α is degraded by a mechanism involving SUMO-dependent E3 ubiquitin-protein ligase RNF4 and pVHL (Fig. 2) (22).

Although numerous studies have focused on HIF-1α and HIF-2α, our understanding of the role of HIF-3α in cancer cells is limited (23). It has been reported that HIF-3α can also be activated under hypoxic conditions and regulate the transcription and protein stability of HIF-1α (24-26). In addition, HIF-3α can activate the transcription of a set of specific target genes, which partially overlaps with genes upregulated by HIF-1α and HIF-2α, but their role remains to be demonstrated in future studies (27-29).

3. Expression of HIFs in HCC and their association with clinical outcomes

A large number of clinical studies have demonstrated a relationship between HIFs and metastasis, recurrence, vascular proliferation and prognosis of patients with HCC (Table I). The data indicate that the expression of HIF-1α in HCC tissues was higher compared with that in corresponding adjacent tissues. Overexpression of HIF-1α is associated with poor prognosis in patients with HCC; however, some recent studies have not reported that expression of HIF-2α or HIF-3α in HCC is associated with prognosis (Table I).

4. Relationship between HIF and HCC

A number of previous studies have demonstrated a complex relationship between HIF and HCC (30,31). The relationship between HIFs and HCC include, metabolism, immune escape, angiogenesis, metastasis, extracellular matrix (ECM) remodeling and activity of cancer stem cells (CSCs) (Fig. 3).

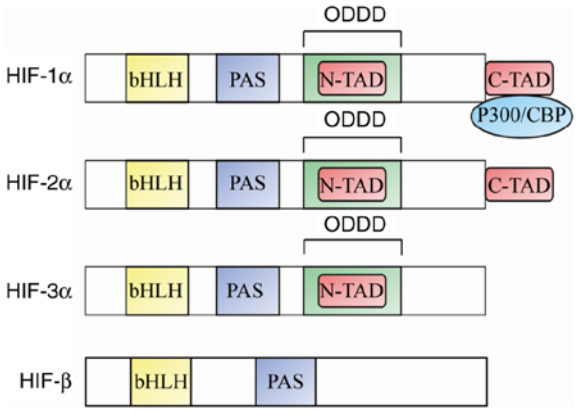

Figure 1. Structure of HIFs and functional domains. HIF-1α and HIF-2α are highly similar in amino acid sequence, and both contain bHLH, PAS and TAD functional domains (C-TAD and N-TAD), among which C-TAD is enriched with various auxiliary transcription factors such as p300/CBP; HIF-3α contains only bHLH, PAS and N-TAD. Furthermore, the HIF-1α, HIF-2α and HIF-3α structures include the ODDD domain, which acts as a recognition site for the tumor suppressor protein pVHL and is involved in protein stabilization and regulation of intracellular oxygen concentration. HIF-β contains bHLH and PAS, and the HIF-β subunit is not regulated by intracellular oxygen concentration and has no transcriptional activity alone; only heterodimers of HIF-α and -β subunits are active. bHLH, basic helix-loop-helix; C, carboxy-terminus; CBP, CREB-binding protein; HIF, hypoxia-inducible factor; N, amino-terminus; ODDD, oxygen-dependent degradation domain; PAS, Per-ARNT-Sim; pVHL, von Hippel-Lindau tumor suppressor; TAD, transactivation domain; p300/CBP, auxiliary transcription factor.

5. Metabolism

The rapid proliferation of cancer cells requires a large amount of energy, resulting in increased consumption of oxygen, which leads to the generation of a hypoxic environment in the tumor tissue. Under hypoxia, tumor cells undergo a transition from aerobic to anaerobic metabolism. This difference in metabolism between normal and cancer cells was first identified in 1920 (32). Normal cells under physiologic oxygen concentration convert glucose into pyruvate, which is further metabolized in the mitochondria via the tricarboxylic acid cycle and oxidative phosphorylation. In these cells, the availability of oxygen inhibits the rate of glycolysis (Pasteur effect), enables mitochondrial respiration, increases ATP levels and inhibits the activity of phosphofructokinase (PFK) responsible for glycolysis (33). Under hypoxic conditions, the final product of anaerobic glycolysis is pyruvic acid, which is subsequently metabolized to lactic acid. In comparison with non-malignant tissues, tumor cells rely more on the use of glycolysis to support their energy needs, even when oxygen is available, a phenomenon called the Warburg effect (34). Tumor cells are known to produce energy by generating ATP in anaerobic glycolysis, a process mainly regulated by HIF-1α (35,36). HIF-1α accelerates the glycolysis pathway of cancer cells by activating related target genes and transcription products. This activation may occur through three distinct mechanisms.

The first mechanism, the metabolism of HCC, is often related to the Warburg effect, involves HIF-1 activation of key enzymes involved in glucose metabolism and glycolysis (37,38). Overexpression of HIF-1α in cancer cells increases the activities of several isoenzymes that are different from those in normal tissues, including adenylate kinase 3 (AK3), aldolase-A (ALD-A) and ALD-C, carbonic anhydrase 9 (CA9), enolase 1 (ENO1), glucose transporter (GLUT)-1 and GLUT-3, GAPDH, hexokinase (HK)-1 and HK2, L-lactate dehydrogenase A chain (LDHA), liver-type PKF (PFKL), phosphoglycerate kinase 1 (PGK1) and 6-phosphofructo-2-kinase/fructose-2,6-bisphosphate 3 (PFKFB3) (Fig. 3).

