

# Role of hypoxia inducible factor-1 in cancer stem cells (Review)

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**Abstract.** Cancer stem cells (CSCs) have been found to play a decisive role in cancer recurrence, metastasis, and chemo-, radio- and immuno-resistance. Understanding the mechanism of CSC self-renewal and proliferation may help overcome the limitations of clinical treatment. The microenvironment of tumor growth consists of a lack of oxygen, and hypoxia has been confirmed to induce cancer cell invasion, metastasis and epithelial-mesenchymal transition, and is usually associated with poor prognosis and low survival rates. Hypoxia inducible factor-1 (HIF-1) can be stably expressed under hypoxia and act as an important molecule to regulate the development of CSCs, but the specific mechanism remains unclear. The present review attempted to explain the role of HIF-1 in the generation and maintenance of CSCs from the perspective of epigenetics, metabolic reprogramming, tumor immunity, CSC markers, non-coding RNA and signaling pathways associated with HIF-1, in order to provide novel targets with HIF-1 as the core for clinical treatment, and extend the life of patients.

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## 1. Introduction

Cancer stem cells (CSCs), a population of cells with similar characteristics to those of stem cells, are associated with the occurrence, recurrence, metastasis and chemoradiation resistance of cancer (1,2). The existence of CSCs is a challenge for tumor treatment, but can also provide a novel direction for clinical treatment. To date, there have been various speculations about the occurrence of CSCs, but it remains unclear. Hypoxia in the tumor microenvironment is usually found in advanced cancer and is associated with low survival rates and poor prognosis (3,4). An increasing number of studies have found that hypoxia can induce cancer cell invasion, metastasis and epithelial-mesenchymal transition (EMT), which can promote stem-like characteristics in cancer cells (5,6). Hypoxia inducible factor-1 (HIF-1), as a pivotal molecule in the regulation of CSCs by hypoxia, participates in tumor growth, immune evasion, metabolic reprogramming and drug resistance by regulating the transcription of target genes (4,6,7). HIF-1 seems to play an important, or even core, role in the generation and maintenance of CSCs, but the explicit mechanism remains to be elucidated. This review attempted to summarize the role and mechanism of HIF-1 in CSCs, in order to provide more targets to solve the limitations of clinical tumor treatment.

## 2. Structural characteristics of HIF-1

HIF-1 is a heterodimer composed of HIF-1 $\alpha$  and HIF-1 $\beta$  (Fig. 1) (8,9). Under normoxic (21% O<sub>2</sub>) conditions, HIF-1 is degraded by intracellular oxygen-dependent ubiquitin protease degradation pathways, which are inhibited during hypoxia (8,10). HIF-1 $\alpha$  is a hypoxia inducible transcription

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*Abbreviations:* CSC, cancer stem cell; EMT, epithelial-mesenchymal transition; HIF-1, hypoxia-inducible factor-1; TAD, transactivation domain; FIH, factor inhibiting HIF-1; MAT2A, methionine adenosyltransferase 2A; SENP1, small ubiquitin-like modifier proteases 1; ncRNA, non-coding RNA; siRNA, small interfering RNA; lncRNA, long ncRNA; miRNA, microRNA; ceRNA, competing endogenous RNA; HRE, hypoxic response element; VHL, Von Hippel-Lindau; SNAI1, Snail homolog 1; Treg, regulatory T cell; OXPHOS, oxidative phosphorylation; YAP, yes-associated protein; TAZ, tafazzin; CTGF, connective tissue growth factor; HMGB1, high-mobility group box 1; VEGF, vascular endothelial growth factor; DUSPs, dual-specificity phosphatases; Gli1, glioma-associated oncogene homolog 1; SIRT1, sirtuin type 1

*Key words:* cancer stem cell, hypoxia, hypoxia inducible factor-1, hypoxia inducible factor-1 $\alpha$ , epigenetic modification, post-translational modification, non-coding RNA, cancer stem cell marker, tumor immunity, metabolic reprogramming, signal pathway

factor that contains two transactivation domains (C-TAD and N-TAD) (11,12). C-TAD can interact with co-activators such as CREB binding protein (CBP)/p300 to regulate the transcription of HIF-1 $\alpha$  target genes. N-TAD participates in stabilizing HIF-1 $\alpha$  (13,14). The core complex formed by HIF-1 $\alpha$  and CBP/p300 mainly depends on the recognition of the two short-helical domains of C-TAD by CBP/p300 (15-17). In addition, these TADs are also regulatory targets for post-translational modifications, such as acetylation and phosphorylation (18). Under normoxic conditions, factor inhibiting HIF-1 (FIH), an asparaginyl hydroxylase, hydroxylates asparagine (N)803 residue within C-TAD in an oxygen-dependent manner to block the cooperative binding of CBP/p300 and C-TAD, thereby eliminating HIF-1 $\alpha$ -mediated target gene transcription (18,19). However, the oxygen-dependent hydroxylation of N803 is inhibited in hypoxic conditions to promote this binding, leading to the transcriptional activation of target genes (13,20). Oxygen-dependent degradation domain, another special structure of HIF-1 $\alpha$ , participates in mediating the degradation of HIF-1 (9). It is worth noting that HIF-1 $\alpha$  must form a heterodimer with HIF-1 $\beta$  before exerting its biological function (8). HIF-1 $\beta$  is stably expressed in cells and maintains the stability of HIF-1 (21,22). The structures included in HIF-1 $\alpha$  and HIF-1 $\beta$  are basic-helix-loop-helix and PER-ARNT-SIM domain, which promote DNA binding and dimerization (9,23). Increasing evidence has indicated that HIF-1 $\alpha$ , as the active subunit of HIF-1, is involved in inducing and maintaining the phenotype of various CSCs (12,24,25). The present review focused more on the association between HIF-1 $\alpha$  and CSCs than of HIF-1.

### 3. Role of epigenetic and post-translational modification of HIF-1 in CSCs

Epigenetic modifications are reversible, heritable changes in gene function that do not alter the DNA sequence (26,27). HIF-1 $\alpha$  can be used as a key regulator of genomic methylation in hepatocellular carcinoma cells (28). The presence of HIF-1 $\alpha$  binding sites on methionine adenosyltransferase 2A (*MAT2A*) can promote the transcription of *MAT2A* to maintain the genome of the demethylation state (28). Unfortunately, most currently available studies have focused on the genetic modification of HIF-1 downstream target genes or key enzymes (28). Research on the epigenetic modification of HIF-1 in CSCs is rare.

