Hypoxia-inducible factors: Regulatory functions and status as a therapeutic target in gastric cancer (Review)

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Abstract. Hypoxia, defined as a condition of insufficient tissue oxygenation, is recognized as a key characteristic of solid tumors and is closely associated with their aggressive phenotypic traits. The cellular response to hypoxia is regulated by hypoxia-inducible factors (HIFs), a family of transcription factors that promote the transcription of gene products involved in driving tumor progression, including processes such as proliferation, angiogenesis, metastasis and drug resistance. In the field of cancer therapeutics, targeting the HIF pathway has emerged as a promising strategy, and the Food and Drug Administration approval in 2021 of Welireg, a novel agent designed to target HIF-2α for the primary treatment of von Hippel-Lindau syndrome, has further validated its favorable prospects in tumor therapy. Gastric cancer (GC) continues to pose a notable global health challenge, as it accounts for ~1 million new cases of cancer each year and is responsible for >650,000 mortalities annually. Currently, a range of therapeutic approaches are available for patients diagnosed with GC, yet the 5-year survival rate remains suboptimal for those with advanced-stage disease. The present review summarizes the regulatory and target roles of HIFs in GC, thus providing references for GC treatment and emphasizing the potential of HIF-targeted therapies to disrupt cancer-associated signaling pathways.

Contents

1. Introduction

Gastric cancer (GC) represents a prominent public health concern globally, characterized by limited effective treatment options, poor prognosis and high mortality rates (1). Anti-GC treatments, which are primarily based on chemotherapy, radiation therapy and targeted therapy, face a major challenge in the form of acquired resistance (2). GC cells acquire resistance through a range of mechanisms and associated signaling, all involving both intrinsic and extrinsic factors (3). According to the Lauren classification, GC is categorized into two major histopathological subtypes with distinct biological behaviors: Intestinal-type and diffuse-type (4). Intestinal-type GC, accounting for 50-60% of cases, arises from intestinal metaplasia (a premalignant lesion), exhibits glandular differentiation and is associated with environmental risk factors [such as *Helicobacter pylori* (*H. pylori*) infection, high-salt diet and smoking] (5). It typically presents as an exophytic or ulcerative mass in the distal stomach, progresses slowly and has a relatively favorable prognosis (5). By contrast, diffuse-type GC (30-40% of cases) lacks glandular structure, is characterized by signet ring cells with intracellular mucin accumulation and is linked to genetic predispositions [such as cadherin-1 (CDH1) mutations] (6). It invades diffusely through the gastric wall (*linitis plastica*), has early metastatic potential and confers a worse outcome. A third subtype, mixed-type GC (10-15% of cases), combines features of both intestinal and diffuse types and exhibits intermediate clinical behavior (6).

GC progression follows a well-defined natural history, from premalignant lesions (gastric atrophy, intestinal metaplasia and dysplasia) to early stage localized tumors, and ultimately to advanced disease with lymph node (LN) and distant metastasis. Multiple factors modulate this process, including: i) Microenvironment (ME) factors: Beyond hypoxia, *H. pylori*

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infection (the strongest risk factor) induces chronic inflammation, oxidative stress and epithelial dysregulation, which synergize with hypoxia-inducible factors (HIFs) to promote carcinogenesis; ii) genetic/epigenetic alterations: Mutations in TP53, CDH1 and epidermal growth factor receptor 2 (ERBB2) and microsatellite instability (MSI) contribute to subtype-specific progression, with HIFs interacting with these pathways to enhance malignancy; and iii) lifestyle and host factors: Obesity, alcohol consumption and immune dysregulation further exacerbate GC development by altering tumor ME (TME) hypoxia and HIF activation.

Pathological staging of GC adheres to the American Joint Committee on Cancer/Union for International Cancer Control/TNM system (8th edition) (7), which classifies tumors based on primary tumor invasion depth (T), lymph node involvement (N) and distant metastasis (M) (7). Pathological staging (pTNM) is the gold standard for prognosis, with pT1 (tumor invading mucosa/submucosa) and pT2 (invading muscularis propria) defining early-stage GC (I-II), and pT3 (serosa invasion) and pT4 (adjacent organ invasion) indicating locally advanced disease (III) (8). LN involvement is stratified as pN0 (no LN metastasis), pN1 (1-2 positive LNs), pN2 (3-6 positive LNs) and pN3 (≥7 positive LNs), with pN3 indicating high metastatic potential (8). Clinical staging (cTNM), based on preoperative imaging and endoscopy, guides treatment selection but is less accurate than pTNM, particularly for LN assessment (9). Clinically, early-stage GC (cI-II) is curable with surgery, while advanced-stage GC (cIII-IV) requires multimodal therapy (3). Notably, HIF expression is associated with TNM stage: HIF-1α upregulation is detected in 40-70% of GC cases, with higher levels in pT3-pT4 tumors, pN2-pN3 LN status and M1 disease, making it an independent prognostic marker (10).

Anti-GC treatments, primarily based on chemotherapy, radiation therapy, targeted therapy and immunotherapy, face a major challenge in acquired resistance. GC cells acquire resistance through intrinsic (genetic mutations and metabolic reprogramming) and extrinsic (TME hypoxia and immunosuppression) mechanisms, all involving HIF-mediated signaling (11). For most patients with end-stage cancer, the primary cause of treatment failure is resistance to cancer therapy, and primary or acquired drug resistance particularly acts as a major impediment in clinical oncology (11). Therefore, studying drug resistance mechanisms is of equal importance to drug development, and both pharmacological factors, including insufficient drug concentration at the tumor site, and cellular factors, such as aberrant activation of signal transducer and activator of transcription 3 (STAT3) signaling, enhanced tumor cell stemness, epithelial-mesenchymal transition (EMT) and overexpression of ATP-binding cassette (ABC) transporters, can contribute to clinical resistance in gastric cancer (12). The mechanisms governing drug resistance in tumors are precise yet complex and multifactorial, and they can be grouped into three categories: i) Inadequacies in pharmacokinetic properties; ii) intrinsic factors of tumor cells; and iii) external conditions of tumor cells in the TME (13).

Accumulating evidence has demonstrated that the TME drives cancer progression through multiple mechanisms, with a prominent role in mediating therapeutic resistance (14). On the one hand, the TME impairs drug penetration, confers surviving cancer cells with proliferative and antiapoptotic properties to facilitate therapeutic resistance, and induces common morphological alterations of the disease (15). On the other hand, it is enriched with soluble factors secreted by both tumor and stromal cells, which in turn contribute to aberrant cell proliferation, pathological angiogenesis, tumor metastasis and the development of drug resistance (16). As the rapid and uncontrolled proliferation of tumor cells restricts oxygen availability, leading to insufficient blood supply or hypoxia, this condition has become a typical ME feature in nearly all solid tumors (16). Hypoxia elicits intratumoral oxygen gradients, and subsequently contributes to the plasticity and heterogeneity of tumors while enhancing the emergence of more aggressive, metastatic phenotypic traits (11). Moreover, the TME undergoes remodeling under hypoxic conditions, which in turn affects the stemness, chemoresistance, epithelial-mesenchymal transition (EMT) and angiogenesis of GC cells and tissues (Fig. 1) (17-19). In this process, the increased expression of HIFs is a pivotal hallmark. The HIF family consists of HIF-1, HIF-2 and HIF-3, and serves a central role in cellular mechanisms triggered in response to hypoxia (20,21).

HIF-1, the most important component of the HIF family, is predominantly made up of two subunits, namely HIF-1α and HIF-1β (22). Under normal oxygen concentrations, HIF-1α undergoes degradation and fails to maintain stable expression, whereas under hypoxic conditions, it translocates into the nucleus and dimerizes with HIF-1β to promote the transcription of downstream genes (Fig. 2) (23). The specific mechanism is as follows: Under normoxic conditions, HIF-1α undergoes prolyl hydroxylation catalyzed by prolyl hydroxylase (PHD). This modified HIF-1α is subsequently recognized and bound by the von Hippel-Lindau tumor suppressor protein and upon this binding, is ubiquitinated and ultimately degraded (24-26). Under hypoxic conditions, PHD inactivation blocks oxygen-dependent prolyl hydroxylation, which inhibits HIF-1α degradation; the accumulated HIF-1α subsequently enters the nucleus, combines with HIF-1β to form a dimer, and this dimer regulates the expression of hypoxia-related genes with the participation of transcriptional co-activators such as histone acetyltransferase p300, finally facilitating cellular adaptation to hypoxia (27-31).