In the second mechanism, induction of glucose transporter regulation, HIF-1α induces overexpression and increased activity of several glycolytic protein isoforms, including GLUT1 and GLUT3. HIF1α-induced glucose transport is important for glycolytic flux control and provides new therapeutic targets for inhibiting HCC growth and progression (Fig. 3) (39).

Transcriptional activity of HIF-1, in the third mechanism, increases the expression of mitochondrial-related enzymes, such as pyruvate dehydrogenase kinase 1 (PDK1), which can inhibit the conversion of pyruvate to acetyl coenzyme A and, as a result, reduce the level of oxidative phosphorylation and oxygen consumption by the mitochondria (Fig. 3) (40).

In addition to the above mechanisms, HIF-1α can reduce intracellular pH by promoting anaerobic glycolysis and increasing the concentration of lactic acid increase (41). Compared with normal tissues, GLUT1, LDHA, HK1, pyruvate kinase PKM2 and voltage-dependent anion-selective channel protein 1 (VDAC-1) expression levels were revealed to be significantly higher in primary HCC tissues and its metastases (42).

6. Immune escape

Progression and metastasis of tumors can take place only if both primary and metastatic tumors have the ability to escape immune surveillance. Numerous studies have demonstrated that hypoxia and HIFs are associated with the evasion of immune response by tumor cells (43,44). The function of immune cells is regulated by HIF1-dependent signaling mechanisms. During hypoxia, HIFs induce the resistance of tumor cells to CD8 cytotoxic T lymphocytes (CTL) and natural killer (NK) cells. The mechanisms involved include inhibition of apoptosis (45) and activation of autophagy (46). Additionally, hypoxia can upregulate the expression of extracellular enzymes CD39 and CD73 that produce adenosine, increasing its concentration in the cell environment. Adenosine strongly inhibits the anti-tumor function of activated T cells and NK cells by binding to its A2A receptor (47). HIFs can also suppress the immune response against the tumor by acting on the macrophages, so-called tumor-associated macrophages (TAMs), infiltrating the tumor microenvironment (48). TAMs have been repeatedly demonstrated to promote the growth, invasion and metastasis of tumor cells by secreting cytokines such as interleukin (IL)-10, transforming growth factor β (TGF-β), IL-6, VEGF and IL-8, as well as matrix metalloproteinases (MMPs) (Fig. 3). The cytokines and MMPs stimulate the tumor cell proliferation, epithelial-mesenchymal transition (EMT), induce neovascularization, promote remodeling of the ECM and inhibit the anti-tumor immune function of the organism (49). In patients with HCC, TAM infiltration in the liver tissue around the tumor has been associated with poor prognosis (50). It has also been