Post-translational modification is one of the most important regulatory mechanisms for dynamically and reversibly regulating proteins that have biological functions (29). A previous study has found that lysine methyltransferase G9a can mono- or di-methylate HIF-1 $\alpha$  on lysine 674, which reduces the transcriptional activity of HIF-1 $\alpha$  and expression of downstream genes by reducing the TAD activity of HIF-1 $\alpha$ ; meanwhile G9a is reduced in glioblastoma cells, maintaining the activity of HIF-1 $\alpha$  and promoting HIF-1-dependent cell migration (30). As a small ubiquitin-like modifier (SUMO) protease, small ubiquitin-like modifier protease 1 (SENPI) forms a positive feedback loop with HIF-1 $\alpha$  in hepatoma cells, which causes HIF-1 $\alpha$  deSUMOylation and stable expression during hypoxia, and can promote the production of liver CSCs (31). In addition, the SENPI/HIF-1 $\alpha$  positive feedback loop promotes hypoxia-induced cell EMT and invasion in

osteosarcoma cells (32). Kinase ERK-mediated phosphorylation of HIF-1 $\alpha$  increases its stability and accumulation in the nucleus to promote the transcriptional activation of target genes (25,33). Protein kinase A in HeLa cells can also phosphorylate threonine 63 and serine 692 of HIF-1 $\alpha$ , inhibiting HIF-1 $\alpha$  degradation and increasing *HIF-1 $\alpha$*  transcription (34). The knockout of Y-box binding protein 1 in gliomas inhibits cell proliferation and blocks the cell cycle by downregulating the phosphorylation level of HIF-1, which may affect the proliferation, differentiation and metastasis of glioma cells (35,36). There is not enough information on the epigenetic and post-translational modification of HIF-1, thus further studies are needed to explore how the proliferation and growth of CSCs can be inhibited via the expression of HIF.

### 4. Role of HIF-1 in non-coding RNA associated with CSCs

Non-coding RNA (ncRNA) is a class of RNA that is transcribed from DNA but is not translated into a protein, types of ncRNA include small interfering RNA (siRNA), long ncRNA (lncRNA) and microRNA (miRNA) (37,38). A previous study demonstrated that the interaction between HIF-1 and ncRNA is significant in the self-renewal and proliferation of CSCs. miR-124 can reverse the resistance of breast CSCs to doxorubicin through the inhibition of the STAT3/HIF-1 $\alpha$  signaling pathway (39). miR-200b can target and inhibit the anti-angiogenic Krüppel-like factor 2 gene during acute hypoxia, thereby stabilizing HIF-1 signaling to promote angiogenesis (40). miR-200c inhibits the metastasis and invasion of lung cancer cells by inhibiting HIF-1 $\alpha$  expression (41). miR-18a targets HIF-1 $\alpha$  and inhibits the distant metastasis of breast cancer through the HIF-1 $\alpha$ -dependent hypoxic response; miR-18a-5p also increases the radiotherapy sensitivity of lung CSCs by inhibiting HIF-1 $\alpha$  (42,43). The promoter of miR-302 responds to HIF-1 $\alpha$ , which is beneficial for enhancing stem-like characteristics of hypoxic cancer cells (44). The expression of miR-210, an important regulator that inhibits DNA repair, is directly regulated by HIF-1 $\alpha$  and promotes the degradation of normoxic gene mRNA (45,46). The knockout of miR-210 suppresses the self-renewal capacity and resistance of glioma stem-like cells induced by hypoxia (47). miR-21 and HIF-1 $\alpha$  are positively correlated in multiple tumors, and miR-126 and HIF-1 $\alpha$  are significantly negatively correlated in colon cancer, thus indicating that their expression could be used for the early diagnosis and screening of cancer (46,48,49). miR-21 and miR-130b activate EMT through the phosphatase and tensin homolog/Akt/HIF-1 $\alpha$  pathway and promote hepatocellular carcinoma metastasis (50). HIF-1 $\alpha$  binds to the miR-1275 promoter, which promotes miR-1275 expression and maintains the pluripotency of stem cells by activating the  $\beta$ -catenin and Notch signaling pathways in lung adenocarcinoma (51). miR-421 is upregulated by HIF-1 $\alpha$  and promotes gastric cancer metastasis and chemotherapy resistance (52). miR-107 inhibits Ewing sarcoma cell proliferation, blocks the cell cycle and promotes apoptosis by targeting HIF-1 $\beta$  (53). miR-99a, which is reduced in breast CSCs, suppresses the stem-like phenotype of breast cancer by inhibiting the mTOR/HIF-1 $\alpha$  signaling pathway (54). In addition, under normoxia, the upregulated miR-31 in head and neck squamous cell carcinoma can target the 3' untranslated region of the FIH transcript to promote the

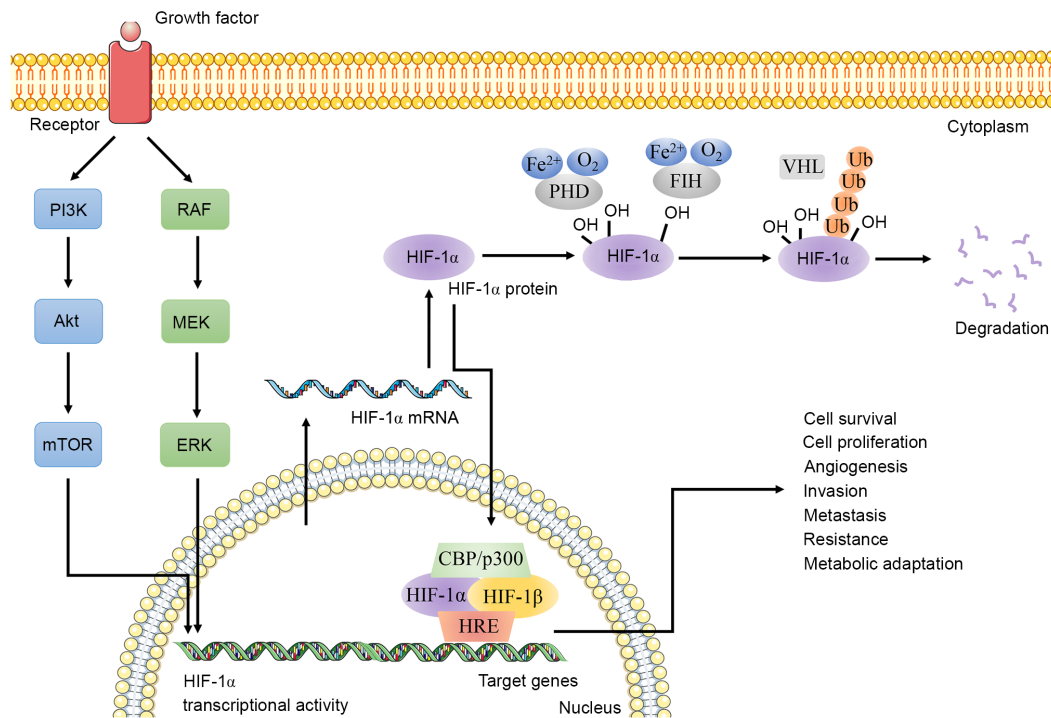


Figure 1. Schematic diagram of HIF-1 $\alpha$  and HIF-1 $\beta$ . Under hypoxic conditions, the PI3K/Akt/mTOR pathway and MAPK (RAF/MEK/ERK) pathway regulate HIF-1 $\alpha$  transcriptional activity. The upregulated HIF-1 $\alpha$  and HIF-1 $\beta$  form a heterodimer to regulate the expression of HIF-1 $\alpha$  target genes with the participation of co-activators CBP/p300. Under normoxia, FIH hydroxylates asparagine (N803) residue within C-TAD to block the cooperative binding of CBP/p300 and C-TAD. PHD, whose activity depends on ferrous, dioxygen and 2-oxoglutarate, is involved in the hydroxylation of HIF-1 $\alpha$ . Additionally, VHL, a tumor suppressor, regulates the expression of HIF-1 $\alpha$  through ubiquitination and proteasome degradation. HIF-1, hypoxia inducible factor-1; CBP, CREB binding protein; FIH, factor inhibiting HIF-1; PHD, prolyl hydroxylase; VHL, Von Hippel-Lindau; Ub, ubiquitination; HRE, hypoxic response element; TAD, transactivation domain.