HIF-2 is composed of HIF-2α and HIF-2β, with HIF-2α serving as the primary functional subunit that is abundant in tissues including vascular endothelial cells and fetal lung fibroblasts, and upon activation, HIF-2α binds to aryl hydrocarbon receptor nuclear translocator (ARNT) to form a heterodimer (32,33). Hypoxia-inducible factor 3 (HIF-3) is a relatively understudied member of the HIF gene family, and it is composed of HIF-3α and HIF-3β subunits. The HIF-3α gene undergoes complex transcriptional regulation, generating multiple alternatively spliced HIF-3α variants through the use of different promoters and transcription initiation sites (34). These variants exhibit differential expression patterns, which are tightly regulated not only by hypoxia but also by multiple non-hypoxic factors (34). Notably, these non-hypoxic regulatory factors include pro-inflammatory cytokines (which regulate HIF-3α via NF-κB-dependent epigenetic modifications), insulin-mediated PI3K/protein kinase B (AKT) signaling (which modulates HIF-3α stability through phosphorylation) and the von Hippel-Lindau (VHL) E3 ubiquitin ligase complex

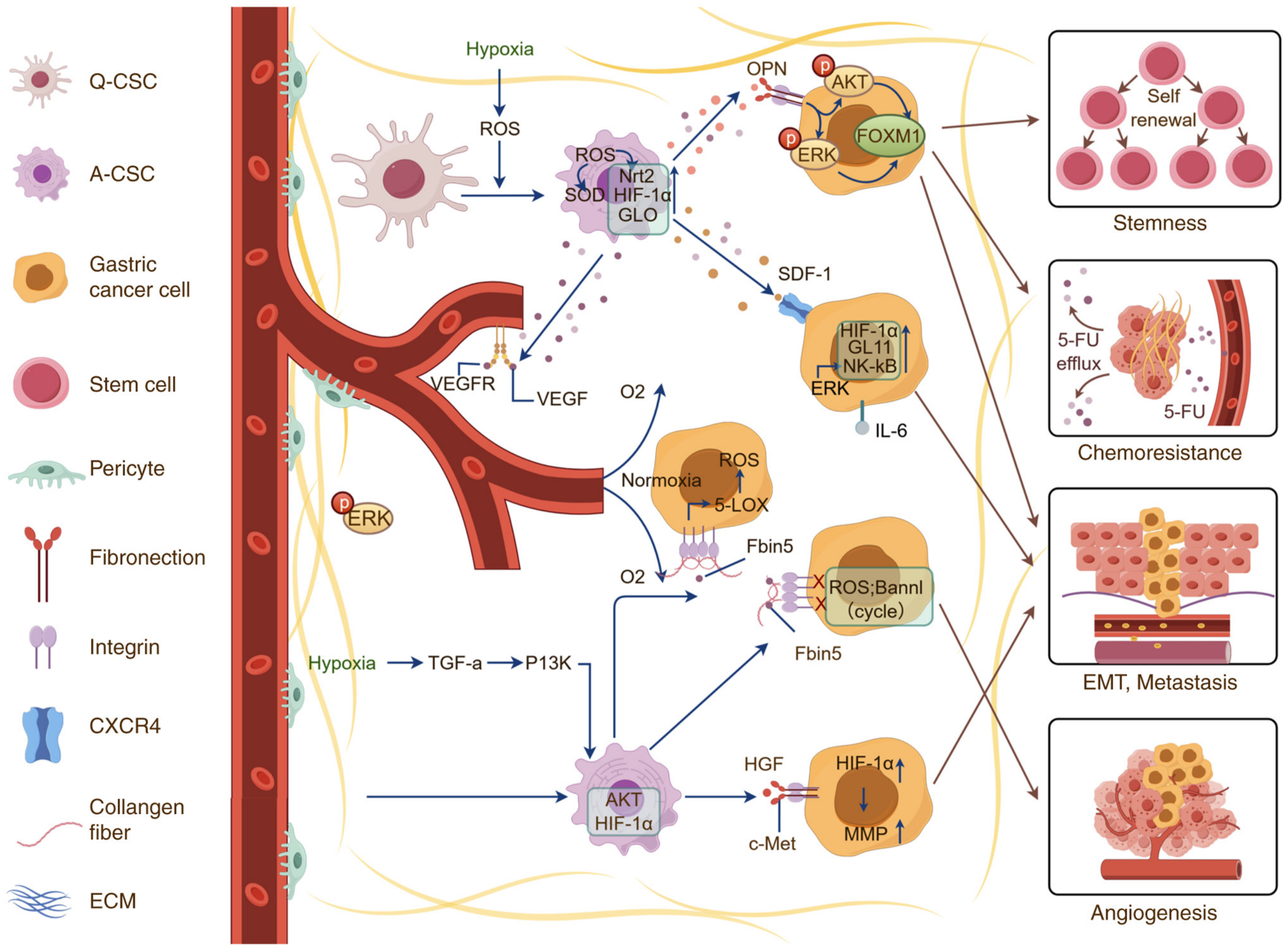

Figure 1. Influence of the tumor microenvironment reconstruction under hypoxic conditions on the progression of gastric cancer. Q-CSC, quiescent cancer stem cell; A-CSC, activated CSC; ROS, reactive oxygen species; Nrf2, nuclear factor erythroid 2-related factor 2; SOD, superoxide dismutase; GLO, glyoxalase; HIF-1α, hypoxia-inducible factor-1α; VEGF, vascular endothelial growth factor; 5-LOX, 5-lipoxygenase; TGF-α, transforming growth factor-α; PI3K, phosphatidylinositol 3-kinase; AKT, protein kinase B; HGF, hepatocyte growth factor; c-Met, mesenchymal-epithelial transition factor; MMP, matrix metalloproteinase; OPN, osteopontin; ERK, extracellular signal-regulated kinase; FOXM1, forkhead box M1; SDF-1, stromal cell-derived factor-1; CXCR4, C-X-C chemokine receptor 4; GLUT1, glucose transporter 1; NF-κB, nuclear factor-κB; IL-6, interleukin-6; Fbin5, fbrillin-5; Bannl, BamHI-associated nuclear protein-like; EMT, epithelial-mesenchymal transition; ECM, extracellular matrix; 5-FU, 5-fluorouracil.

(which targets specific HIF-3α variants for ubiquitination and degradation in an oxygen-dependent manner) (34). Full-length HIF-3α protein functions as an oxygen-regulated transcriptional activator (35).

In 2003, HIF-1α was first identified as exhibiting stable expression in GC tissues and was involved in the initiation and progression of GC (36). Since this initial discovery, numerous subsequent investigations have confirmed that HIF exerts a regulatory effect on the initiation and progression of GC and the development of HIF-targeted agents could represent a promising therapeutic strategy for advanced GC (37-40). Therefore, the present review focuses on the role of HIF in GC, specifically addressing its regulatory effects on GC cell proliferation, metastasis, apoptosis, drug resistance, angiogenesis, stemness and metabolism, and also covers several HIF-targeted therapeutic agents for GC.

2. Hypoxia and the TME

Tumor cells induce the formation of new blood vessels as an adaptive response to low oxygen and nutrient levels, a process termed *de novo* angiogenesis (11). The newly generated blood vessels exhibit leakiness due to their discontinuous endothelium and impaired lymphatic drainage, ultimately leading to vascular hyperpermeability and increased permeation (41). Hence, hypoxia induces vascular leakage and dysregulated lymphatic drainage in the tumor, ultimately resulting in elevated interstitial fluid pressure (42). The TME denotes the local biological environment where solid tumors reside, which comprises cancer cells and adjacent stromal cells, specifically normal host cells (such as fibroblasts, various immune cells and blood/lymphatic cells) recruited by cancer cells and embedded in densely packed extracellular matrix (43-45). The secondary development of adverse metabolic and physical MEs leads to an imbalance between the positive and negative regulators that govern the activation and dysregulation of angiogenesis, desmoplasia and inflammation (44,46-48). Most neoplasms harbor hypoxic regions, and the formation of an abnormal vasculature alongside a hypoxic ME promotes aberrant angiogenesis, desmoplasia and inflammation, all of which contribute to tumor progression and therapeutic resistance (49,50). A previous review highlighted