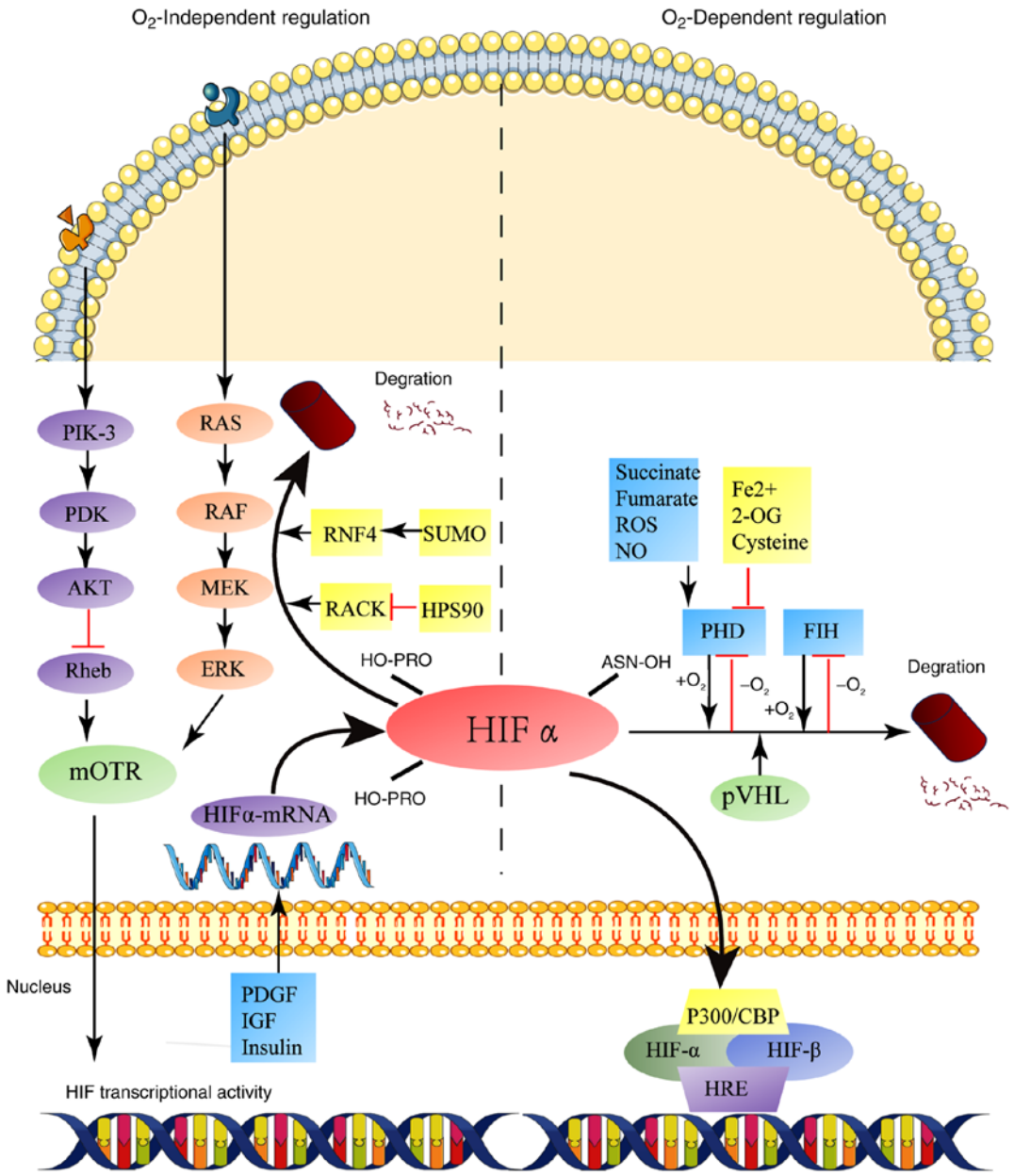

Figure 2. O_2-dependent and O_2-independent regulation of HIF-1α. At normal oxygen levels (+O_2), prolyl hydroxylase domain proteins hydroxylate two proline residues of HIFα. pVHL recognizes hydroxylated HIFα and mediates proteasomal degradation. Additionally, FIH hydroxylates the asparagine residue of HIFα, inhibiting its interaction with transcriptional coactivator p300/CBP. Conversely, the hydroxylation and degradation of HIFα is inhibited under hypoxia (-O_2), which transfers HIFα to the nucleus, dimerizes with HIFβ, and interacts with P300/CBP transcriptional activator to bind to target gene initiation and HRE and upregulate its expression. 2-OG, 2-oxyglutarate; ASN-OH, hydroxylated asparagine; CBP, CREB-binding protein; FIH, factor inhibiting HIF-1α; HIF, hypoxia-inducible factor; HRE, hypoxia response element; Hsp90, heat shock protein 90; HO-PRO, hydroxylated proline; IGF, insulin-like growth factor; MEK, MAPK/ERK kinase; NO, nitric oxide; PDGF, platelet-derived growth factor; PDK, pyruvate dehydrogenase kinase; pVHL, von Hippel-Lindau tumor suppressor protein; RACK, receptor for activated protein C kinase; Rheb, Ras homolog enriched in brain; RNF4, E3 ubiquitin-protein ligase RNF4; ROS, reactive oxygen species; SUMO, small ubiquitin-related modifier.

reported that in late-stage HCC, a large number of triggering receptor expressed on myeloid cells 1 (TREM-1)-positive TAMs indirectly affect the cytotoxic function of $CD8^+$ T cells and trigger their apoptosis (51). A previous study demonstrated that specific scavenging of macrophages with chlorophosphate liposomes resulted in significant suppression of tumor growth and angiogenesis (52). The role of TAMs was also documented in a study in which their inhibition delayed the growth of HCC in nude mice (53). The role of macrophages in HCC was also underscored by the demonstration that expression of hypoxia-induced high mobility group box-1 protein (HMGB1) promotes tumor invasion and metastasis in animal models of HCC by regulating macrophage-derived IL-6 (54). A previous study demonstrated that hypoxia promotes the immunosuppressive phenotype of HCC cell lines through upregulation of HIF1-dependent C-C motif chemokine 20 (CCL20) expression, and CCL20 significantly induces indoleamine 2,3-dioxygenase (IDO) expression in monocyte-derived macrophages (55). This study also showed a link between elevated CCL20 levels and poor survival in patients with liver cancer, suggesting a link between microenvironment of immunosuppressive hypoxic tumors and promotion of metastasis (55).

Table I. Expression of HIFs in HCC and their association with clinical outcomes.