transactivation activity of HIF, leading to increased tumorigenicity (55). Similar results were also found in oral squamous cell carcinoma and colorectal cancer (56,57). The upregulated lncRNA LOC554202 in non-small cell lung cancer is positively correlated with miR-31, thereby targeting FIH to promote the development of acquired gefitinib resistance (58). miR-31-5p, which is upregulated in lung cancer, induces glycolytic gene expression by regulating the FIH/HIF pathway, and ultimately promotes cell proliferation and tumor growth (59). miR-21 and miR-184, which are also upregulated in head and neck squamous cell carcinoma, have similar tumorigenic mechanisms to those of miR-31 (60).

Several hypoxia-related lncRNAs, such as HOTAIR, H19, lncRNA-NUTF2P3-001, lncRNA-UCA1, lncRNA-EFNA3, ANRIL, HINCUTs and GAPLINC, are directly regulated by HIF-1 $\alpha$ , as their promoters have hypoxic response elements (HREs), which are required for HIF-1 $\alpha$ -mediated transcriptional activation (61,62). The low expression of LINC00996 in colorectal cancer cells may participate in the occurrence and metastasis of colorectal cancer by regulating the HIF-1 signaling pathway (63). HIF-1 $\alpha$  can promote the transcription of lincRNA-p21 (64). Conversely, hypoxia-related lncRNA-p21 can bind to HIF-1 $\alpha$ , which can prevent the interaction of HIF-1 $\alpha$  and Von Hippel-Lindau (VHL) and cause the accumulation of HIF-1 $\alpha$  in cells (64). Beyond that, the knockout of lincRNA-p21 can also induce apoptosis through the HIF-1 $\alpha$ /Akt/mTOR/P70S6 kinase 1 (S6K)-pathway and increase the sensitivity of radiotherapy (65). By forming a complex with HIF-1 $\alpha$ , lncHIFCAR/MIR31HG promotes the binding of HIF-1 $\alpha$  to the target promoters and increases the

sphere-forming and metastatic ability of oral cancer cells (66). lncRNA PCGEM1 may be used as a scaffold to form a complex with HIF-1 $\alpha$  and transcription factor Snail homolog 1 (SNAIL) and regulate the invasion and metastasis of gastric cancer cells (67). Hypoxia-induced lncRNA CRPAT4 is regulated by HIF-1 $\alpha$  and plays a carcinogenic role by promoting the growth and migration of cancer cells (68). The presence of siRNA targeting *HIF-1 $\alpha$*  may provide a novel direction for specific treatment against HIF-1 $\alpha$ , and it could achieve molecular therapy by inducing apoptosis and increasing the sensitivity of radiotherapy (69,70).

In the regulation of HIF-1 expression, the cooperation of miRNA and related lncRNA is equally important. The significantly upregulated lncRNA TUG1 in osteosarcoma protects the *HIF-1 $\alpha$*  mRNA 3' untranslated region from miR-143-5p, thereby promoting osteosarcoma metastasis (71). lncRNA MIR31HG is the host gene of miR-31, which is located in the first intron of MIR31HG and has consistent transcriptional regulation (66,72). Studies have found that MIR31HG is a hypoxia-inducible lncRNA and acts as a HIF-1 $\alpha$  co-activator to regulate the HIF-1 transcriptional network (66). Mechanistically, MIR31HG directly interacts with HIF-1 $\alpha$  to promote the recruitment of HIF-1 $\alpha$  and p300 to target gene promoters (66). It is worth noting that, although the expression of MIR31HG is positively correlated with miR-31 in certain types of cancer, the knockout of MIR31HG has no effect on miR-31, indicating that the tumor regulatory effect of MIR31HG may be independent of miR-31 (73). A variety of lncRNAs serve as competing endogenous RNAs (ceRNAs) to inhibit the interaction of miRNAs with their targets, thereby

forming a lncRNA-miRNA-mRNA ceRNA network, which can regulate multiple signaling pathways, including the HIF-1 $\alpha$  pathway (74,75). In addition, the HIF-1 $\alpha$ -mediated hypoxia-induced upregulation of lncRNA-NEAT1 in hepatocellular carcinoma regulates the expression of the uridine-cytidine kinase 2 gene, which is associated with low survival rates of patients with liver cancer, by suppressing miR-199a-3p, and ultimately promotes tumor growth (76).

Although there are only a small number of studies on HIF-1-related ncRNAs, the existing independent studies are sufficient to illustrate HIF-1 as an important regulator or participant in CSC-related ncRNA (Table I), which may eradicate CSCs and prolong the life of patients by targeting ncRNA or HIF-1.

### 5. Role of HIF-1 in CSC markers

Markers of CSCs induce the pluripotency of cancer cells and are used to distinguish CSC subpopulations, some of which have been found to be associated with metastasis (77,78). Studies have found that HIF-1 is associated with the generation of CSC markers. The data has indicated that HIF-1 $\alpha$  can induce the production of multiple stem cell markers, such as OCT4, SOX2, NANOG and Krüppel-like factor 4 (KLF4) (44,79,80). In addition, the silencing of HIF-1 $\alpha$  can hinder the progression of cancer by inhibiting the expression of stem cell markers (81). HIF-1 was found to bind directly to the *CD47* promoter to facilitate gene transcription, which helps to escape phagocytosis of macrophages and maintain the stem phenotype of breast CSCs (7,82). Endogenous HIF-1 $\alpha$  is recruited to the promoter of *CD24*, which promotes CD24 expression, as well as tumor formation and metastasis (83). HIF-1 $\alpha$  appears to bind to the *CD133* promoter and promote the production of CD133<sup>+</sup> glioblastoma, and colon and pancreatic CSCs via OCT4 and SOX2 (81,84-87). In addition, a correlation has been found between HIF-1 $\alpha$  and CD133 in the cytoplasm, rather than other parts of the cell, such as the gland cavity (88). In turn, CD133 promotes HIF-1 $\alpha$  expression and its translocation to the nucleus under hypoxia (89). However, there is a different opinion that hypoxia-induced HIF-1 $\alpha$  expression leads to a decrease in CD133 expression in gastrointestinal cancer cells that overexpress CD133. Under normoxic conditions, the inhibition of mTOR signaling in CD133-overexpressing gastrointestinal cancer cells suppresses HIF-1 $\alpha$  expression and promotes that of CD133 (90). In breast CSCs, HIF-1 increases the stability of *NANOG* mRNA through the transactivation of RNA demethylase ALKBH5, which is involved in encoding N6-methyladenosine demethylase (7). In prostate cancer samples, the co-localization of HIF-1 $\alpha$ , OCT4 and NANOG suggests that HIF-1 $\alpha$  may regulate the production of CSCs by regulating stem factors (44). Surprisingly, OCT4 isoform OCT4B in cervical cancer cells promotes neovascularization by upregulating HIF-1 $\alpha$  production (91). The subtype of aldehyde dehydrogenase, 4-trimethylaminobutyraldehyde dehydrogenase (ALDH1A1), which is associated with the self-renewal, metastasis and resistance of cancer cells, is regulated by HIF-1 $\alpha$  in breast cancer (81). In turn, ALDH1A1 promotes HIF-1 $\alpha$  expression via retinoic acid signaling (81,92). In addition to promoting the production of mesenchymal or EMT marker proteins, HIF-1 $\alpha$  also inhibits the expression of