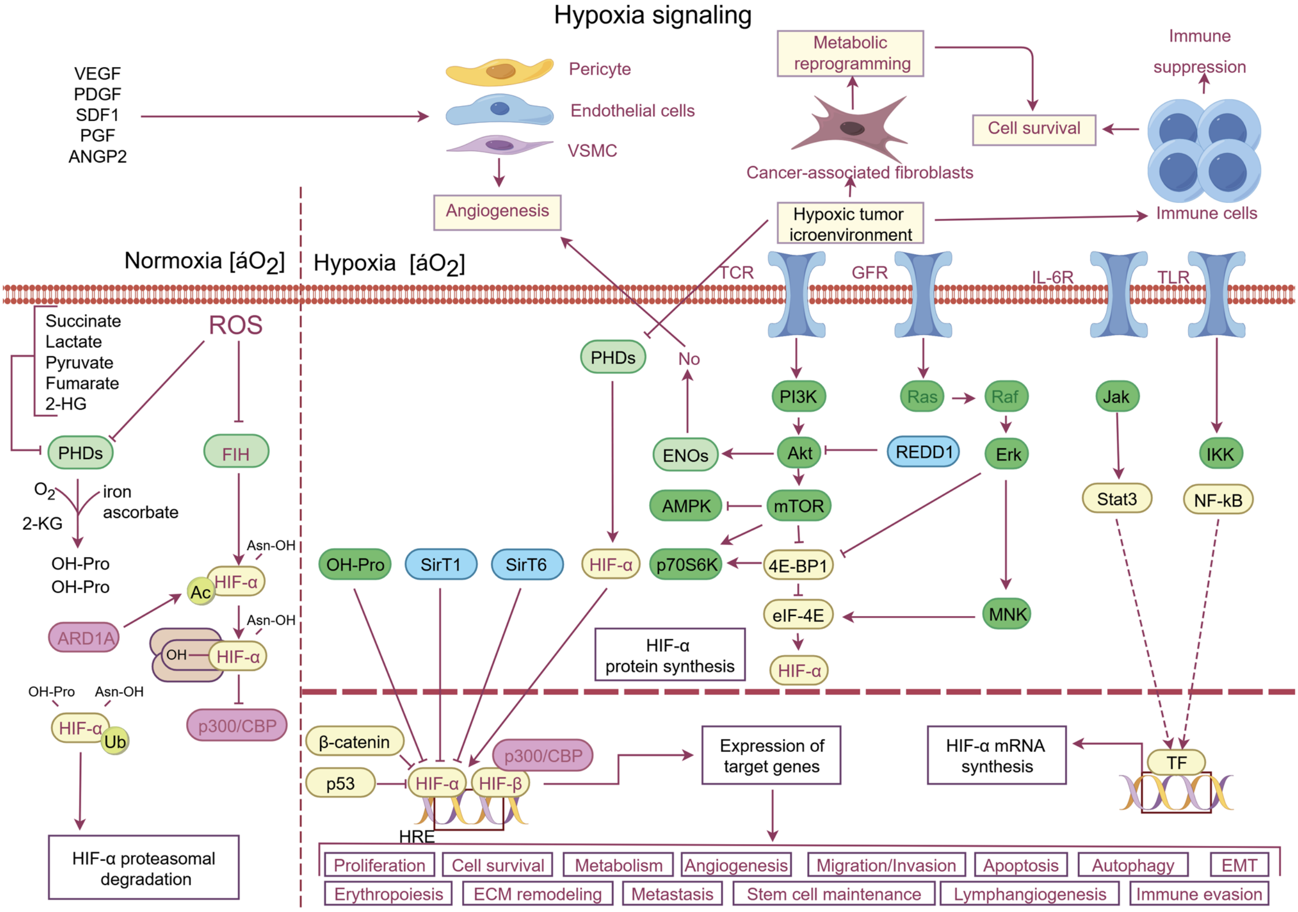

Figure 2. Hypoxia activates downstream signaling pathways. Normoxic degradation of HIF-α: In normoxia (normal oxygen tension), HIF-α is hydroxylated by PHDs and FIH, utilizing O_2 and 2-KG as cofactors. This modification triggers binding to the VHL complex, leading to Ub and proteasomal degradation. Metabolites such as succinate, lactate, pyruvate, fumarate and the oncometabolite 2-HG, along with ROS, can inhibit PHD activity, while sirtuins (SIRT1/SIRT6) modulate HIF-α stability via deacetylation. Hypoxic stabilization and activation of HIF-α: In hypoxia [low oxygen tension, (aO_2)], reduced O□ availability inhibits PHD/FIH function, stabilizing HIF-α. Stabilized HIF-α translocates to the nucleus, heterodimerizes with aryl hydrocarbon receptor nuclear translocator (ARNT/HIF-1β) and recruits co-activators p300/CBP to bind HREs in target gene promoters. This drives transcription of genes involved in proliferation, cell survival, metabolic reprogramming, angiogenesis (via VEGF, PDGF, SDF-1, FGF, ANGPT2), ECM remodeling, metastasis, stem cell maintenance, migration/invasion, apoptosis, autophagy, lymphangiogenesis, EMT and immune evasion. Upstream signaling and microenvironment interactions: Extracellular signals, including GFRs, TCRs, IL-6R and TLRs, activate pathways such as PI3K/AKT/mTOR, Ras/ERK, JAK/STAT3 and NF-κB to modulate HIF-α translation and transcription. Hypoxia also drives angiogenesis by activating endothelial cells and VSMCs, reprograms CAFs for metabolic support and suppresses immune cell function, collectively promoting gastric cancer progression. VEGF, vascular endothelial growth factor; PDGF, platelet-derived growth factor; SDF-1, stromal cell-derived factor-1; FGF, fibroblast growth factor; ANGPT2, angiopoietin-2; 2-HG, 2-hydroxyglutarate; PHDs, prolyl hydroxylase; ARNT, aryl hydrocarbon receptor nuclear translocator; p300/CBP, E1A binding protein p300/CREB binding protein; SIRT1, sirtuin 1; TCR, T cell receptor; GFR, growth factor receptor; IL-6R, interleukin-6 receptor; TLR, toll-like receptor; ENOs, enolases; AMPK, AMP-activated protein kinase; PI3K, phosphatidylinositol 3-kinase; AKT, protein kinase B; mTOR, mechanistic target of rapamycin; REDD1, regulated in development and DNA damage responses 1; Ras, Rat sarcoma viral oncogene homolog; ERK, extracellular signal-regulated kinase; p70S6K, p70 ribosomal S6 kinase; 4E-BP1, eukaryotic translation initiation factor 4E-binding protein 1; eIF4E, eukaryotic translation initiation factor 4E; MNK, MAPK-interacting kinase; Jak, Janus kinase; IKK, IκB kinase; STAT3, signal transducer and activator of transcription 3; NF-κB, nuclear factor-κB; HRE, hypoxia response element; EMT, epithelial-mesenchymal transition; FIH, factor inhibiting HIF; 2-KG, α-ketoglutarate; VHL, von Hippel-Lindau; Ub, ubiquitination; ROS, reactive oxygen species; VSMCs, vascular smooth muscle cells; CAFs, cancer-associated fibroblasts.

that cancers evade host regulatory mechanisms and disrupt systemic homeostasis by secreting a spectrum of neurohormonal mediators (including cytokines, neurotransmitters and pituitary hormones) and immune factors, as validated in both human and animal models (51). It is hypothesized that these tumor-derived molecules enable bidirectional crosstalk with central neuroendocrine axes (such as hypothalamic-pituitary-adrenal and thyroid axes) and peripheral autonomic/sensory nerves, allowing tumors to hijack host homeostatic regulation to support their progression (51). This paradigm suggests that malignant cells actively manipulate central neuroendocrine and immune systems, reshaping systemic balance at the expense of the host, to facilitate tumor expansion (51).

HIF-1α orchestrates hypoxia-induced signaling that regulates multiple steps of the metabolic substrate transport cascade, mainly glucose and lactate transport, to support cellular adaptation to hypoxic microenvironments (52). Research findings have demonstrated that cancer-associated fibroblasts (CAFs) and myeloid cells facilitate tumor metastasis (53). Under hypoxic conditions, activated HIF-1α enhances the activity of Snail and Twist, two transcription factors that downregulate E-cadherin expression and drive EMT (54-56). Of note, although EMT-associated signaling is not required for the metastatic process, it can enhance multiple malignant traits of tumor cells, including invasion, senescence, cancer stem cell-like phenotype and chemoresistance (57). HIF-1α can additionally modulate the expression of enzymes responsible for collagen fiber polymerization and alignment regulation, as well as integrin activity, to promote cancer migration (52). Moreover, hypoxia induces leakiness and compression of blood and lymphatic vessels, a process mediated by HIF-regulated factors including angiopoietin-2, vascular endothelial growth factor (VEGF) and angiopoietin-like 4, thereby facilitating the transmigration of metastatic cancer cells through the vessel wall (58).

The hypoxic ME supports glycolysis and subsequent lactic acid generation mediated by glycolytic key enzymes and lactate dehydrogenase A; this excess lactic acid accumulation leads to an acidic extracellular pH (59-61). Moreover, HIF can facilitate the reverse conversion of carbon dioxide and water, generated via the activation of carbonic anhydrase IX or XII into bicarbonate ions (HCO_3^-). HCO_3^- then diffuses across the cell membrane, leading to HCO_3^- accumulation in the TME and a subsequent reduction in extracellular pH (62). Numerous studies have demonstrated that reduced intracellular pH of endosomes and lysosomes in tumor cells can facilitate tumor metastasis via protease activation (42,63). Indeed, changes in extracellular pH induce drug resistance via suppressing cellular and humoral immune functions, as acidic pH is prevalent at sites of inflammation and other immunologically active regions (64-67). A reduction in pH mainly inhibits the chemotaxis, respiratory activity and bactericidal ability of polymorphonuclear leukocytes (68-70). Under acidic pH conditions, impaired cytotoxicity and proliferation of lymphocytes have been reported, and similarly, cytotoxic T lymphocytes exhibit decreased lysis of various tumor cell lines in this acidic extracellular environment, while neutralization of T cell effector function and tumor acidity can improve the response to immunotherapy (63,71-73). Furthermore, studies focusing on macrophages and eosinophils have indicated that acidic conditions induce the activation of complement proteins and the alternative complement pathway, which is accompanied by increased binding of antibodies to leukocytes under lower pH (63,72,74).