HIF	Author, year	Result	Conclusion	Patient samples (n)	(Refs.)
HIF-1α	Wada *et al*, 2006	Positive expression of HIF-1α in HCC tissues was high	Overexpression of HIF-1α indicates poor prognosis in patients with HCC	HCC (60); normal (0)	(126)
	Dai *et al*, 2009	HIF-1α protein and mRNA expression of in HCC tissues were high	Overexpression of HIF-1α indicates poor prognosis in patients with HCC	HCC (110); high HIF-1α (42), low HIF-1α (68)	(127)
	Xia *et al*, 2012	Positive expression of HIF-1α in HCC tissues was higher compared with that in corresponding adjacent tissues	Overexpression of HIF-1α indicates poor prognosis in patients with HCC	HCC (416); corresponding adjacent tissue (416)	(128)
	Xiang *et al*, 2012	Positive expression of HIF-1α in HCC tissues was high	Overexpression of HIF-1α indicates poor prognosis in patients with HCC	HCC (69); high HIF-1α (30), low HIF-1α (39)	(129)
	Zheng *et al*, 2013	HIF-1α protein and mRNA expression of in HCC tissues were high	Overexpression of HIF-1α indicates poor prognosis in patients with HCC	HCC (953); high HIF-1α (475), low HIF-1α (478)	(130)
	Wang *et al*, 2014	MMP2 and HIF-1α protein and mRNA expressions in HCC tissues was higher compared with that in adjacent tissues	Overexpression of HIF-1α indicates poor prognosis in patients with HCC	HCC (44); corresponding adjacent tissue (44)	(131)
	Cao *et al*, 2014	A positive correlation between the expression of HIF-1α and vascular invasion of HCC	Overexpression of HIF-1α indicates poor prognosis in patients with HCC	HCC (851); normal (0)	(132)
	Liu *et al*, 2014	Positive correlation between HBx mutant and HIF-1α expression in HCC tissues	Overexpression of HIF-1α indicates poor prognosis in patients with HCC	HCC (101); normal (0)	(133)
	Wang *et al*, 2018	Positive expression of HIF-1α in HCC tissues was higher compared with that in chronic hepatitis	Overexpression of HIF-1α indicates poor prognosis in patients with HCC	HCC (419); chronic hepatitis (49)	(134)
HIF-2α	Bangoura *et al*, 2007	Expression of HIF-2α in HCC tissues was higher compare with that in normal tissues	Overexpression of HIF-2α indicates poor prognosis in patients with HCC	HCC (315); corresponding adjacent tissue (192); normal (22)	(135)
	Sun *et al*, 2013	Expression of HIF-2α in HCC tissues was low	Expression of HIF-2α is not related to prognosis	HCC (246); high HIF-2α (118), low HIF-2α (128)	(136)
	Yao *et al*, 2015	Positive correlation between expression of HIF-2α and vascular invasion of HCC	Expression of HIF-2α is not related to prognosis	HCC (1066); normal (0)	(137)
	Yang *et al*, 2016	Protein level of HIF-2α in HCC tissues was lower compared with that in adjacent tissues	Expression of HIF-2α is not related to prognosis	HCC (206); corresponding adjacent tissue (206)	(138)
	Jiang *et al*, 2018	Expression of HIF-2α in HCC tissues was lower compared with that in adjacent tissues	Expression of HIF-2α is not related to prognosis	HCC (84); corresponding adjacent tissue (84)	(139)
HIF-3α	Liu *et al*, 2016	Inconsistent expression of HIF-3α between HCC tissues and adjacent tissues	Expression of HIF-3α is not related to prognosis	HCC (126); corresponding adjacent tissue (84)	(140)

HBx, hepatitis B virus protein X; HCC, hepatocellular carcinoma; HIF, hypoxia-inducible factor; MMP, matrix metalloproteinase.

