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REVIEW

HIFs: The central drivers of tumors and their role as molecular switches in targeted therapy?

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Tumor treatment

Abstract Hypoxia-inducible factors (HIFs) serve as the central signaling hub within the hypoxic tumor microenvironment, coordinating tumor proliferation, metastasis, and therapy resistance. This protein family comprises HIF-1α, HIF-2α, HIF-3α, and HIF-1β, with distinct subcellular localization patterns reflecting their isoform-specific oxygen-sensing mechanisms. Tumor-associated HIF expression is regulated through a multifaceted network involving non-coding RNAs (ncRNAs), mitochondrial metabolites, and post-translational modifications (PTMs). These aberrantly expressed HIFs then orchestrate biologically important processes including metabolic reprogramming, angiogenesis, and pro-tumorigenic inflammation. It is important to note that current evidence regarding HIF-3α function remains limited and requires further validation *in vivo*. This review first systematically deciphers the mechanisms governing HIF dysregulation in tumors, before elucidating the key biological processes involved. We then synthesize advances in HIF-targeting inhibitors. These pivotal findings provide a solid theoretical foundation and novel insights for both anticancer therapies targeting this critical "molecular switch" and translational research focusing on HIFs as promising therapeutic targets.

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1. Introduction

The hypoxic microenvironment within the tumor microenvironment refers to a pathological state characterized by inadequate local oxygen supply. This condition arises from insufficient angiogenesis, excessive metabolic demands, or abnormal vascular structure in tumor tissue and represents a key driver of tumor progression. HIFs serve as the central regulatory mechanism enabling tumor cells to adapt to this hypoxic stress. By precisely modulating gene expression, HIFs facilitate tumor cell survival under hypoxia and promote malignant progression. HIFs were first identified in 1995 by Wang et al.[1] in mammalian cells exposed to reduced oxygen tension. Their seminal study demonstrated that HIFs are essential for the hypoxia-induced transcriptional activation of the erythropoietin gene enhancer. The transcriptionally active form of HIFs is a heterodimer composed of one of three oxygen-labile α subunits (HIF-1α, HIF-2α, or HIF-3α) and a constitutively expressed β subunit (HIF-1β). The α subunits (HIFα) primarily dictate functional specificity. For instance, HIF-1α upregulates lactate dehydrogenase A (LDHA) expression, fueling tumor cells through activation of the Warburg effect and thereby promoting hepatocellular carcinogenesis[2]. Similarly, HIF-1α-induced *circRNF13* significantly enhances malignant phenotypes, including proliferation, invasion, and metastasis, in pancreatic cancer cells[3]. The functional mechanism of HIFs relies on the formation of the HIFα/HIF-1β heterodimer under hypoxia. This complex specifically recognizes and binds to hypoxia-response elements (HREs), *cis*-regulatory sequences with the core consensus motif 5′-[A/G]CGTG-3′, located in the promoter or enhancer regions of target genes. This binding initiates the transcriptional activation of a broad array of genes that mediate cellular adaptation to low oxygen. This sophisticated molecular machinery underpins the pivotal role of HIFs within the hypoxic tumor microenvironment.

To date, HIFs have been extensively implicated in cancer, with studies confirming their dysregulation across multiple malignancies, including hepatocellular carcinoma (HCC), breast cancer (BC), colorectal cancer (CRC), and lung cancer (LC)[4-7]. Extensive research has established their critical roles in tumor biology. Therefore, building upon existing knowledge of HIFs and acknowledging their oxygen-dependent subcellular localization and structure, this review systematically integrates the multilevel regulatory networks governing their aberrant expression and dysfunctional protein activity in tumors. These networks encompass regulation by ncRNAs, PTMs, and mitochondrial metabolites. Furthermore, we summarize the diverse biological functions orchestrated by HIFs, such as modulating programmed cell death, metabolic reprogramming, tumor metastasis, self-renewal of cancer stem cells, remodeling the tumor immune microenvironment, and conferring therapy resistance. Given these established pivotal functions of HIFs in tumors, this article further reviews the current status of HIFs as key targets for anticancer drug development, focusing on research advances in specific inhibitors (*e.g.*, small-molecule compounds). This synthesis provides novel perspectives for existing cancer treatment strategies and addresses the challenge of clinical drug resistance.