Notably, reactive oxygen species (ROS) levels are demonstrated to be elevated in cancer cells under hypoxic conditions (75). Decreased oxygen utilization impairs electron transfer through the mitochondrial electron transport chain (ETC) complexes, which in turn promotes electron leakage from the ETC and ultimately results in the overproduction of ROS (76). Moreover, excessive ROS production disrupts genomic stability and impairs the function of DNA repair pathways (77). ROS are further capable of inducing cell survival or apoptosis through a mechanism known as oxidative stress, thereby contributing to enhanced cytotoxicity and apoptosis (78). Notably, at high concentrations (10-30 μM), ROS can induce damage to cellular biomolecules including proteins, DNA and RNA, and trigger mutations that either drive carcinogenesis in normal cells or confer multidrug resistance (MDR) in cancer cells (79). However, most cancer cells still survive under internal oxidative stress, hence avoiding apoptosis and developing resistance to chemotherapy (80). Elevated ROS exposure can drive cancer cell resistance via activating redox-sensitive transcription factors, including nuclear factor κB nuclear factor (erythroid-derived 2)-like factor 2, c-Jun and HIF-1α (80). Subsequently, the activation of these genes enhances the activation of the antioxidant system and promotes the expression of cell survival proteins (80). In addition, ROS promote the transition from apoptosis to autophagy in methotrexate-resistant choriocarcinoma Jeg-3 cells, thereby supporting the survival of these cells against methotrexate (81). ROS can also stimulate the differentiation of cancer stem cells, thus promoting EMT and inducing metabolic reprogramming involved in the resistance of cancer cells (79).

Hypoxic stress induces immunosuppression through regulating angiogenesis, as well as promoting immune evasion and tumor resistance (82-84). Notably, macrophages serve as a key component of the immune infiltrate in solid tumors via their differentiation into tumor-associated macrophages (TAMs), which are preferentially localized in hypoxic regions of tumors (85). Furthermore, cytokines derived from tumors can induce the conversion of TAMs into polarized type 2 (M2) macrophages, which exhibit enhanced immunosuppressive activity and thereby contribute to tumor progression (86-88). Additionally, myeloid-derived suppressor cells (MDSCs) directly contribute to immune tolerance, and in hypoxic zones, HIF-1 directly modulates the differentiation and function of MDSCs with these tumor-derived MDSCs exhibiting greater immunosuppressive activity than splenic MDSCs (89).

Previous studies have shown the upregulation of the expression of programmed death-ligand 1 (PD-L1) under hypoxia (89-91). HIF-1 serves as a key regulator of both PD-L1 mRNA and protein expression, specifically by directly binding to a hypoxia response element (HRE) within the proximal promoter of PD-L1 (89). The originally elevated immunosuppressive function of tumor derived MDSCs under hypoxia was found to be abrogated following PD-L1 blockade. Consistent with PD-L1 blockade, the hypoxia-driven upregulation of IL-6 and IL-10 in MDSCs was notably attenuated (92). Currently, immunotherapeutic strategies that elicit antitumor immunity exhibit limited efficacy due to the diverse mechanisms by which tumors evade immunosurveillance (92). Antibody blockade of the T-cell immune checkpoint receptors programmed cell death protein-1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 exhibit poor efficacy in certain tumors due to sparse or absent T cells in the TM, and hypoxia-driven modulation of T-cell exclusion and apoptosis helps sustain this state (93-95). While T cells can enter hypoxic tumors, hypoxia-driven acidification of the extracellular environment impairs their ability to proliferate or exert cytotoxic effector functions (72,96). Taken together, tumor hypoxia predicts poor outcomes across numerous types of cancer, and hypoxia plays a key role in establishing and maintaining tumor immune privilege or resistance to immunotherapy (97).

3. HIF-1

Structural features of HIF-1. HIF-1 is a basic helix-loop-helix (bHLH) transcription factor that mediates homeostatic adaptations to hypoxic conditions (98). HIF-1 functions as a heterodimer composed of HIF-1α (encoded by the HIF-1A gene) in complex with HIF-1β (encoded by the ARNT

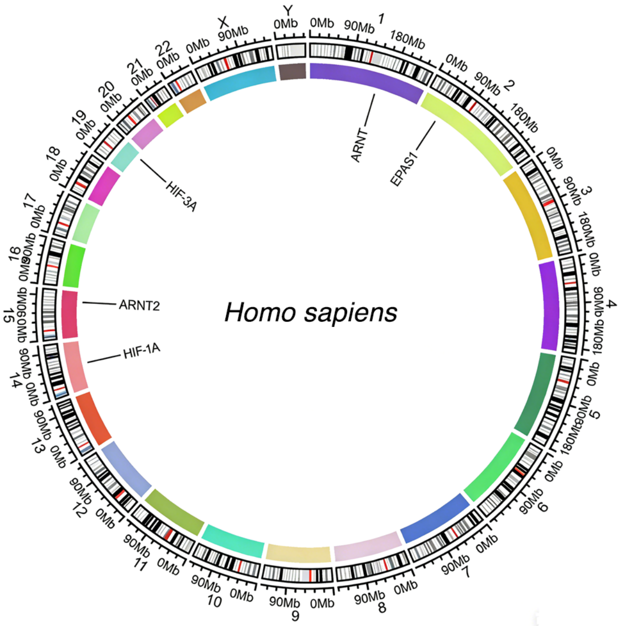

Figure 3. Schematic diagram of the localization of HIF-1α (HIF1A), HIF-1β (ARNT), HIF-2α (EPAS1), HIF-2β (ARNT2) and HIF-3α (HIF-3A) on human chromosomes. HIF, hypoxia-induced factor; ARNT, aryl hydrocarbon receptor nuclear translocator; EPAS1, endothelial PAS domain-containing protein 1.

gene) (99). Previous studies reported the assignment of the HIF-1A gene to mouse chromosome 12 and the HIF-1A gene to human chromosome 14, respectively, with HIF-1A mapped to human chromosome 14q21-q24 via somatic cell hybrid analysis and fluorescence *in situ* hybridization and HIF-1A localized through interspecific backcross analysis to a region of >30 centimorgans on mouse chromosome 12 that exhibits conservation of synteny with the segment of human chromosome 14 spanning from PAX9 at 14q12-q13 to IGHC at 14q32.33 (Fig. 3) (98,100). Furthermore, ARNT, also known as HIF-1β, is chromosomally localized to human chromosome 1q21 (Fig. 3) and structurally categorized as a bHLH-Per-Arnt-Sim (PAS) family transcription factor, featuring conserved functional domains including the bHLH domain (for dimerization and DNA binding), PAS A/B domains (for protein-protein interactions, especially with HIF-1α) and a C-terminal transactivation domain (for mediating transcriptional activation of downstream target genes) (101).

Both HIF-1α and HIF-1β possess a bHLH domain, which is critical for their binding to the HRE within the promoter region of target genes. The N-terminal region of HIF-1α additionally contains PAS domains, which enable its heterodimerization with HIF-1β (Fig. 4) (102,103). Two transactivation domains (TADs) are located in the C-terminal segment of HIF-1α: An N-terminal TAD (N-TAD) and a C-terminal TAD (C-TAD), and these TADs are responsible for modulating the interaction between HIFs and co-activators (104). Notably, HIF-1α harbors an oxygen-dependent degradation domain (ODDD) that overlaps with the N-TAD-a structural characteristic that differentiates HIF-1α from HIF-1β (Fig. 4). The ODDD functions as a recognition motif for the VHL tumor suppressor protein and is involved in regulating the stability of HIF-1α in an oxygen-dependent manner (104). When two proline residues within the ODDD are hydroxylated by oxygen-sensitive (PHD) domain-containing proteins, HIF-1α undergoes rapid proteasomal degradation (105). In contrast to HIF-1α, which has a short half-life, HIF-1β maintains a stable protein expression level because it lacks the ODDD and N-TAD (Fig. 4).

Role of HIF-1 in GC. Numerous previous studies have demonstrated that HIF-1 exerts important regulatory effects on proliferation, metastasis, metabolism, apoptosis, angiogenesis, cancer cell stemness, drug resistance and other aspects of GC cells (106-112). HIF-1α can promote GC cell proliferation by binding to the promoter of hypoxia-induced proliferation-associated long non-coding RNA (lncRNA; HYPAL) to promote its transcription, which in turn activates the Wnt/β-catenin signaling pathway via the HYPAL/microRNA (miR)-431-5p/CDK14 axis and induces GC cell proliferation (106). An additional study further revealed that HIF-1α can bind to the promoter region of miR-17-5p to activate the transcription of both pre-miR-17-5p and mature miR-17-5p; this miR-17-5p then binds to the untranslated region of programmed cell death 4 (PDCD4), a suppressor gene in GC that primarily functions to inhibit cell proliferation, ultimately leading to the degradation of PDCD4 mRNA (113). Furthermore, whilst the upregulation of HIF-1α can promote the proliferation of GC cells, tumor suppressor gene Linc-pint is capable of inhibiting GC cell proliferation by downregulating HIF-1α expression (114). Additionally, 3-deazaneplanocin A, a histone methyltransferase inhibitor that likely acts by regulating histone methylation, can inhibit HIF-1A expression and thus suppress the proliferation of BGC-823 GC cells; observations from a study indirectly confirm the critical role of HIF-1A in GC cell proliferation (115). An additional study demonstrated that lncRNA ZEB2-AS1 is upregulated in GC and regulates cell proliferation via the miR-143-5p/HIF-1α axis (116).