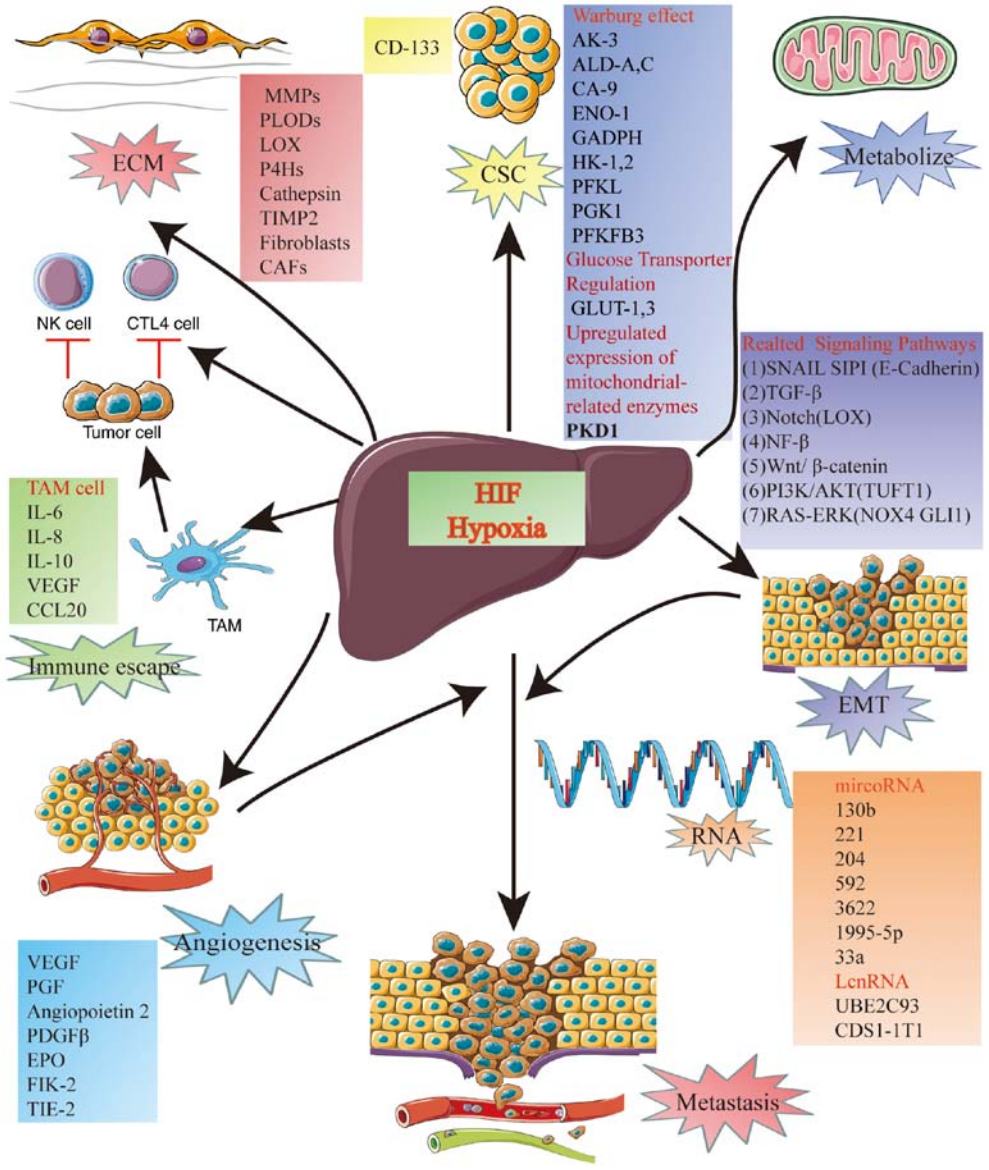

Figure 3. Relationship between HIF and HCC. The complex relationship between HIF and HCC includes metabolism, immune escape, angiogenesis, metastasis, extracellular matrix remodeling, and cancer stem cells. ALD, aldolase; AK3, adenylate kinase 3; CA9, carbonic anhydrase 9; CCL20, CAFs, cancer-related fibroblasts; C-C motif chemokine ligand 20; ECM, extracellular matrix; EMT, epithelial-mesenchymal transition; ENO1, enolase 1; EPO, erythropoietin; GLUT, glucose transporter; HK, hexokinase; LOX, lysyl oxidase; MMPs, matrix metalloproteinases; NOX4, NADPH oxidase 4; P4Hs, prolyl-4-hydroxylases; PDGF, platelet-derived growth factor; PFKFB, 3,6-phosphofructo-2-kinase/fructose-2,6-bisphosphate 3; PFKL, liver-type phosphofructokinase; PGF, placental growth factor; PGK1, phosphoglycerate kinase 1; PLODs, procollagen lysyl hydroxylases; TAM, tumor-associated macrophage; TGF-β, transforming growth factor β; TIE-2, tyrosine-protein kinase receptor TIE-2; TIMP2, tissue inhibitor of metalloproteinase 2; TUFT1, tuftelin1; VEGF, vascular endothelial growth factor.

7. Angiogenesis

The rapid growth of tumors necessitates the *de novo* formation of a large number of blood vessels to transport oxygen and nutrients. Angiogenesis is a complex process that involves the degradation of the extracellular matrix, the activation, proliferation and migration of vascular endothelial cells, and the establishment of a new vascular network (56). The most important signaling molecule in this process is VEGF (Fig. 3), which specifically promotes the proliferation and migration of vascular endothelial cells. Compared with the normal vascular system, the blood vessels of tumors are leaky, distorted and disordered. Inhibition of the expression of HIF-1α in endothelial cells suppresses tumor growth, whereas inhibiting the expression of HIF-2α enhances the formation of blood vessels supplying the tumor (57). However, these blood vessels are disordered and do not correct the hypoxic state of the tumor microenvironment. This phenomenon is caused by differential regulation of NO homeostasis, which in turn regulates vascular endothelial growth factor expression in the NO-dependent feedback loop (57). HIF-1α is a major regulator of VEGF expression. The HIF-1α/p300/CBP complex binds to the HREs in five regions of the VEGF promoter. Under hypoxia, high levels of accumulated HIF-1α upregulates the expression of a series of angiogenic factors, such as VEGF, and enhances the stability of VEGF mRNA, ultimately activating tumor angiogenesis (58,59). Lee *et al* (60) used acridine flavin to inhibit the heterodimerization of HIF-1α and HIF-1β and revealed that

the expression of VEGF in tumor cells decreased significantly. This result provided additional evidence for the role of HIF-1α in the activation of VEGF. Another study demonstrated that the levels of HIF-1α, as well as VEGF protein and mRNA, detected after 20 weeks of HCC were significantly higher than before 20 weeks in an experimental rat HCC model, suggesting that HIF-1α and VEGF may have important functions during HCC development (61). Sorafenib, an inhibitor of multiple kinases, has been tested in clinical trials of HCC carcinoma, and the mechanism of its action has been reported to be closely related to anti-angiogenesis (62); it can effectively inhibit the expression of HIF-1α, thereby reducing the expression of VEGF and, ultimately, leading to a decrease in angiogenesis in tumors. In addition to VEGF, many other signaling molecules are also highly expressed under hypoxic conditions via HIF-dependent mechanisms, including angiopoietin 2 (ANG2), placental growth factor (PGF), PDGF-β and stromal-derived factor 1 (SDF-1); all of these growth factors promote angiogenesis in tumors (63). ANG-like protein 4 (ANGL4) has also been identified as gene target of HIF-1α (64); ANGL4 affects HCC angiogenesis and metastasis by modulating the expression of vascular cell adhesion molecule and integrin β1.

In contrast to HIF-1α, HIF-2α is only expressed during normal development of blood vessels and lungs (65). It has also been detected in tumor vascular endothelial cells, tumor cells and TAMs (66); and hypoxia-inducible expression of HIF-2α has been reported in the brain, lung, heart, liver, duodenum, pancreas and kidney of mice (67). HIF-2α mainly acts on angiogenesis-related genes, including VEGF, erythropoietin (EPO), VEGF receptor 2 (VEGFR2), angiogenin, and tyrosine-protein kinase receptor TIE-2 (68,69); experiments using different tumor cell lines and animal models have demonstrated that HIF-2α activates tumor angiogenesis by upregulating VEGF. Additionally, HIF-2α forms a complex with transcription-assisted activator ETS proto-oncogene 1 (ETS-1), and binds to HRE4 on the promoter of VEGFR2, activating its expression (70).