epithelial marker proteins, which can be confirmed by the use of HIF-1 $\alpha$  inhibitors (93-95). HIF-1 $\alpha$  can be used as a malignant marker of chondrosarcoma, due to its association with neovascularization (96). In conclusion, CSC markers can be used to isolate CSC subpopulations, and have been demonstrated to be involved in the self-renewal of CSCs, as well as cancer invasion and metastasis. Under hypoxic conditions, HIF-1 $\alpha$ , as a direct or indirect upstream regulator of the marker protein, may become a novel target for the elimination of CSCs.

### 6. Role of HIF-1 in tumor immunity of CSCs

Hypoxia not only regulates the production of CSCs, but also participates in regulating the immune system. Hypoxia promotes the B cell differentiation potential of lymphoid-primed multipotent progenitors through HIF-1 $\alpha$ , resulting in the production of B cells (97). Under hypoxic conditions, HIF-1 $\alpha$  also regulates innate immune responses, induces regulatory T cells (Tregs), and mediates immune escape from cytotoxic T lymphocytes and other complex immune responses (98-100). In previous years, HIF-1 $\alpha$ -mediated tumor immunity has been proposed as a direction to solve the problems associated with tumor therapy (101-103), so the immune response of CSCs mediated by HIF-1 $\alpha$  is also worth exploring when investigating antitumor therapies.

During EMT, in addition to the induction of cancer stemness, immunosuppression is also observed, which can lead to increased malignancy of the tumor, drug resistance and metastasis (79). Studies have found that hypoxia further increases the production of immunosuppressive factors, inhibition of monocyte phagocytosis, inhibition of T cell proliferation, and activation and induction of Tregs in glioblastoma multiforme-related CSCs, which may be achieved via the phosphorylated STAT3/HIF-1 $\alpha$ /vascular endothelial growth factor (VEGF) pathway (104-106). During HIF-1 $\alpha$ -induced EMT of liver cancer cells, the upregulated cytokine CCL20 promotes the expression of indoleamine 2,3-dioxygenase in monocyte-derived macrophages, which inhibits the activation and proliferation of T cells and induces Tregs by increasing the degradation of tryptophan (107). Immune escape and immunosuppression are equally important for the existence of CSCs (108). One of the breast CSC marker proteins, CD47, can bind to the signal regulatory protein  $\alpha$  on the surface of macrophages to escape macrophage phagocytosis, and the induction of CD47 depends on the direct regulation of HIF-1 $\alpha$  (82). There are two types of tumor-associated macrophages, M1 and M2, which inhibit or promote tumor growth, respectively. The M2 type is more common in the tumor microenvironment and promotes tumor invasion (108,109). Hypoxia induces nuclear factor- $\kappa$ B (NF- $\kappa$ B) and HIF-1 $\alpha$  successively, leading to the infiltration of M2 macrophages in the tumor microenvironment and tumorigenesis (110). As compared with normal cells, triple-negative breast cancer cells have more HIF-1 $\alpha$ -specific IgG, which indicates that HIF-1 $\alpha$  is immunogenic (111). Treatment using a HIF-1 $\alpha$  vaccine recruits type I T cells to the tumor tissue and effectively inhibits basal-like breast CSCs, which can inhibit tumor metastasis (111). In order to adapt to chronic hypoxia, CD8<sup>+</sup> T cells increase the expression of active HIF-1 $\alpha$  and increase their own effector functions (112). The production of NANOG in hypoxic tumor cells depends

Table I. Association between HIF-1 and non-coding RNA.

Non-coding RNA	Category	Relationship with HIF-1	Cancer type	(Refs.)
miR-124	miRNA	Inhibits STAT3/HIF-1 $\alpha$ pathway	Breast cancer	(39)
miR-200b	miRNA	Inhibits KLF2 gene and stabilizes HIF-1 $\alpha$ signal	Human endothelial cells	(40)
miR-200c	miRNA	Inhibits HIF-1 $\alpha$ expression	Lung cancer	(41)
miR-18a	miRNA	Inhibits HIF-1 $\alpha$ expression	Breast cancer	(43)
miR-18a-5p	miRNA	Inhibits HIF-1 $\alpha$ expression	Lung cancer	(42)
miR-302	miRNA	Regulated by HIF-1 $\alpha$	HeLa cells	(44)
miR-210	miRNA	Regulated by HIF-1 $\alpha$	Glioma; pancreatic cancer; colorectal cancer	(45-47)
miR-21	miRNA	Activates PTEN/Akt/HIF-1 $\alpha$ pathway; positive correlation with HIF-1 $\alpha$ ; targets FIH	Hepatocellular carcinoma; breast cancer; colon cancer; glioma	(46,48-50)
miR-126	miRNA	Negative correlation with HIF-1 $\alpha$	Colon cancer	(46)
miR-130b	miRNA	Activates PTEN/Akt/HIF-1 $\alpha$ pathway	Hepatocellular carcinoma	(50)
miR-1275	miRNA	Regulated by HIF-1 $\alpha$ and activates Notch and $\beta$ -catenin pathway	Lung adenocarcinoma	(51)
miR-421	miRNA	Upregulated by HIF-1 $\alpha$	Gastric cancer	(52)
miR-107	miRNA	Targets HIF-1 $\beta$	Ewing sarcoma	(53)
miR99a	miRNA	Inhibits mTOR/HIF-1 $\alpha$ signal pathway	Breast cancer	(54)
miR-31	miRNA	Targets the 3' untranslated region of FIH transcript	Head and neck squamous cell carcinoma; oral squamous cell carcinoma; colorectal cancer; lung cancer	(55-58)
miR-31-5p	miRNA	Targets the 3' untranslated region of FIH transcript	Lung cancer	(59)
miR-184	miRNA	Targets FIH	head and neck squamous cell carcinoma	(60)
LOC554202	lncRNA	Positively correlated with miR-31	Lung cancer	(58)
LINC00996	lncRNA	Regulates HIF-1 $\alpha$ signal	Colorectal cancer	(63)
LincRNA-p21	lncRNA	Regulated by HIF-1 $\alpha$ and induces HIF-1 $\alpha$ accumulation	HeLa cells	(64,65)
LncHIFCAR/MIR31HG	lncRNA	Promotes the binding of HIF-1 $\alpha$ to target genes	Oral cancer	(66)
PCGEM1	lncRNA	Forms a complex with HIF-1 $\alpha$ and SNAI1	Gastric cancer	(67)
CRPAT4	lncRNA	Regulated by HIF-1 $\alpha$	Clear cell renal cell carcinoma	(68)
TUG1	lncRNA	Protects HIF-1 $\alpha$ mRNA 3' untranslated region from miR-143-5p	Osteosarcoma	(71)
miR31HG	lncRNA	Serves as a HIF-1 $\alpha$ co-activator	Oral cancer	(66,72,73)
NEAT1	lncRNA	Induced by HIF-1 $\alpha$ and regulates the expression of UCK2 gene through suppressing miR-199a-3p	Hepatocellular carcinoma	(76)