Metastasis is the primary cause of mortality in most human malignant tumors, including hepatocellular carcinoma, GC and colorectal cancer (117-119). HIF-1α can promote the metastasis of GC by facilitating the EMT of GC cells (107). Furthermore, HIF-1α can directly bind to the promoter of liver X receptor-α (LXRα) to promote its transcription; elevated LXRα levels subsequently activate the EMT of GC cells, thereby enhancing the metastatic capacity of GC (120). Another line of research has shown that HIF-1α can induce GC cells to secrete exosomes enriched with miR-301a-3p, thereby promoting GC cell metastasis via the miR-301a-3p/PHD3/HIF-1α positive feedback loop (121). Functional studies have shown that collagen triple helix repeat containing 1 (CTHRC1) increases C-X-C chemokine receptor type 4 (CXCR4) expression by upregulating HIF-1α, ultimately promoting the migration and invasion of GC cells. Inhibiting HIF-1α expression can reduce CXCR4 expression and suppress the migration and invasion of GC cells, which demonstrates that the HIF-1α/CXCR4 signaling pathway mediates the promoting effect of CTHRC1 on the migration and invasion of GC cells (122). Moreover, hypoxia promotes migration and invasion of GC cells by activating HIF-1α and inhibiting N-myc downstream-regulated gene 2 (NDRG2) associated signaling pathways, which are widely recognized to exert tumor-suppressive roles via constraining cell motility, invasiveness and metastatic potential in gastric cancer and multiple malignancies (123).

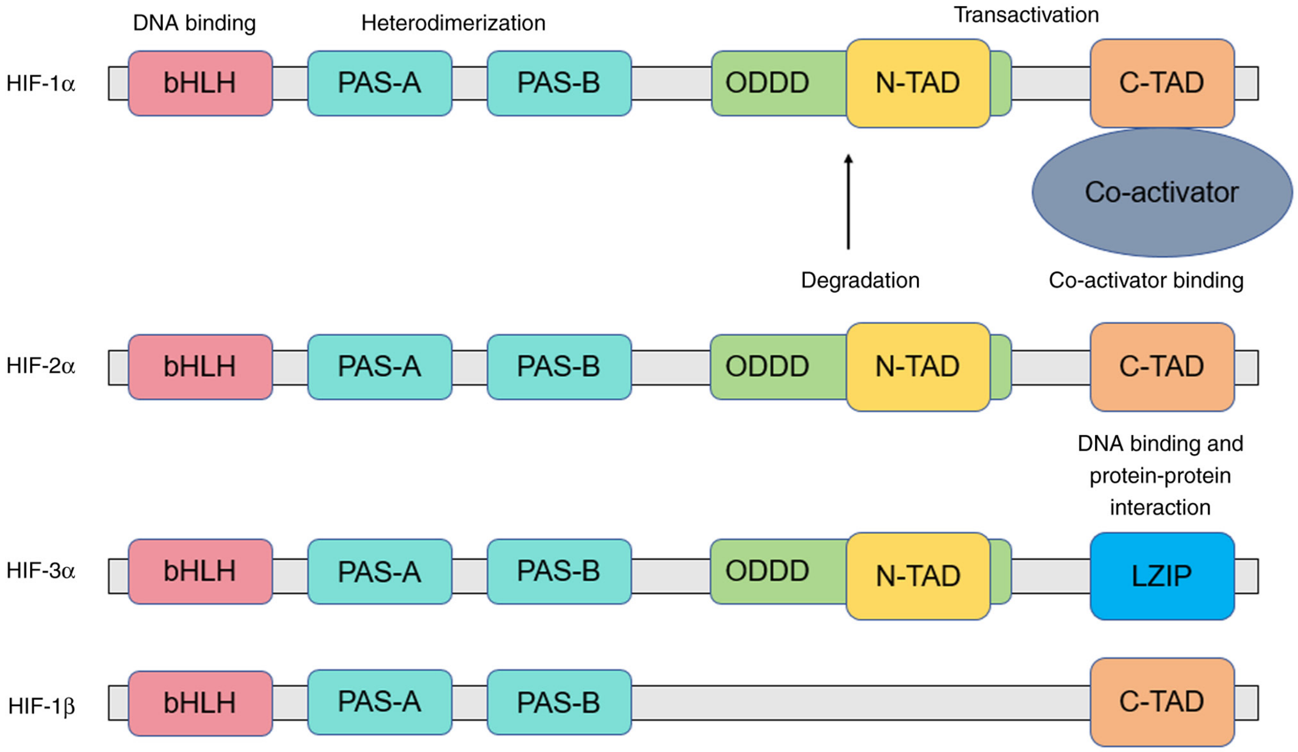

Figure 4. Domain structures of HIF-1α in comparison with other HIF proteins and their potential functions. bHLH, basic helix-loop-helix; PAS, Per-Arnt-Sim; N-TAD, N-terminal transactivation domain; C-TAD, C-terminal transactivation domain; ODDD, O_2-dependent degradation domain; LZIP, leucine zipper domain.

Apoptosis refers to autonomous and orderly gene-controlled cell death that maintains internal environmental stability and is not a phenomenon of autologous injury under pathological conditions, but an active death process aimed at adapting to the living environment (124-126). HIF-1 can upregulate the expression of the adhesion molecule MGr1-Ag/37LRP by activating ERK, thereby inhibiting apoptosis in GC cells (108). Research has further shown that HIF can inhibit the apoptosis of GC cells by upregulating integrin alpha-5 (127). However, the role of HIF in GC cell apoptosis remains controversial, as some studies have demonstrated that HIF can promote GC cell apoptosis (128,129). To summarize, the role of HIF in GC cell apoptosis remains controversial to date, necessitating further investigations to clarify its function in GC.

Drug resistance represents a major barrier to achieving effective cancer treatment, notably compromising the therapeutic efficacy of both conventional chemotherapeutics (such as platinum-based drugs) and targeted agents (such as EGFR inhibitors) (130,131). Clinically, the emergence of drug resistance often leads to treatment failure, frequent disease recurrence and substantially reduced overall survival rates in patients with various cancers, including lung, breast and gastrointestinal malignancies, underscoring its critical impact on clinical outcomes (132-134). The molecular mechanisms driving cancer drug resistance are complex and multifactorial, involving processes such as upregulation of drug efflux transporters (such as P-glycoprotein), acquired mutations in drug target genes (such as KRAS or BRAF), dysregulation of cell survival signaling pathways (such as PI3K/Akt/mTOR) and the adaptive changes in the hypoxic or immunosuppressive TME (82,135-139). Despite decades of research advancing the understanding of these resistance mechanisms, translating this basic science knowledge into clinically applicable strategies to overcome or prevent resistance remains a central challenge in oncology. Therefore, addressing drug resistance, whether through developing novel agents that target resistance-related molecules, designing rational combination therapies to bypass resistance or implementing personalized treatment strategies based on molecular profiling has become a key priority to improve the durability and effectiveness of cancer treatment. HIF-1 can promote drug resistance in GC cells by regulating the expression of pyruvate kinase muscle 1 (PKM1), a gene associated with chemotherapy resistance in GC (109). Knocking down HIF-1α via small interfering RNA can attenuate the drug resistance of GC cells and enhance the cytotoxic effect of 5-fluorouracil (5-FU) on these cells (140). A study has demonstrated that HIF-1α directly binds to the promoter of miR-27a to upregulate its expression, with miR-27a subsequently promoting drug resistance in GC cells by inhibiting the expression of multidrug resistance protein 1 (MDR1)/P-gp, LRP and Bcl-2 (141). The role of HIF-1 in GC drug resistance is relatively well-established; HIF-1 enhances drug resistance in GC, a finding corroborated by numerous studies (142-144).

Anti-angiogenesis has long been recognized as a pivotal strategy in the design of antitumor drugs, primarily targeting the abnormal neovascularization that tumors depend on to obtain nutrients, oxygen and a pathway for metastatic spread (145,146). By interfering with the activation of pro-angiogenic signaling pathways (such as the VEGF/VEGFR pathway) or the maturation of tumor-associated blood vessels, anti-angiogenic therapies effectively disrupt the 'vascular niche' of tumors, thereby suppressing their growth and limiting their ability to invade surrounding tissues (147). This approach has been clinically validated: Numerous anti-angiogenic agents (such as bevacizumab, a VEGF-specific monoclonal antibody) have been approved for the treatment of solid tumors such as colorectal and non-small cell lung cancer, further confirming its status as a core antitumor strategy (148-150). Studies have shown that HIF-1α can promote angiogenesis in GC, a process potentiated by natriuretic peptide receptor A, the primary receptor for atrial natriuretic peptide, which plays a significant role in driving GC development and progression (151-154). Additionally, another study has indicated that HIF-1α can facilitate angiogenesis in gastric cancer by upregulating the expression of VEGF-A (148). HIF-1α drives gastric angiogenesis via the β-catenin/VEGF signaling pathway, thereby promoting GC progression (110,153,155,156).