8. Metastasis

Intrahepatic and extrahepatic metastasis is the major contributor to poor prognosis in patients with HCC. Invasion and metastasis of tumors is a complex process in which the first step involves EMT. In the process of EMT, polar epithelial cells transform into mobile stromal cells, gaining the ability to migrate to distant sites. HIF-1α is a crucial regulator of EMT under hypoxic conditions, acting through seven distinct mechanisms detailed in the subsections below (Fig. 3).

Snail homolog 1 (SNAI1) and SMAD-interacting protein 1 (SIP1) signaling pathways. Inactivation of epithelial (E)-cadherin, a protein essential for cell adhesion, results in the weakening of cell-cell contacts and increased mobility, initiating EMT. HIF-1α inhibits the expression of E-cadherin by upregulating SNAI1 and SIP1, transcriptional inhibitors of E-cadherin (71). HIF-1α regulates SNAI1 by binding to two HREs on the SNAI1 promoter, affecting the expression of E-cadherin, as well as N-cadherin and vimentin, activating EMT in HCC cells and promoting HCC invasion and metastasis (72).

TGF-β signaling pathway. The TGF-β signaling pathway is widely involved in embryonic development, tissue and organ formation, cell proliferation, apoptosis, differentiation and migration. TGF-β has a dual function in the development of tumors. TGF-β signaling pathway induces EMT, facilitating the invasion and metastasis of tumors (73). It has been also demonstrated that hypoxia is an important stimulator of EMT by activating HIFs (74). Under hypoxic conditions, HIF expression in hepatocytes promotes TGF-β signaling; HIF and TGF-β signaling contribute to the mechanism of hypoxia-stimulated hepatocyte EMT (74). It has been reported that the TGF-β1 pathway serves an important role in the regulation of liver cancer by regulating SMAD4, SMAD2/3, cleaved Notch1, and β-catenin proteins (75).

Notch signaling pathway. The Notch signaling pathway regulates embryonic development and differentiation, and proliferation and apoptosis of mature cells. Notch signaling induces EMT primarily by two mechanisms. The first one involves the upregulation of SNAI1 achieved by Notch-mediated recruitment of HIF-1α and the resulting increase in lysyl oxidase (LOX), which stabilizes SNAI1, thus promoting EMT (76). The second mechanism relies on the interaction of Notch with the TGF-β/SMAD pathway, which also activates EMT (77). Although the molecular mechanisms underlying hypoxia and Notch pathway activation are not clear, there is indeed a link between them. Hypoxia activates Notch-responsive promoters and increases expression of Notch direct downstream genes; the Notch intracellular domain interacts with HIF-1α, and after activation of Notch under hypoxic conditions, HIF-1α is recruited to the Notch reactive promoter (78).

NF-κB signaling pathway. The presence of a bi-directional correlation between HIF and NF-κB has also been reported, in which NF-κB can induce HIF and HIF can also regulate NF-κB (79). Cancer is characterized by the presence of hypoxia and inflammation. Hypoxia has been demonstrated to promote inflammation through the regulation of gene expression by oxygen-sensitive transcriptional regulators, including HIF and NF-κB (80). The basis for this association includes the regulation of the components of the NF-κB pathway and the transcriptional regulation of HIF-1 under hypoxia (81).

Wnt signaling pathway. Wnt regulates the growth, proliferation, invasion and metastasis of cancer cells. Under hypoxic conditions, an increase of Wnt3a upregulates the expression of β-catenin and promotes EMT (82). A previous study reported that the Wnt/β-catenin signaling pathway enhances the transcriptional activity of HIF-1α and inhibits the apoptosis of HCC, as well as inducing EMT and triggering HCC metastasis (83). In addition, hypoxia promotes HCC cell migration and angiogenesis by regulating the expression of B-cell CLL/lymphoma 9 (BCL9), which activates Wnt/β-catenin signaling pathway (84).

PI3K/AKT signaling pathway. PIK3/AKT signaling is crucially involved in tumor development. Hypoxia induces the expression of tuftelin1 (TUFT1) in a HIF-1α-dependent manner (85). In turn, TUFT1 activates the Ca^{2+}/PI3K/AKT

pathway, promoting HCC cell growth, metastasis and EMT *in vitro* and *in vivo*.

ROS signaling pathway. Hypoxia significantly promotes the progression of EMT and is associated with activation of the non-canonical Hedgehog (Hh) signaling pathway. HIF-1α knockdown attenuates hypoxia-induced membrane-spanning protein SMO and glioma-associated oncogene 1 (GLI1) expression and inhibits EMT progression. In addition, SMO inhibitors or GLI1 small interfering (si)RNA can also reverse hypoxia-driven EMT under hypoxic conditions. It is suggested that non-canonical Hh signaling serves an important role in hypoxia-induced EMT. Hypoxia increases reactive oxygen species (ROS) production, and ROS inhibitors (NACs) block GLI1-dependent EMT processes under hypoxic conditions. In hypoxic HCC cells, nicotinamide adenine dinucleotide phosphate (NADPH) oxidase 4 (NOX4) expression was found to increase at mRNA and protein levels. siRNA-mediated knockdown of NOX4 expression abolishes hypoxia-induced ROS production and hypoxia-induced GLI1-dependent EMT. Hypoxia triggers ROS-mediated GLI1-dependent EMT progression by inducing NOX4 expression. Non-canonical Hh pathway regulates HIF-1α/NOX4/ROS signaling pathway under hypoxic conditions to regulate EMT processes in HCC cells (86).