HIF-1, hypoxia inducible factor-1; miR/miRNA, microRNA; lncRNA, long non-coding RNA; KLF2, Krüppel-like factor 2; PTEN, phosphatase and tensin homolog; SNAI1, Snail homolog 1; FIH, factor inhibiting HIF-1; UCK2, uridine-cytidine kinase 2.

on the expression of HIF-1 $\alpha$ , and upregulated NANOG reduces the sensitivity of hypoxic tumor cells to the lysis of cytotoxic T lymphocytes; however, this process is not caused by the increased phenotype of CSCs, but NANOG increased the viability of the tumor cells (113). At the same time, some

studies have proposed that hypoxia-induced NANOG, which also depends on HIF-1 $\alpha$ , promotes the self-renewal of melanoma cells and induces Tregs and macrophages by directly regulating TGF- $\beta$ 1, but whether this immunosuppression is associated with CSCs has not been reported (114). In summary,

HIF-1 $\alpha$ -mediated immunosuppression and immune escape are crucial in CSCs. This common regulatory mechanism in the tumor microenvironment gives CSCs a new definition and provides novel ideas for tumor immunotherapy.

### 7. Role of HIF-1 in metabolic reprogramming of CSCs

It is commonly known that cancer cells can metabolize and reprogram under hypoxic conditions to complete the conversion of oxidative phosphorylation (OXPHOS) to glycolysis to meet their own energy needs (7,115). However, a study recently proposed the concept of metabolic plasticity, that is, even within the same cancer cell population, cancer cells can complete the conversion of glycolysis to OXPHOS, while maintaining metabolic reprogramming and energy requirements (116). Indeed, hypoxic cells do not metabolize all glucose to lactic acid, and non-hypoxic cells do not metabolize all glucose to carbon dioxide and water, which makes metabolic balance particularly important (117). Among them, HIF-1 plays a crucial role as a regulator in metabolic reprogramming, and the role of HIF-1 in CSC metabolism is worthy of attention.

HIF-1, as the main regulator of several glycolytic transporters and enzymes, including glucose transporter, monocarboxylate transporter, hexokinase and lactate dehydrogenase, regulates glycolytic transformation (95,118). HIF-1 $\alpha$  also promotes the production of carbonic anhydrases, which interact with extracellular acidification to change the pH of the intracellular and extracellular environment of the cell, thereby affecting the absorption of anticancer drugs and producing drug resistance (119,120). Colon CSC clones with liver receptor homolog-1-overexpression, a target of GATA binding protein 6, were found to have increased intracellular hypoxia, HIF-1 $\alpha$  and reactive oxygen species (ROS); it was further proven that glycolysis and OXPHOS co-exist in the clones but mainly mitochondrial respiration (121). The knockout of CSC marker protein CD44 induces glycolysis to OXPHOS via a complex signaling pathway involving HIF-1 $\alpha$  (115). The loss of ATP synthase, especially the D subunit ATP5H, leads to the accumulation of ROS in cells and the stabilization of normoxic HIF-1 $\alpha$  and activation of the HIF-1 $\alpha$  pathway, affecting mitochondrial metabolic reprogramming, the production of stem-like ability, and therapeutic resistance (122). The  $\alpha$ -KG analogue dimethyl 2-ketoglutarate allows excess succinate/fumarate to be transferred from the mitochondria to the cytoplasm, where it can impair prolyl hydroxylase and thus stabilize and activate HIF-1 $\alpha$ , eventually leading to increased glycolysis and the acquisition of the stem-like characteristics of breast cancer cells (118). In addition, the upregulation of HIF-1 $\alpha$ , under hypoxia, inhibits the expression of mitochondrial phosphoenolpyruvate carboxykinase, which leads to a weakened tricarboxylic acid cycle and the enrichment of fumarate, ultimately leading to increased ROS levels and breast CSC growth (123). In conclusion, HIF-1 appears to mainly act as an intermediate participant regulating the complex conversion mechanism of glycolysis and OXPHOS and the generation and maintenance of stemness in CSCs.

### 8. Role of HIF-1 in signaling pathways associated with CSCs

HIF-1 is regulated by multiple signaling pathways in CSCs and also participates in regulating the characteristics of CSCs

through signaling pathways, such as the Notch, MAPK/ERK and Wnt signaling pathways (81). Studies have found that the PI3K/Akt/mTOR pathway maintains the transcription, translation and biological activity of HIF-1 $\alpha$  (54,124). Hypoxia also induces tuftelin 1 in a HIF-1 $\alpha$ -dependent manner; subsequently, tuftelin1 activates the Ca<sup>2+</sup>/PI3K/Akt pathway to induce EMT and metastasis in hepatocellular carcinoma (50). HIF-1 $\alpha$  promotes the survival of prostate CSCs by inhibiting mTOR and activating Akt phosphorylation, which may be accomplished by the feedback regulation of PI3K via P70-S6K-mediated insulin receptor substrate 1 phosphorylation (125). The mitochondrial autophagy regulator NIX interacts with Ras homolog enriched in the brain to activate mTOR/Akt/HIF signaling, and subsequently increase the self-renewal capacity of glioma stem cells (126). The Wnt/ $\beta$ -catenin signaling pathway activates the transcription of *HIF-1 $\alpha$* , inhibits the apoptosis of hepatocellular carcinoma and promotes the occurrence of EMT, and then triggers the metastasis of hepatocellular carcinoma (50). Conversely, HIF-1 $\alpha$  maintains the stemness of esophageal squamous cell carcinoma by activating the Wnt/ $\beta$ -catenin signaling pathway (127). HIF-1 $\alpha$  induces the generation of breast CSCs and the enhancement of self-renewal capacity by upregulating the expression of yes-associated protein (YAP) and tafazzin (TAZ) in the Hippo pathway (7,86). HIF-1 $\alpha$ , which can also function as a bidirectional co-activator of TAZ, is recruited by TAZ to the promoter of encoding connective tissue growth factor (*CTGF*) to activate the transcription of *CTGF*, which is involved in promoting the onset of EMT and maintaining the stem-like phenotype of breast CSCs (6,128). In addition, high-mobility group box 1 (HMGB1) released from injured or dying cells following X-ray radiation induces the dedifferentiation of CD133- pancreatic cancer cells, and promotes pancreatic CSC production and pancreatic cancer metastasis via the HMGB1/toll-like receptor 2 (TLR2)/YAP/HIF-1 $\alpha$  axis, in which HMGB1-TLR2 promotes HIF-1 $\alpha$  and YAP nuclear localization and HIF-1 $\alpha$  DNA binding ability (129). The ROS-mediated transition of breast CSCs from a quiescent mesenchymal state to a proliferative epithelial state is promoted by the activation of the Notch pathway and AMP-activated protein kinase/HIF-1 $\alpha$  axis (130,131).