2. Subcellular localization and structure of HIFs

2.1. The oxygen-sensing journey of HIFs: Regulatory translocation from cytoplasm to nucleus

In the hypoxic tumor microenvironment, HIFs function as the central molecular nexus for cellular adaptation to low-oxygen signaling, governed by precise subcellular localization and functional activation. Under normoxic conditions, HIFα subunits predominantly localize to the cytoplasm, yet rapidly translocate to the nucleus in response to hypoxic stimulation. This dynamic shuttling directly regulates their transcriptional activity and downstream biological functions (Fig. 1).

Under normoxia, HIF-1α is mainly distributed in the cytoplasm. Upon hypoxia induction, HIF-1α undergoes rapid nuclear translocation mediated by its C-terminal nuclear localization signal (NLS), with a half-maximal nuclear accumulation time of approximately 30 min. It fully relocates to the nucleus within 1 h of hypoxia treatment at 37 °C, exhibiting a homogeneous distribution without forming distinct nuclear bodies[8]. In contrast, HIF-2α also translocates to the nucleus under hypoxia but displays a heterogeneous, speckled intranuclear distribution. The number, size, and motility of these nuclear speckles are not regulated by oxygen tension, and HIF-2α molecules freely exchange between the speckles and nucleoplasm, albeit with significantly slower mobility compared to HIF-1α[9]. HIF-3α exhibits splice-variant-specific localization patterns: detectable in both the cytoplasm and nucleus under normoxia, with hypoxia further enhancing its nuclear signal[10]. Specifically, long variants such as HIF-3α2, 7, and 9 accumulate in the nucleus during hypoxia, whereas the short variant HIF-3α4 remains localized in the cytoplasm and perinuclear regions and does not undergo nuclear translocation even under hypoxic conditions[11]. Unlike the oxygen-sensitive HIFα subunits, HIF-1β is stably expressed in the nucleocytoplasmic compartment, independent of oxygen concentration, and functions as the structural subunit that facilitates transcriptional activation by HIFα. Together, they constitute a functionally complementary regulatory system.

The localization and activity of HIFα are regulated in a stepwise manner by oxygen gradients: under normoxia, prolyl hydroxylase domain (PHD) proteins 1−3 hydroxylate HIFα, targeting it for von Hippel−Lindau (VHL)-mediated proteasomal degradation, thereby maintaining its low cytoplasmic expression[12]. Under moderate hypoxia, inhibited PHD activity allows HIFα to accumulate in the cytoplasm. However, factor inhibiting HIF (FIH)-mediated hydroxylation blocks its interaction with the transcriptional co-activators p300/CBP, restricting its transcriptional activity[13]. Under severe hypoxia, complete inhibition of both PHD and FIH activity enables HIFα to translocate into the nucleus. There, it dimerizes with HIF-1β, recruits co-activators, and binds to HREs to activate target gene transcription[14]. In