A relationship has also been identified between HIF signaling and p53 family members. A previous study reported that due to the binding of p53 protein to HIF-1α, p53 is stabilized, and hypoxia induction of transcriptionally active wild-type p53 gene is achieved (87). Conversely, p53 and p73 interact with HIF-1α, suppressing its activity, thereby inhibiting the migration and metastasis of tumor cells (88,89). A number of studies have demonstrated that microRNAs (miRNAs) are also closely related to the migration and metastasis of tumors, and their effects involve the activity of HIF-1α. For example, miRNA (miR)-130b and miR-21 can activate EMT through the PTEN/AKT/HIF-1α pathway and enhance HCC metastasis (90,91). Hypoxia-induced downregulation of miR-204, which acts as a post-transcriptional regulator of vasodilator-stimulated phosphoprotein (VASP) expression, promotes intrahepatic metastasis of HCC (92). miR-199a-5p (93), miR-592 (94) and miR-3662 regulate the Warburg effect and HCC progression (95) by reducing the expression of HIF-1α. Hypoxia induction and up-regulation of HIF can lead to downregulation of miR-33a expression in HCC cells; miR-33a controls EMT and invasiveness of HCC by downregulating Twist1 (96). miR-26a impacts HCC angiogenesis through the PIK3C2/AKT/HIF-1α/VEGFA pathway (97).

In addition to miRNAs, long non-coding RNAs (lncRNAs) can also promote HCC metastasis. The lncRNA UBE2CP3 triggers the proliferation and migration of HCC cells by activating ERK/HIF-1α/p70S6K/VEGFA signal transduction (98). Previous *in vitro* experiments demonstrated that the lncRNA CPS1-intronic transcript 1 significantly suppresses proliferation, migration and invasion of cells by reducing the activity of Hsp90 and HIF-1α, thus inhibiting the EMT (99).

9. ECM remodeling

ECM remodeling serves a crucial role in tumor invasion and metastasis (100). Several enzymes involved in ECM deposition and remodeling are regulated by hypoxia and HIFs, including MMPs, procollagen lysyl hydroxylases (PLODs), LOXs, collagen prolyl-4-hydroxylases (P4Hs) and cathepsins (Fig. 3) (101). Hypoxia can also downregulate the expression of tissue inhibitor of metalloproteinase 2 (TIMP2) in HCC cells by a HIF1α-dependent mechanism (102). Fibroblasts are the most important cell type involved in ECM production and remodeling; in addition, they are one of the most abundant types of stromal cells in tumors, where they can be reprogrammed into cancer-related fibroblasts (CAFs) (103). *In vitro* and *in vivo* studies have demonstrated that the HIF-1α/LOX pathway is involved in ECM remodeling and promotion of HCC metastasis by a mechanism dependent on hepatitis transactivator protein X (104).

10. Cancer stem cells

CSCs have an important function in the initiation, development, recurrence and metastasis of tumors. Studies on HIF and stem cells focused on the role of HIF in hematopoietic stem cells (105); based on data suggesting the involvement of HIF in the function of hematopoietic stem cells, studies have demonstrated that the HIF signaling pathway serve an important role in the induction and maintenance of CSC and EMT phenotypes, and regulates its function by regulating multiple complex signaling molecules within the tumor microenvironment (106). A recent study reported that hypoxia significantly enhances stem cell-related properties of HCC cells, an effect that can be abolished by the knockdown of HIF-1α or HIF-2α (3). Additionally, HIF-1α-specific small interfering RNA treatment markedly reduces the expression of CD133 in CSCs at the RNA and protein levels (107). Importantly, EMT activation can induce CSC characteristics. Notch1 mediates the process of EMT-induced CSCs by direct interaction with HIF-1α; upregulation of the intracellular expression of Notch by HIF-1α can activate EMT and induce HCC cells to acquire the features of CSC *in vitro* (108).

11. HIF-1α as a therapeutic target

Given the importance of HIF-1α in promoting the initiation and development of tumors, the possibility of a therapy targeting HIFs has become a focus of intense research effort. To date, a number of drugs or compounds inhibiting HIF-1α have been identified, but the drugs applicable for HCC treatment are still unsatisfactory. HIF-1α inhibitors can be classified into eight categories. i) Drugs affecting the HIF-1α signaling pathway. Typically, these molecules inhibit mTOR and PI3K signaling. Recombinant analgesic-antineoplastic peptide (rAGAP) is a protein comprising small ubiquitin-related modifiers linked to ubiquitin-histidine tags. rAGAP inhibits the AKT/PI3K pathway, suppressing angiogenesis and tumor progression (109). Circular RNA circ-EPHB4 derived from the gene coding for a member of the ephrin (Eph) receptor tyrosine kinase family, EphB4, prevents tumor growth by modulating the HIF-1α and AKT/PI3K signaling (110). The drug salidroside significantly increases the sensitivity of HCC to platinum and inhibits hypoxia-induced EMT by blocking the HIF-1α signaling (111). Rapamycin counteracts the process of EMT and angiogenesis, thus inhibiting the