HIF-1 $\alpha$  maintains the stemness of leukemia and glioblastoma stem cells through the Notch signaling pathway (81,86). Studies have also suggested that the hypoxia/Notch1/SOX2 axis is essential for the development of ovarian CSCs (81). The combination of HIF-1 $\alpha$  and notch intracellular domain activates Notch-responsive promoters and increases the expression of Notch downstream genes, such as *Hes1* and *Hey2*, and *Hes1* is important in the stemness maintenance and self-renewal of leukemia stem cells (50,81). In addition, studies have suggested that there is negative feedback regulation of the *Hes1* expression, which is completed by the combination of *Hes1* and N-boxes on the *Hes1* promoter (132). Furthermore, HIF-1 $\alpha$  may enhance the Notch pathway-induced *Hes1* expression by inhibiting the negative feedback regulation of the *Hes1* gene, and ultimately promote the maintenance of the stemness of mouse cholangiocarcinoma CSCs (132,133). STAT3 induced by HIF-1 $\alpha$  through the JAK or adenylate receptor 2B pathway can upregulate interleukin-6 and Nanog, which can maintain the

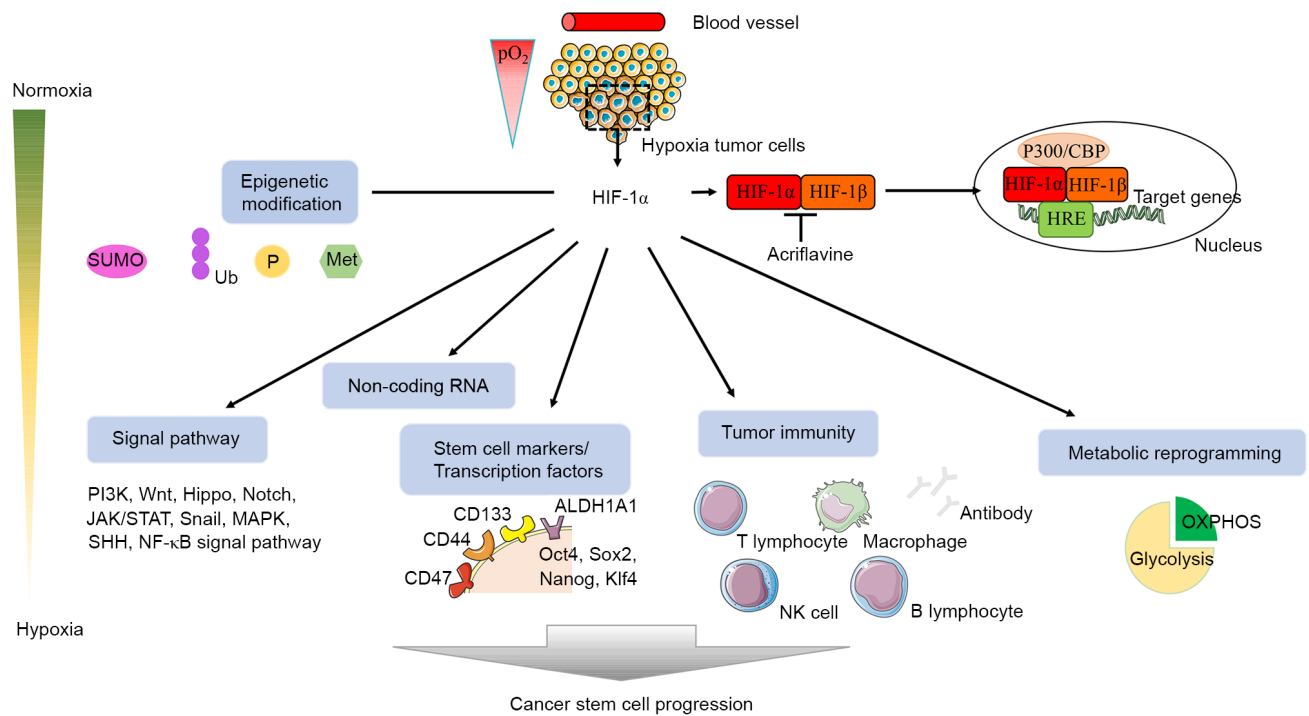


Figure 2. Hypoxia regulates CSCs with HIF-1 as the core. HIF-1 $\alpha$  and HIF-1 $\beta$  form a heterodimer and bind to HRE on the target genes to activate transcription, which can be suppressed by acriflavine, a HIF-1 $\alpha$  inhibitor. This chart attempts to show the role and regulation of HIF-1 in CSCs from multiple directions, including epigenetic modification, signaling pathway, non-coding RNA, stem cell marker, immunity and metabolic reprogramming. CSCs, cancer stem cells; HIF-1, hypoxia inducible factor-1; SUMO, small ubiquitin-like modifier; Ub, ubiquitination; P, phosphorylation; Met, methylation; HRE, hypoxic response element; OXPHOS, oxidative phosphorylation; CBP, CREB binding protein; NK, natural killer; Klf4, Krüppel-like factor 4; ALDH1A1, 4-trimethylaminobutyraldehyde dehydrogenase; SHH, Sonic Hedgehog.

CSC phenotype (81). Under hypoxic conditions, the increased HIF-1 $\alpha$  in glioma stem-like cells activates the JAK1/2-STAT3 signaling pathway by promoting the production of VEGF, a HIF-1 $\alpha$  target, and ultimately enhances the self-renewal ability of glioma stem-like cells (134). HIF-1 $\alpha$  inhibits the expression of E-cadherin and promotes EMT in hepatocellular carcinoma via the SNAI1 signaling pathway, in which HIF-1 $\alpha$  binds to two HREs on the *SNAI1* promoter to upregulate SNAI1, a transcriptional inhibitor of E-cadherin (50,135). At the same time, researchers found that HIF-1 $\alpha$  promotes EMT in gastric CSCs by activating the Snail signaling pathway, and the same result was found in ovarian cancer (136,137). Dual-specificity phosphatases (DUSPs) negatively regulate MAPK pathway activity (138). Chemotherapy induces an increase in DUSP9 expression and a decrease in that of DUSP16 in a HIF-1-dependent manner; it then upregulates NANOG and KLF4 through the reduction of ERK activity and the increase of P38 activity, respectively, finally promoting the development of breast CSCs (138). Studies have found that hypoxia activates the Sonic Hedgehog signaling pathway to induce the production of CSC markers in cholangiocarcinoma cells in a HIF-1 $\alpha$ -dependent manner, which can be blocked by HIF-1 $\alpha$  inhibition (139). The expression level of glioma-associated oncogene homolog 1 (Gli1) in the Hedgehog pathway in prostate cancer was higher in the HIF-1 $\alpha$ <sup>+</sup> group, indicating that hypoxia promotes the expression of Gli1 and that the increased Gli1 expression is significantly associated with EMT of prostate cancer cells (140). Under hypoxia, upregulated HIF-1 $\alpha$  promotes the expression of its downstream target gene, sirtuin type 1 (*SIRT1*), by activating the NF- $\kappa$ B signaling pathway,