Cancer stem cells (CSCs) represent a small subpopulation within tumors that generate heterogeneous tumor cells while possessing self-renewal capacity and are regarded as critical factors driving tumor progression (157-159). One study demonstrated that HIF-1α can drive the progression of GC by promoting the stemness of GC cells (111). Other research has confirmed that HIF-1α further facilitates peritoneal dissemination of GC by enhancing the stemness of its cells (160). Currently, research on the role of HIF in gastric CSCs remains limited, and no drugs targeting CSCs have achieved successful clinical application; thus, this role warrants further investigation.

Metabolism is intricately linked to tumor initiation, progression and therapeutic response, with tumor cells exhibiting hallmark metabolic reprogramming that distinguishes their glucose, lipid and protein metabolism from that of normal cells. Notably, tumor cells typically rely on aerobic glycolysis (the Warburg effect) even under oxygen-sufficient conditions, this preference for glycolysis enables rapid production of ATP and biosynthetic precursors (such as pyruvate and lactate) to support unchecked proliferation, whereas normal cells primarily use oxidative phosphorylation for efficient energy generation (161). Beyond glucose metabolism, tumor cells also upregulate *de novo* lipid synthesis (rather than utilizing exogenous lipids) to build cell membranes for expanding cell populations, and they exhibit dysregulated protein metabolism, including increased uptake of amino acids (such as glutamine) and enhanced protein synthesis, to meet the demands of maintaining stemness and resisting nutrient stress (162,163). Collectively, these metabolic alterations are not merely adaptive changes but active drivers of tumor biology, highlighting the importance of targeting tumor-specific metabolic pathways as a potential therapeutic strategy. Studies have demonstrated that HIF-1α promotes GC progression by enhancing glycolysis in GC cells (112,164,165). HIF-1α also regulates glycolysis in GC cells via the FOXO4/Lactate dehydrogenase A (LDHA) axis and thereby influences the progression of GC cells (164). Another line of research has shown that HIF-1α can promote glycolysis in GC cells via the circular RNA (circ-)MAT2B/miR-515-5p axis and thereby facilitate the occurrence and development of GC (165). Notably, extracellular matrix protein-1 facilitates GC cell metastasis and glucose metabolism by inducing the integrin β4/focal adhesion kinase/SOX2/HIF-1α signaling pathway (166). Moreover, miR-186 can inhibit aerobic glycolysis in GC via HIF-1α regulation (167). While 5-FU is known to exert an antitumor effect by inhibiting nucleic acid metabolism, HIF-1, which is closely associated with GC metabolism, can promote GC progression by enhancing glycolysis under hypoxic conditions, making it a promising target for GC drug development (168,169).

4. HIF-2

Structural features of HIF-2. HIF-2 is a member of the basic bHLH-PAS transcription factor family that mediates cellular adaptive responses to hypoxia, with distinct functional specificity compared with HIF-1 (99,170,171). Functionally, HIF-2 acts as a heterodimer, typically composed of the oxygen-sensitive HIF-2α subunit [encoded by the endothelial PAS domain-containing protein 1 (EPAS1) gene] and a constitutively expressed β subunit, which can be either an ARNT (HIF-1β) or ARNT2 (HIF-2β) depending on tissue context (170,172,173). The EPAS1 gene, which encodes HIF-2α, is localized to the human chromosome 2p21 region, while the ARNT2 gene, which encodes HIF-2β, is localized to the human chromosome 15q23-q25 region (Fig. 3). Structurally, both HIF-2α and its β partners contain a conserved bHLH domain at the N-terminus, which is essential for sequence-specific binding to the HRE (core sequence 5'-TACGTG-3') in target gene promoters (174-177).

Role of HIF-2 in GC. HIF-2α has been linked to the malignant behavior of several types of cancers. In cervical cancer, it was identified as a hub gene among hypoxia and ferroptosis related genes (178). Furthermore, in a previous study, HIF-2α was markedly upregulated in cervical cancer tissues and could increase the proliferation, invasion and migration of cervical cancer cells while reducing apoptosis (179). In esophageal squamous cell carcinoma (ESCC), molecular deregulation of EPAS1 was observed, with 7.5% of patients harboring mutations in this gene; these alterations were associated with tumor location and T stages (180). Suppression of EPAS1 in ESCC cells led to reduced proliferation, wound healing, migration and invasion (180). HIF-2β (ARNT2) also plays a role in the development of cancer. In oral squamous cell carcinoma (OSCC), ARNT2 was found to be downregulated, and overexpression of ARNT2 led to decreased cellular proliferation, suggesting its potential as a therapeutic target against OSCC progression (181). In GC, the expression of ARNT2 was lower in cancer tissues compared with adjacent non-tumor tissues and overexpression of ARNT2 inhibited cell proliferation (182).

HIF-2α plays a crucial role in hypoxia-induced pathways, which are relevant to the development and progression of GC. In hypoxic conditions, HIF-2α is stabilized and activates the transcription of numerous genes involved in cell survival, angiogenesis and metabolism. In a study on non-small cell lung cancer, hypoxic-stabilized HIF-2α proteins transactivated DNA methyltransferase 1-the major maintenance DNA methyltransferase responsible for preserving genomic methylation patterns following DNA replication by preferentially targeting hemi-methylated DNA and catalyzing methyl group transfer to cytosine nucleotides-which in turn caused promoter hypermethylation and transcription inhibition of HIF-2α itself, creating a negative-feedback regulation loop (183). This mechanism may also be present in GC cells, where hypoxia is a common ME condition. Hypoxia can drive the upregulation of HIF-2α, leading to increased expression of genes such as VEGF, which promotes angiogenesis (178). Angiogenesis is essential for tumor growth as it provides the necessary nutrients and oxygen to the growing tumor cells (123). In addition, HIF-2α can regulate genes involved in cell metabolism, enabling cancer cells to adapt to the hypoxic environment (179). For example, it may upregulate genes involved in glycolysis, allowing cancer cells to generate energy even in low-oxygen conditions (179). Currently, research on HIF-2 in GC remains insufficiently clear, and a number of its mechanisms have not yet been fully elucidated.

5. HIF-3

Structural features of HIF-3. HIF-3 is a heterodimer, which consists of HIF-α and oxygen-insensitive β subunits and is a member of the ARNT family (101). HIF-3α is located at chromosome 19q13.13-13.2 (Fig. 3). HIF-3α shares a conserved bHLH-PAS domain architecture with HIF-1α and HIF-2α but exhibits unique structural modifications (101,170). The N-terminal bHLH domain mediates DNA binding to HREs with the consensus sequence 'TACGTG' (170). Adjacent to the bHLH domain are two PAS domains (PAS-A and PAS-B), which facilitate heterodimerization with the β-subunit (ARNT) and ligand binding (170,171). Notably, the PAS-B domain of HIF-3α contains a 510 Å^3 hydrophobic cavity, a structural feature absent in HIF-1α and HIF-2α, enabling it to selectively bind endogenous lipids such as oleoylethanolamide and monoacylglycerols (99,170,171). This lipid-binding capability suggests HIF-3α acts as a metabolic sensor integrating hypoxia and lipid signaling (170,171). Unlike HIF-1α and HIF-2α, HIF-3α lacks the C-TAD (170). Instead, its C-terminus contains a unique leucine zipper domain and a LxxLL motif, which mediates protein-protein interactions with co-regulators such as HSP90 (170,171). The absence of C-TAD reduces the intrinsic transcriptional activity of HIF-3α, but it retains partial activity through N-TAD, which shares 58 and 52% sequence identity with HIF-1α and HIF-2α, respectively (171).

Role of HIF-3 in GC. HIF-3 is a critical regulator in cancer progression, primarily through its α-subunit (HIF-3α) and its splice variants, such as inhibitory PAS domain protein (IPAS) (184). Unlike HIF-1α and HIF-2α, HIF-3α acts as a context-dependent modulator rather than a canonical transcription factor. For instance, IPAS competitively inhibits HIF-1α binding to HREs, thereby suppressing downstream genes involved in angiogenesis (such as VEGF) and glycolysis (such as GLUT1), which are pivotal for tumor growth under hypoxic conditions (184,185).

Currently, relevant studies on the role of HIF-3 in GC are scarce and the specific mechanisms remain unclear. While the pathogenic roles of HIF-1α and HIF-2α in GC cancer such as promoting angiogenesis, glycolysis and EMT have been extensively characterized, HIF-3 has long been overlooked due to its structural complexity (such as multiple splice variants with potentially divergent functions) and the lack of specific tools to dissect its isoform-specific effects. Notably, existing investigations on HIF-3 in GC are often limited to *in vitro* cell line experiments or small-scale tissue samples, with inconsistent findings regarding its pro-tumor or anti-tumor properties-certain studies suggest inhibitory effects via antagonizing HIF-1α, while others imply pro-metastatic roles through undefined signaling axes (182,184,185). Furthermore, the crosstalk between HIF-3 and key oncogenic pathways in GC (such as TGF-β/Smad, Wnt/β-catenin or PI3K/Akt) has rarely been systematically explored, and its clinical relevance such as associations with patient prognosis, tumor stage or response to anti-hypoxic therapies remains largely unvalidated. This knowledge gap not only hinders a comprehensive understanding of the hypoxic regulatory network in GC but also limits the development of targeted strategies that harness HIF-3 for therapeutic intervention.