growth and lung metastasis in a rat model of HCC (112). Ruscogenin reduces the expression of MMP-2, MMP-9, urokinase plasminogen activator, VEGF and HIF-1α by interfering with the PI3K/AKT/mTOR signaling pathway, resulting in an inhibition of tumor growth (113). The dietary phytochemical sulforaphane prevents angiogenesis of HCC by inhibiting STAT3/HIF-1α/VEGF signal transduction (114). N1-guanyl-1,7-diaminoheptane (GC7) enhances the sensitivity of HCC to doxorubicin by reversing the EMT signaling pathway induced by HIF-1α (115). Everolimus suppresses tumor growth and angiogenesis by blocking AKT/mTOR signaling pathway *in vitro* by promoting cell apoptosis and inhibiting endothelial cell proliferation (116). Finally, Huaier polysaccharide TP-1 is a naturally occurring bioactive macromolecule, found in Huaier fungus, prevents tumor growth and metastasis by downregulating HIF-1α-VEGF and AUF-1/AEG-1 signal transduction pathways (117). ii) Drugs inhibiting the expression of HIF-1α mRNA. Two compounds, RO70179 and EZN-2968, have been demonstrated to markedly reduce the expression of HIF-1α in HCC tissues (118). iii) Drugs inhibiting the synthesis of HIF-1α protein. Topotecan, an inhibitor of topoisomerase, has been reported to block the entry of the ribosome on HIF-1α mRNA, preventing translation of the protein (119). Additionally, vorinostat, a histone deacetylase inhibitor, decreases interaction between acetyl-Hsp90 and HIF-1α, inhibiting HIF-α nuclear translocation (120). iv) Drugs promoting the degradation of HIF-1α protein. A previous study has reported that evodiamine in combination with vorinostat accelerated the degradation of HIF-1α in HCC cells under hypoxic conditions (121). v) Drugs inhibiting HIF-1α stabilization. Curcumin can induce the clearance of ROS by upregulating nuclear factor E2-related factor 2 (Nrf2) and glutathione (GSH), which inhibit the stabilization of HIF-1α, and, in turn, suppress the expression of connective tissue growth factor (CTGF), providing a protective effect on HCC (122). vi) Drugs blocking the binding of HIF-1α to target genes; for example, doxorubicin (115). vii) Drugs inhibiting HIF-1α-mediated transcriptional activation; for example, bortezomib (123). viii) Drugs used for systemic therapy. A previous study demonstrated that inhibition of HIF-1α by systemic therapy with digoxin significantly delayed the development of HCC (124). In addition, metformin was reported to enhance the potential of regorafenib by regulating the levels of HIV TAT-interactive protein (TIP30) and HIF-2α, and inhibits the recurrence and metastasis of HCC after hepatectomy (125).

12. Conclusions and future perspectives

The expression of HIF-1α in HCC is significantly higher compared with expression in normal liver cells. HIF-1α is a crucial regulator of the adaptation of HCC cells to the hypoxic microenvironment and can affect the proliferation, growth, invasion, metastasis, angiogenesis, apoptosis and drug resistance of HCC cells by modulating the expression of multiple target genes. A number of studied have demonstrated the feasibility of using HIF-1α as a therapeutic target, which suggested that interventions modifying the activity of HIF-1α by direct or indirect ways may become effective for the treatment of HCC. Despite the growing number of studies on HIF-1α and identification of many HIF-1α inhibitors, their therapeutic application has not moved beyond the pre-clinical stage. Clinical use of these inhibitors faces multiple problems which have to be solved urgently. They include limitations in the specificity of HIF-1α inhibitors and lack of definitive cytotoxicity of HIF-1α inhibitors toward cancer cells. Therefore, compounds need to be developed and screened for clinical application. In the case of YC-1 and other similarly well-investigated inhibitors, further research on their pharmacology and toxicology is still needed. Although gene therapy targeting HIF-1α brings new hope to the treatment of HCC, finding the target gene is only the first step in the long road to clinical application. How to construct a safe and efficient vector, how to search for specific transcriptional regulatory elements in HCC, and how to rationally apply a combined therapy targeting multiple genes are critical questions that must be conclusively answered. Therefore, studies on the function of HIF-1 in HCC have to be expanded, necessitating additional time before the targeted therapy of HIF-1α for HCC can be implemented clinically. In addition, the understanding of the function of HIF-2 and HIF-3 in HCC has only begun to emerge, although it is already documented that HIF-2α affects HCC energy metabolism, angiogenesis, cell proliferation and tumor growth. Other studies have provided information regarding the stability, transcriptional activity and role of HIF-2α in HCC growth and progression, but the exact role in HCC remains unclear. It is generally believed that HIF-2α can be activated in most hypoxic solid tumors, but whether its activation promotes or inhibits tumor growth depends on the biological environment of the tumor. HIF-2α can participate in modulating the progression of HCC through different signaling pathways. However, the specific role of HIF-2α in HCC is still controversial, and definite conclusions have can only be provided by additional experiments. Thus, in-depth analysis of the function of HIF-2α in HCC may help to better understand the mechanism of development and metastasis of this tumor type and to improve the treatment methods. In conclusion, significant additional research effort is necessary to achieve an in-depth understanding of the role of HIFs in HCC.

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Authors' contributions

YG, ZX, DH and QX conceived and designed the review. YG, ZX, LY, YG, QZ, LH, DH and QX were involved in the collection and collation of references. YG and ZX collected and assembled the data presented in Table I. YG and ZX drew the figures. YG and ZX wrote the manuscript. All authors approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

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Competing interests

The authors declare that they have no competing interests.

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