and increased SIRT1 promotes the maintenance of stem-like characteristics of ovarian cancer cells (141). Of note, studies have suggested that hypoxia-related factors switch HIF-1 $\alpha$  to HIF-2 $\alpha$  by activating the NF- $\kappa$ B pathway to increase the malignancy of bladder cancer and maintain the expression of stem cell markers (142).

In addition, some signaling pathways also regulate the HIF-1 $\alpha$ -related complex. NF- $\kappa$ B-mediated inflammatory signaling can prevent the HIF-1 $\alpha$  transcription network by directly competing for the binding of p300 to the promoter of HRE-encoding genes (143). Raf Kinase Trapping to Golgi in clear-cell renal cell carcinoma prevents the formation of the HIF-1 $\alpha$ /p300 complex and transactivation of HIF-1 $\alpha$  by inhibiting the MAPK pathway (144). Since PI3K promotes the induction of HIF-1 $\alpha$  levels and there is a protein kinase B (PKB) phosphorylation site on p300, the PI3K/PKB pathway can boost the binding of HIF-1 $\alpha$ /phosphorylated p300 to glucokinase gene (*GK*)-HRE, thereby promoting insulin-mediated *GK* gene expression (145). LB-1, a triptolide derivative, prevents the formation of the HIF-1 $\alpha$ /p300/p-STAT3 complex by down-regulating the PI3K/Akt/mTOR pathway that regulates HIF-1 $\alpha$  at the translation level, and ultimately exerts anti-tumor properties (146). In turn, the increase in the Wnt signaling pathway mediated by CBP plays an important role in hypoxia-induced leukemia stem cells (147,148). In fact, multiple factors in the HIF-1 $\alpha$  signaling pathway can also interfere with the formation of the HIF-1 $\alpha$ /p300 complex. CBP/p300-interacting transactivator with an ED-rich tail 2 in hypoxia signaling was also found to prevent p300 from recruiting to N-TAD and C-TAD, thereby inactivating HIF-1 $\alpha$  (149). The ferritin heavy chain in



Table II. Association between HIF-1 and signaling pathways.

Signaling pathway	Relationship with HIF-1	Cancer type	(Refs.)
PI3K/Akt/mTOR	Maintains the transcription, translation and biological activity of HIF-1 $\alpha$ ; activated by HIF-1 $\alpha$ -dependent tuftelin1; regulated by HIF-1 $\alpha$ ; involved in regulating the formation of HIF-1 $\alpha$ /p300 complex	Breast cancer; hepatocellular carcinoma; prostate cancer; pancreatic cancer	(50,54,124,125,146)
Wnt/ $\beta$ -catenin	Activates the transcription of HIF-1 $\alpha$ ; also activated by HIF-1 $\alpha$	Hepatocellular carcinoma; esophageal squamous cell carcinoma	(50,127)
Hippo	Regulated by HIF-1 $\alpha$ ; TAZ recruits HIF-1 $\alpha$ to promote CTGF expression	Breast cancer	(6,7,86,128)
Notch	Regulated by HIF-1 $\alpha$	Leukemia; glioblastoma; ovarian cancer	(50,81,86)
JAK/STAT	Activated by HIF-1 $\alpha$	Glioma	(81,134)
SNAI1	Regulated by HIF-1 $\alpha$	Hepatocellular carcinoma	(50,135)
Snail	Activated by HIF-1 $\alpha$	Gastric cancer; ovarian cancer	(136,137)
MAPK	Regulated by DUSPs in a HIF-1-dependent manner under chemotherapy conditions; involved in regulating the formation of HIF-1 $\alpha$ /p300 complex	Breast cancer; clear-cell renal cell carcinoma	(138,144)
Sonic Hedgehog	Activated by hypoxia in a HIF-1-dependent way	Cholangiocarcinoma; prostate cancer	(149,140)
NF- $\kappa$ B	Activated by HIF-1 $\alpha$ ; also activated by hypoxia-related factors to switch HIF-1 $\alpha$ to HIF-2 $\alpha$ ; competes for the binding of p300 to the promoter of HRE-encoding genes	Bladder cancer; ovarian cancer	(141-143)
PI3K/PKB pathway	Promotes the binding of HIF-1 $\alpha$ /phosphorylated p300 to GK-HRE	Hepatocytes	(145)
pSTAT3/HIF-1 $\alpha$ /VEGF pathway	Promotes the occurrence of immunosuppression	Glioblastoma multiforme	(104-106)

HIF-1, hypoxia inducible factor-1; TAZ, tafazzin; CTGF, connective tissue growth factor; DUSPs, dual-specificity phosphatases; VEGF, vascular endothelial growth factor; SNAI1, Snail homolog 1; GK, glucokinase; HRE, hypoxic response element; p, phosphorylated.

the hypoxia signaling pathway has also been demonstrated to interfere with p300 recruitment to HIF-1 $\alpha$  by promoting FIH-mediated hydroxylation of N803 (150). In prostate cancer, N-myc downstream-regulated gene 3 regulates Akt-dependent HIF-1 $\alpha$  hypoxia signaling through dissociating the p300 from HIF-1 $\alpha$  (151).

In conclusion, HIF-1 $\alpha$  promotes self-expression by interacting with multiple signaling pathways and participates in the maintenance of stem-like characteristics of CSCs (Table II).

### 9. Potential targets for CSC therapy

It is worth noting that the regulatory effect of HIF-1 is also different in specific types of cancer (Table III). As HIF-1/HIF-1 $\alpha$  is a key factor regulating CSCs, its inhibitor may be used for adjuvant therapy. Acriflavine, a HIF-1 inhibitor, prevents the dimerization of HIF-1 $\alpha$  and HIF-1 $\beta$ ,

leading to undimerized HIF-1 $\alpha$  degradation and inhibition of hypoxia-induced gene expression (82). Acriflavine can effectively inhibit the stemness and growth of chronic myeloid leukemia cells (81). Digoxin, also a HIF-1 inhibitor, or acriflavine can prevent glioblastoma stem cells from responding to hypoxia by reducing the expression of receptor for advanced glycation end products, which is a membrane receptor that senses the necrotic stimulation of cells that die due to hypoxia (152). The targeted inhibition of *HIF-1* by siRNA can increase the radiotherapy sensitivity of malignant gliomas, but the limited delivery efficiency of siRNA still needs to be resolved (153,154). The HIF-1 $\alpha$  vaccine is proposed to inhibit breast cancer metastasis from the perspective of tumor immunity (111). Not only that, the combination of HIF-1 $\alpha$  and co-activators can also become a potential therapeutic target. Even under hypoxic conditions, 3-(5'-hydroxymethyl-2'-furyl)-1-benzyl indazole can stimulate



Table III. Potential effects of HIF-1 modulation in specific types of cancer.