6. Small molecule drugs targeting HIFs to inhibit gastric cancer

Small-molecule drugs (SMDs) are typically defined as organic compounds with a molecular weight generally not exceeding 1,000 Da and most of them possess physicochemical properties such as good cell membrane permeability and structural modifiability, which lay the foundation for their subsequent biological activity (186). Due to their favorable pharmacokinetic characteristics (such as easy absorption, distribution and metabolic adjustability) and relatively low production costs, SMDs have been widely applied in the clinical treatment of various diseases, including tumors, cardiovascular disorders and infectious diseases, and have long occupied a core position in therapeutic regimens (187). The theoretical system supporting SMD research and development which covers key fields such as medicinal chemistry, structure-activity relationship analysis and high-throughput screening has become increasingly mature, providing solid technical support for the efficient discovery and optimization of novel small-molecule therapeutic agents (188-190).

Numerous SMDs capable of suppressing the progression of GC through HIF targeting have been identified (Table I). A previous study demonstrated that apigenin, a flavonoid component present in traditional medicines, fruits and vegetables, inhibits HIF-1α-induced autophagy-related cell death (191). Low-dose tipifarnib-a non-peptidomimetic quinolinone farnesyltransferase inhibitor (FTI) that exerts antineoplastic effects by inhibiting protein farnesylation, suppressing mTOR signaling, and reducing ROS levels-inhibits tumors by suppressing the expression of HIF-1α, and dextran sulphate-a sulfated polysaccharide (anionic derivative of dextran) with anticoagulant, antiviral, and protein-sequestering properties-can inhibit EMT in GC cells by inhibiting the expression of HIF (192,193). A study constructed R8-modified vinorelbine-plus-schisandrin B liposomes, validated via *in vitro* experiments on BGC-823 cells and *in vivo* experiments on nude mice bearing BGC-823 cell xenografts, were shown to synergistically induce GC apoptosis, enhance tumor cell targeting and inhibit GC metastasis by downregulating HIF-1α, thereby exerting antitumor effects and providing a safe and effective therapeutic strategy for GC (194). Moreover, numerous small-molecule therapeutic agents exert an inhibitory effect on GC progression by targeting HIF (195-201). Despite the identification of numerous small-molecule agents

Table I. Small molecule drugs targeting hypoxia-inducible factor-1α to inhibit gastric cancer.

Drugs	Mechanism	(Refs.)
Apigenin	Promotes autophagy	(191)
Tipifarnib	Inhibits metastasis	(192)
Dextran sulfate	Inhibits metastasis	(193,207)
Quercetin	Promotes autophagy	(194)
Celecoxib	Promotes autophagy	(195)
Ginsenoside Rg3	Inhibits angiogenesis	(196)
Oleanolic acid	Inhibits aerobic glycolysis	(196)
Resveratrol	Inhibits metastasis	(197)
Sulforaphane	Inhibits angiogenesis	(197)
Glaucocalyxin A	Inhibits metastasis	(198)
Schisandrin B	Inhibits metastasis	(198)
Epigallocatechin-3-gallate	Promotes apoptosis	(200)
FS-7 (a flavonoid salicylate derivative)	Inhibits glycolysis	(200)
Wogonin	Inhibits proliferation	(201)

that inhibit GC progression by targeting HIF, none have yet translated to clinical application, highlighting the need for additional basic and clinical research.

7. Key factors influencing GC development and natural history

GC development and progression are driven by the interplay of environmental, genetic, microenvironmental and host factors, all of which interact with HIF-mediated hypoxia responses.

Environmental and lifestyle factors. *H. pylori* infection is the primary risk factor for GC (75-80% of cases), inducing chronic gastritis, atrophy and metaplasia (202). *H. pylori* (particularly CagA$^+$ strains) upregulates HIF-1α via ROS production and inflammation, accelerating premalignant lesion progression (203). Eradication of *H. pylori* reduces HIF-1α expression and GC risk by 30-40% (204).

Dietary factors. High-salt intake (≥5 g/day) induces gastric mucosal damage and hypoxia, upregulating HIF-1α (205). Red meat and processed food consumption increases N-nitrosamine exposure, which synergizes with HIFs to promote DNA damage (206). Conversely, fruits, vegetables (rich in flavonoids) and green tea (contains epigallocatechin gallate) inhibit HIF-1α and reduce GC risk (207).

Smoking and alcohol. Cigarette smoke contains polycyclic aromatic hydrocarbons that stabilize HIF-1α and induce EMT (208). Heavy alcohol consumption (≥3 drinks/day) causes gastric mucosal hypoxia and acetaldehyde accumulation, enhancing HIF-2α expression (209).

Genetic and epigenetic factors. i) Driver mutations: TP53 mutations (40-50% of GC) enhance HIF-1α stability by inhibiting PHD activity; ii) CDH1 mutations (5-10% of diffuse-type GC) disrupt E-cadherin, promoting hypoxia and HIF-1α-dependent EMT (210); and iii) ERBB2 amplification (10-15% of GC) activates PI3K/Akt signaling to upregulate HIF-1α and VEGF (210).

Epigenetic modifications. DNA methylation of CDKN2A and DNA mismatch repair protein Mlh1 (MSI-high GC) correlates with HIF-1α upregulation (211). Histone acetylation (p300/CBP) enhances HIF-1α transcriptional activity (212). lncRNAs (such as H19 and MALAT1) and miRNAs (such as miR-143 and miR-515-5p) regulate HIF expression in a subtype-specific manner (165,213).

TME and stromal factors. CAFs secrete TGF-β and IL-6 to stabilize HIF-1α, promoting desmoplasia and hypoxia (214). Diffuse-type GC has a higher CAF density than intestinal-type GC, contributing to its TME rigidity and hypoxia (214). These alterations collectively foster a highly immunosuppressive, pro-tumorigenic microenvironment that accelerates diffuse-type GC progression, invasion and therapeutic resistance.

Immune cells. TAMs and MDSCs enhance HIF-1α expression via cytokine secretion (IL-1β and TNF-α) (215). CD8$^+$ T cell exhaustion, mediated by HIF-1α/PD-L1 signaling, correlates with poor prognosis in advanced GC (215). This forms a positive immunosuppressive feedback loop: TAMs and MDSCs secrete IL-1β and TNF-α to upregulate HIF-1α, which in turn transcriptionally elevates PD-L1 expression in tumor and stromal cells; elevated PD-L1 binds to its receptor on CD8$^+$ cytotoxic T cells, triggering functional exhaustion, impairing tumor-specific cytotoxicity and enabling immune evasion, thereby facilitating unrestricted GC proliferation, invasion and metastasis, and ultimately resulting in dismal clinical outcomes.

Natural history and staging-related considerations. The natural history of GC varies by subtype: Intestinal-type GC progresses from premalignant lesions to invasive cancer over 10-20 years, while diffuse-type GC develops rapidly (3-5 years) with early metastasis (216). Pathological staging strongly influences prognosis. The 5-year survival rates are 90-95% for stage 1, 60-70% for stage II, 30-40% for stage III and <10% for stage IV (216). HIF expression correlates with staging. HIF-1α positivity increases from 20-30% in stage I to 70-80% in stage IV, while HIF-2α is more frequently expressed in stage III-IV intestinal-type GC (217). LN metastasis (pN2-pN3) is associated with higher HIF-1α levels (99), as hypoxic tumors have increased lymphatic invasion potential.

8. Recent advances in GC diagnosis

Endoscopic diagnosis. White light endoscopy: The standard screening tool for GC, but limited in detecting early lesions (sensitivity 60-70%).

Enhanced endoscopic techniques. i) Narrow-band imaging. Improves visualization of mucosal microvessels and glands, increasing early GC detection sensitivity to 85-90% (218); ii) confocal laser endomicroscopy. Enables *in vivo* histological evaluation, distinguishing benign from malignant lesions with 90-95% accuracy (219); and iii) artificial intelligence (AI)-assisted endoscopy. AI algorithms analyze endoscopic images to identify early GC and premalignant lesions, with sensitivity and specificity comparable to expert endoscopists (220). AI-based systems also correlate mucosal hypoxia (via vessel density) with HIF expression, providing prognostic information (221).

Molecular and imaging diagnosis. Liquid biopsies: Circulating tumor DNA (ctDNA) detection of driver mutations (TP53 and ERBB2) and HIF pathway genes (HIF-1A and EPAS1) enable non-invasive staging and treatment monitoring (222). ctDNA levels correlate with TNM stage, with detectable ctDNA in 20% of stage I, 50% of stage II, 70% of stage III and 90% of stage IV GC (223).

Imaging modalities. i) Positron emission tomography-computed tomography: F-FDG uptake reflects HIF-mediated glycolysis, aiding in staging (sensitivity 80-85% for LN metastasis) and treatment response assessment (1,3); ii) magnetic resonance imaging (MRI): Diffusion-weighted imaging and dynamic contrast-enhanced MRI evaluate tumor hypoxia and angiogenesis, correlating with HIF-1α expression (1,3); and iii) contrast-enhanced ultrasound. Assesses tumor vascularity, with hypovascular lesions (diffuse-type GC) showing higher HIF-1α expression (1,3).