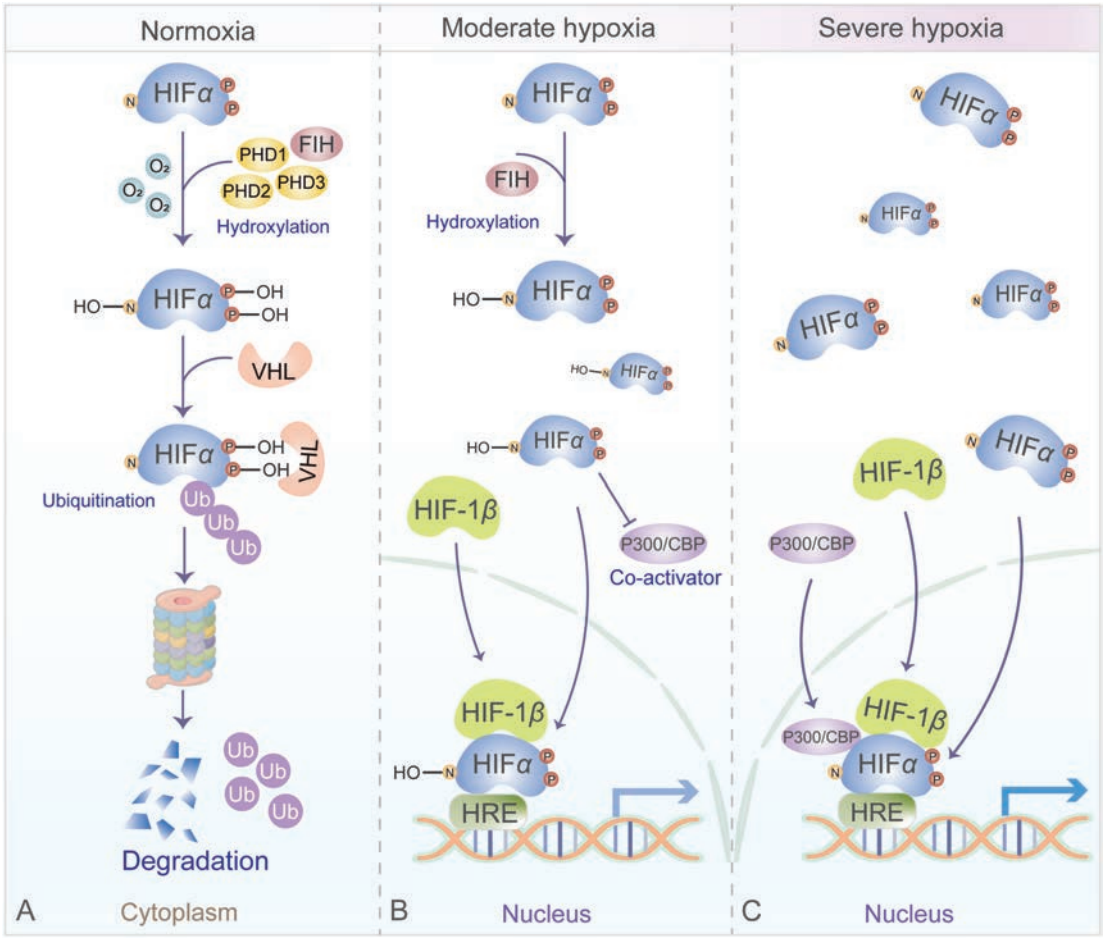

Figure 1 Subcellular localization of HIFs. (A) Under normoxia, HIFα predominantly localizes to the cytoplasm. This is primarily due to PHD1−3-mediated hydroxylation, which promotes VHL-dependent ubiquitination and proteasomal degradation. Concurrently, hydroxylation by FIH further inhibits its transcriptional activity, preventing stable accumulation or nuclear translocation. (B) Under moderate hypoxia, HIFα accumulates significantly within the cytoplasm. Reduced PHD activity allows it to escape VHL-mediated degradation. However, FIH can still inhibit its binding to transcriptional coactivators p300/CBP. Consequently, while some HIFα can translocate to the nucleus, its transcriptional activity remains constrained. (C) Under severe hypoxia, HIFα overcomes the suppressive hydroxylation by both PHDs and FIH, reaching peak levels within the nucleus. Here, it forms an active heterodimer with HIF-1β and recruits the p300/CBP coactivator complex, potently activating the transcription of hypoxia-responsive genes (HRGs).

summary, HIFα transduces oxygen signals *via* an oxygen concentration-dependent "localization−activity coupling" mechanism. This oxygen-sensing machinery constitutes the core mechanism by which HIFα senses microenvironmental changes and underpins its critical role in tumor adaptation to hypoxia.

2.2. *Deciphering the structures of HIF subtypes*

The HIFα subunit comprises three isoforms (Fig. 2). Among these, HIF-1α and HIF-2α exhibit 53.4% amino acid sequence homology in human cells, while HIF-1α and HIF-3α share 57.1% homology[15]. While this homology constitutes a common structural and functional foundation, the key to their functional specificity likely resides in differences across their functional domains.

Structurally, HIFα isoforms exhibit high conservation, each containing an N-terminal basic helix−loop−helix (bHLH) domain and a Per−Arnt−Sim (PAS) domain. The bHLH domain recognizes and specifically binds to HREs in target genes, while the PAS domain facilitates heterodimer formation between the α and β subunits. Additionally, HIFα possesses a C-terminal oxygen-dependent degradation (ODD) domain that senses oxygen concentration changes to regulate protein stability. A key structural divergence lies in the C-terminal regions: HIF-1α and HIF-2α contain a transactivation domain (TAD) that recruits transcriptional co-activators to promote target gene transcription, whereas HIF-3α lacks this domain[16,17].