Cancer type	Potential effect of HIF-1	Refs.
Brain tumor	Promotes CD133 <sup>+</sup> glioblastoma production and maintains self-renewal; regulates tumor immune microenvironment; also regulates cell proliferation and metastasis	(30,35,36,47,81,86,87,104-106,128,134,152-154)
Liver cancer	Promotes CSC production and EMT occurrence; regulates genomic methylation	(28,31,50,76)
Osteosarcoma	SENP1/HIF-1 $\alpha$ positive feedback loop promotes EMT occurrence and cell invasion	(32,71)
Breast cancer	Participates in the regulation of breast CSC chemotherapy resistance, self-renewal, and breast cancer metastasis; promotes immune escape	(6,7,39,43,54,81,82,86,92,111,118,123,128,130,138)
Lung cancer	Participates in the regulation of lung CSC radiotherapy resistance and lung cancer invasion and metastasis; also maintains stemness	(41-43, 51,58,59)
Gastric cancer	Promotes gastric cancer metastasis and chemotherapy resistance; promotes EMT occurrence	(52,67,136)
Ewing sarcoma	Participates in the regulation of cell proliferation and survival	(53)
Colorectal cancer	Participates in colorectal cancer occurrence and metastasis; promotes CSC production	(46,48,49,57,63,81,84,121)
Oral cancer	Regulates sphere formation, metabolism and metastasis	(56,66)
Pancreatic cancer	Promotes CSC production	(85,129)
Prostate cancer	Regulates CSC production and survival; also related to EMT occurrence	(44,125,140,151,142,146)
Cervical cancer	Participates in regulating neovascularization	(91)
Melanoma	Promotes melanoma cell self-renewal and regulates tumor immune microenvironment	(114)
Esophageal cancer	Maintains stemness	(127)
Leukemia	Maintains stemness and self-renewal	(50,81,86,147,148)
Ovarian cancer	Maintains stemness and promotes EMT occurrence	(81,136,137,141)
Cholangiocarcinoma	Participates in regulating CSC stemness	(132,133,139)
Bladder cancer	The switch of HIF-1 $\alpha$ to HIF-2 $\alpha$ is related to the malignancy and stemness maintenance of bladder cancer	(142)

HIF-1, hypoxia inducible factor-1; CSC, cancer stem cell; EMT, epithelial-mesenchymal transition; SENP1, small ubiquitin-like modifier proteases 1.

Table IV. Potential therapeutic targets associated with HIF-1.

Potential targets	Possible mechanism	(Refs.)
MAT2A	Maintains the demethylation status of genes	(28)
SENP1	Serves as a SUMO protease and forms a positive feedback loop with HIF-1 $\alpha$	(31,32)
ERK	Phosphorylates HIF-1 $\alpha$ and increases its expression and stability	(25,33)
PKA	Prevents HIF-1 $\alpha$ degradation	(34)
YB-1	Participates in regulating HIF-1 phosphorylation	(35,36)
Indoleamine 2,3-dioxygenase	Breaks down tryptophan and regulates tumor immunity	(107)
Carbonic anhydrase	Regulates intracellular PH	(119,120)

HIF-1, hypoxia inducible factor-1; MAT2A, methionine adenosyltransferase 2A; SENP1, small ubiquitin-like modifier proteases 1; PKA, protein kinase A; YB-1, Y-box binding protein 1; SUMO, small ubiquitin-like modifier.

FIH to bind to C-TAD and reduce the recruitment of p300 to inhibit HIF-1 $\alpha$  in a N803 hydroxylation-independent manner (155). Bortezomib, which is used for clinical testing of multiple tumors, has similar FIH-mediated anticancer

effects (156). Osmium metal complex 1 can be used as an inhibitor to directly interfere with the interaction between HIF-1 $\alpha$  and p300 to stop the HIF-1 $\alpha$  expression and inhibit cell proliferation (157). Chetomin, discorhabdin L (2) and melatonin play a similar role (153,158-160). The combination of enzalutamide, an androgen receptor antagonist, and chetomin effectively inhibits the growth of castration-resistant prostate cancer cells (158). TEL03, a perylene derivative, acts as a dual targeted inhibitor of STAT3 and HIF-1 $\alpha$ , interrupts the phosphorylation of STAT3 and inhibits its transcription; it also inhibits the combination of HIF-1 $\alpha$  and CBP/p300 to induce HIF-1 $\alpha$  degradation, thereby inducing apoptosis and suppressing tumor growth (161). LB-1 also prevents the formation of the HIF-1 $\alpha$ /p300/p-STAT3 complex by targeting both the HIF-1 $\alpha$  and STAT3 pathways to inhibit the growth of prostate cancer cells (146). Minnelide, a pro-drug of triptolide, has shown clinical prospects in a recent phase I trial of advanced gastrointestinal malignancies, with the phase II trial in preparation (162). In addition, the inhibition of key enzymes and signaling pathways (Table II), key gene knockout, as well as CSC-related immune and metabolic regulation, all comprise potential targets (Table IV) for CSC therapy.

## 10. Conclusions and perspectives

CSCs are a population with the potential for differentiation and self-renewal, and participate in tumor metastasis, recurrence and treatment resistance (81,163). Understanding the mechanisms through which CSCs produce and maintain stemness may help overcome the limitations of clinical cancer treatment. Hypoxia regulates angiogenesis, tumorigenesis, immune response, cancer recurrence and metastasis, and participates in EMT progression and CSC production (81,82,164). HIF-1 stably expressed under hypoxic conditions binds to HRE on the promoter of key genes and regulates glycolysis, angiogenesis, cell apoptosis, tissue invasion and PH regulation (165,166). HIF-1 $\alpha$ , as the active subunit of HIF-1, is a primary transcription regulator in hypoxic adaptive responses (81,82). Therefore, the present review focused more on the role of HIF-1 $\alpha$  in CSCs instead of HIF-1, in order to propose novel methods for the eradication of CSCs from various perspectives, including epigenetic modification, immune response, metabolic reprogramming, stem cell marker, and ncRNA and signaling pathways associated with CSCs (Fig. 2).

The current tumor treatment methods, combined with adjuvant therapy with HIF-1/HIF-1 $\alpha$  as the core, may prevent the recurrence and metastasis of cancer cells, and ultimately improve the cure rate and prolong the life of patients.

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## Authors' contributions

QZ wrote the manuscript. ZH, YZ, JC and WL reviewed the manuscript critically. All authors read and 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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