Pathological diagnosis. i) Immunohistochemistry (IHC): HIF-1α, HIF-2α and PD-L1 IHC staining aids in subtype classification and prognosis prediction. HIF-1α IHC positivity (≥10% tumor cells) is associated with diffuse-type GC and poor prognosis (224); and ii) next-generation sequencing (NGS): Tumor tissue NGS identifies MSI status, tumor mutational burden and HIF pathway alterations (such as HIF-1A amplification, EPAS1 mutations), guiding targeted and immunotherapy selection (224). MSI-high GC (10-15% of cases) exhibits lower HIF-1α expression and better response to PD-1 inhibitors (225).

9. Conclusions and future perspectives

The present review systematically synthesizes the regulatory roles, molecular mechanisms and therapeutic potential of HIFs in GC, a malignancy with high global morbidity and mortality and suboptimal outcomes for advanced-stage patients. First, hypoxia, an iconic hallmark of the TME in GC, drives TME remodeling by inducing acidification ROS accumulation and immunosuppression (such as M2 polarization of TAMs, MDSC recruitment and PD-L1 upregulation) and aberrant angiogenesis, all of which converge to promote GC progression and therapeutic resistance (11,14). Central to this hypoxic response is the HIF family, whose three subtypes (HIF-1, HIF-2, HIF-3) exhibit distinct structural features and functional heterogeneity in GC. HIF-1, the most well-characterized subtype, exerts a pleiotropic oncogenic role in GC: Its α-subunit (HIF-1α) regulates GC cell proliferation via the HYPAL/miR-431-5p/CDK14 or HIF-1α/miR-17-5p/PDCD4 axis, drives EMT through direct transactivation of LXRα or exosomal miR-301a-3p secretion, enhances chemoresistance by modulating PKM1 or MDR1/P-gp, promotes angiogenesis via VEGF-A or β-catenin/VEGF signaling and supports aerobic glycolysis (Warburg effect) through the FOXO4/LDHA or circ-MAT2B/miR-515-5p axis (106,113,120,121). By contrast, HIF-2 (primarily HIF-2α encoded by EPAS1) remains less well studied in GC; existing evidence links it to vascular endothelial function and GC cell metabolism, but its precise role in proliferation, metastasis or resistance, especially across GC subtypes (intestinal vs. diffuse), remains elusive (226-228). HIF-3, the least explored subtype, exhibits context-dependent activity; its splice variant IPAS competitively inhibits HIF-1α-mediated transactivation of pro-tumor genes, yet some studies suggest pro-metastatic effects via uncharacterized signaling axes, highlighting unresolved controversies in the functional role of HIF-3 (35,184,185,229-233). Finally, a panel of small-molecule agents (such as apigenin, tipifarnib and schisandrin B) have been summarized that target HIFs to suppress GC progression, although all remain confined to preclinical models without clinical translation.

The findings presented in the present review reinforce the centrality of HIFs as integrators of hypoxic TME signals and GC malignant phenotypes, aligning with the broader consensus that hypoxia-driven HIF activation is a non-negotiable step in solid tumor progression (10,11). Induction of melanogenesis robustly upregulates HIF-1α expression and its downstream target genes related to angiogenesis and glycolysis, along with a subset of HIF-1-independent genes, in melanoma cells and tissues, highlighting the critical role of HIF-1α in mediating the metabolic regulatory effects of specific cellular processes (234). A critical insight is the bidirectional crosstalk between HIFs and the TME: HIFs not only respond to hypoxia but also actively reshape the TME. For example, HIF-1α-induced lactate production (via LDHA) acidifies the extracellular ME, which in turn inhibits T-cell cytotoxicity and enhances MDSC immunosuppressive activity; concurrently, ROS generated by mitochondrial dysfunction under hypoxia stabilizes HIF-1α, creating a positive feedback loop that amplifies pro-tumor signaling (235-237). This crosstalk explains why targeting HIFs may simultaneously disrupt multiple hallmarks of GC (such as angiogenesis, immune evasion and metabolic reprogramming) rather than acting on a single pathway.

Another notable observation is the subtype-specific functional diversity of HIFs. HIF-1α is widely regarded as a universal oncogenic driver in GC, consistent with its overexpression in most GC tissues and association with poor prognosis (34). By contrast, HIF-2α exhibits tissue-specific expression (such as vascular endothelial cells) and may play a more context-dependent role. For instance, it promotes angiogenesis in GC via VEGF but has also been linked to differentiation in certain cell types (34). HIF-3α, meanwhile, represents a 'double-edged sword'; its full-length isoform may act as a transcriptional activator, while splice variants such as IPAS antagonize HIF-1α (34). This heterogeneity underscores the need for subtype-specific targeting strategies, as pan-HIF inhibitors may disrupt physiological hypoxia responses (such as wound healing) and cause off-target toxicity which is a major barrier to clinical translation. From a therapeutic perspective, the preclinical efficacy of HIF-targeted small molecules (Table I) validates HIFs as viable targets for GC. For example, low-dose tipifarnib inhibits HIF-1α without affecting Ras signaling, addressing the toxicity concerns of earlier FTIs; R8-modified vinorelbine-schisandrin B liposomes enhance tumor targeting while downregulating HIF-1α, overcoming the poor bioavailability of numerous small molecules (192,194). However, a critical translational gap persists as no HIF-targeted agent has entered clinical trials for GC, despite the Food and Drug Administration approval of Welireg (a HIF-2α inhibitor) for von Hippel-Lindau syndrome. This gap likely stems from two challenges: i) The lack of predictive biomarkers to identify patients most likely to benefit (such as HIF-1α-high vs. HIF-2α-high GC); and ii) the potential for adaptive resistance, as HIF inhibition may activate compensatory pathways (such as PI3K/Akt/mTOR). Future studies should prioritize combinatorial strategies, for example, HIF inhibitors combined with immune checkpoint blockers given that HIF-1α regulates PD-L1 expression; or HIF inhibitors plus anti-angiogenic agents (such as bevacizumab), to synergistically disrupt the vascular niche.

While the present review discusses the current state of HIF research in GC, it is important to acknowledge several limitations that reflect broader gaps in the field. First, the evidence base for HIF-2α and HIF-3α in GC remains sparse and heterogeneous. Most studies on HIF-2α focus on other cancers (such as cervical cancer and ESCC), and GC-specific data are limited to *in vitro* experiments with a narrow panel of cell lines (such as BGC-823or SGC-7901). Similarly, HIF-3α studies in GC are confined to small-scale tissue samples or cell models, with conflicting reports on its pro- vs. anti-tumor roles. This paucity of data limits our ability to draw definitive conclusions about these subtypes, emphasizing the need for more GC-specific research. Second, the review focuses primarily on HIF-mediated mechanisms in generic GC, overlooking the profound heterogeneity of the disease. GC is classified into distinct histological (intestinal, diffuse and mixed) and molecular subtypes, and HIF expression and function may vary across subtypes. For example, diffuse-type GC is characterized by EMT and high metastatic potential, but it remains unclear whether HIF-1α serves a more prominent role in this subtype than in intestinal-type GC. This lack of subtype-specific analysis limits the clinical relevance of the present review, as personalized therapy requires understanding HIF biology in distinct GC subsets. Third, the discussion of SMDs is restricted to preclinical studies, with no consideration of pharmacokinetic and pharmacodynamic challenges or clinical safety. Numerous HIF inhibitors exhibit poor solubility, short half-lives or off-target effects (such as inhibiting PHDs involved in collagen synthesis), which may explain their failure to advance to clinical trials. Additionally, the review does not address the potential for HIF-independent hypoxia responses (such as AMPK activation or autophagy), which may contribute to resistance to HIF-targeted therapy and warrants further exploration. Finally, the review relies heavily on *in vitro* and xenograft models, which poorly recapitulate the human GC TME. Xenograft models use immunocompromised mice, precluding analysis of HIF-mediated immune interactions (such as T-cell exhaustion or MDSC recruitment) (14); 3D cell culture models, while more physiologically relevant, are underutilized in HIF-GC research. These model limitations may lead to overestimation of HIF inhibitor efficacy, highlighting the need for more translational models (such as patient-derived xenografts, organoids) in future studies.

In summary, the present review highlights that HIFs, particularly HIF-1α, play a central role in GC progression by integrating hypoxic TME signals to regulate proliferation, metastasis, metabolism and immune evasion. While HIF-2α and HIF-3α remain less well understood, their subtype-specific functions suggest they may represent untapped targets. Despite notable preclinical progress in developing HIF-targeted small molecules, translational challenges (such as lack of biomarkers and adaptive resistance) and gaps in our understanding of HIF biology (such as subtype heterogeneity and pathway crosstalk) persist. Addressing these limitations through future research will be critical to realizing the potential of HIF-targeted therapy as a novel strategy for improving outcomes in patients with GC.

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Competing interests

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