The structural differences among HIF isoforms may lead to distinct preferences in target gene selection and biological functions. HIF-1α primarily regulates glycolysis-related genes, including those for glucose transporter 1 (*GLUT1*), hexokinase 2 (*HK2*), and *LDHA*. This regulation promotes energy metabolic reprogramming in tumor cells by driving the Warburg effect and enhancing their ability to adapt to the hypoxic microenvironment. Additionally, it participates in regulating the balance between cell proliferation and apoptosis, influencing malignant tumor progression[18,19]. HIF-2α, in contrast, tends to regulate stem cell factors (such as *SCF*) and vascular endothelial growth factor

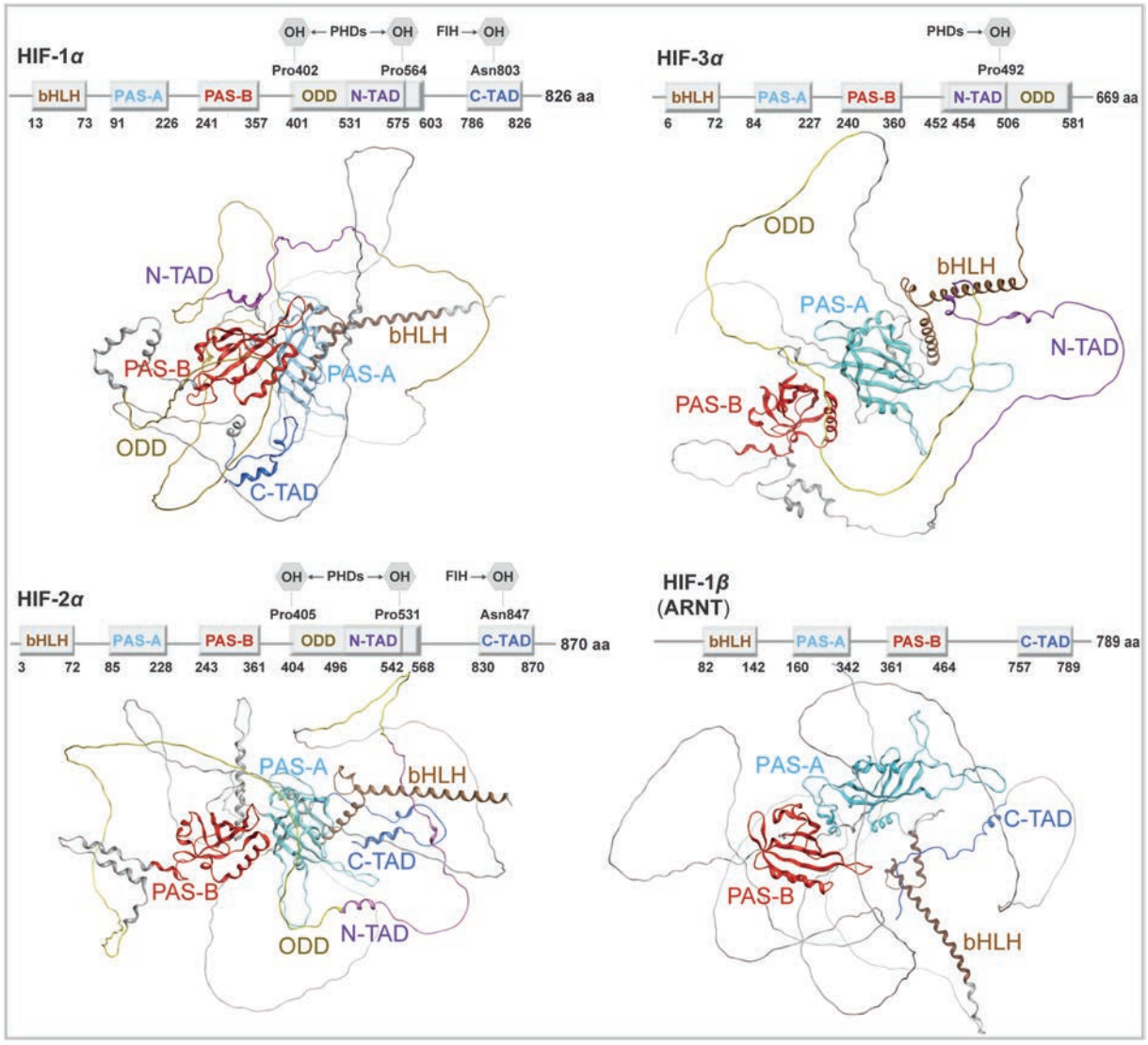

Figure 2 Structure of HIFs.The HIF family comprises HIFα and HIF-1β subunits, each consisting of 669−870 amino acids and possessing conserved bHLH and PAS domains. Among the HIFα isoforms (HIF-1α, HIF-2α, HIF-3α), all contain an ODD domain and a TAD. However, HIF-3α lacks the C-terminal transactivation domain (C-TAD). Within the ODD domain, PHD enzymes specifically hydroxylate proline residues (Pro402/Pro564 in HIF-1α; Pro405/Pro531 in HIF-2α; Pro492 in HIF-3α). Within the TAD, FIH hydroxylates an asparagine residue (Asn803 in HIF-1α; Asn847 in HIF-2α). In contrast to HIFα, the constitutively expressed HIF-1β subunit contains bHLH, PAS, and C-TAD domains but lacks an ODD domain, rendering it incapable of oxygen sensing.

(*VEGF*), not only playing a central role in angiogenesis but also promoting tumor immune escape by shaping an immunosuppressive microenvironment, particularly acting as a key driver in clear cell renal cell carcinoma[20,21]. In comparison, the function of HIF-3α is more complex. Its long variants (such as HIF-3α2) can activate specific target genes like erythropoietin (*EPO*), participating in physiological processes such as erythropoiesis, while short variants primarily act as negative feedback regulators, inhibiting the transcriptional activity of HIF-1/2α to finely tune the intensity of the hypoxic response[22]. The structural differences among HIF-α isoforms drive this functional differentiation, thereby establishing a molecular foundation for the design of targeted isoform-selective inhibitors. Meanwhile, HIF-1β, as the structurally expressed β-subunit, is an indispensable component for the formation of the functional transcriptional complex. It heterodimerizes with the oxygen-sensitive HIF-α subunits, and together they recognize and bind to the HRE, providing the essential molecular framework for the transcriptional initiation of hypoxia-responsive genes[23].

3. HIF dysregulation in cancer: Multifaceted regulatory networks at play

Within the tumor microenvironment, aberrant activation of HIFs relies on multilayered and dynamic regulatory circuitry. First, their transcriptional levels are directly regulated: factors such as the viral sarcoma oncogene homolog (v-Src) and the rat sarcoma viral oncogene homolog (RAS), along with upstream stimulatory factor 2 (USF2), can initiate HIF-α transcription[24-26]. Meanwhile, HIF-1α can also recruit co-activators, including steroid receptor coactivator-1 (SRC-1) and transcriptional intermediary factor 2

(TIF2), to enhance its activity[27]. In contrast, heat shock transcription factor 2/4 (HSF2/4) and forkhead box A1 (FOXA1) exert transcriptional repression[28,29]. More importantly, the expression and activity of HIFs are also finely regulated by the following three key dimensions: ncRNAs modulate *HIF* mRNA and protein levels *via* epigenetic mechanisms; PTMs dynamically regulate HIF stability; and aberrant mitochondrial metabolites induce alterations in HIF activity and stability (Fig. 3). These interconnected axes collectively maintain the homeostatic state of HIFs in tumors.

3.1. *HIF expression: Is multilayered regulation orchestrated by non-coding RNAs?*

HIF expression is precisely regulated at both mRNA and protein levels by diverse ncRNAs, including microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs), a process that exhibits mechanistic diversity and context-dependent dual regulatory effects during tumor progression. At the mRNA level, Sun et al.[30] demonstrated that under hypoxic conditions, *miR-103a-3p* promotes HIF-1α transcriptional activation by suppressing core components of the Hippo pathway. This leads to upregulated *HIF-1α* mRNA levels, thereby driving a metabolic vicious cycle in CRC. This finding exemplifies the regulatory role of ncRNAs at the transcriptional layer.

At the protein level, ncRNAs exhibit functional divergence in their regulatory roles: the lncRNA *MIR31HG* promotes head and neck squamous cell carcinoma (HNSCC) proliferation by upregulating HIF-1α protein expression and downregulating p21[31]. Conversely, *circEXOC6B* mediates tumor-suppressive effects by downregulating HIF-1α protein levels through disruption of the HIF-1α–RRAGB–mTORC1 positive feedback loop[32], establishing a functional antagonism characterized by "upregulation-promotion" *versus* "downregulation-inhibition". Furthermore, while both achieve elevated HIF-1α protein levels, *HIF1A-AS1* enhances HIF-1α translation efficiency by recruiting phosphorylated Y-box-binding protein 1 (pYB1) to *HIF-1α* mRNA[33]; LncRNA *FAM83A-AS1* inhibits HIF-1α protein degradation by blocking its interaction with the VHL protein[34]. Despite converging on HIF-1α upregulation, these ncRNAs target distinct processes (translation and degradation pathways, respectively), collectively driving tumor malignant phenotypes and illustrating the diversity of positive regulatory mechanisms.

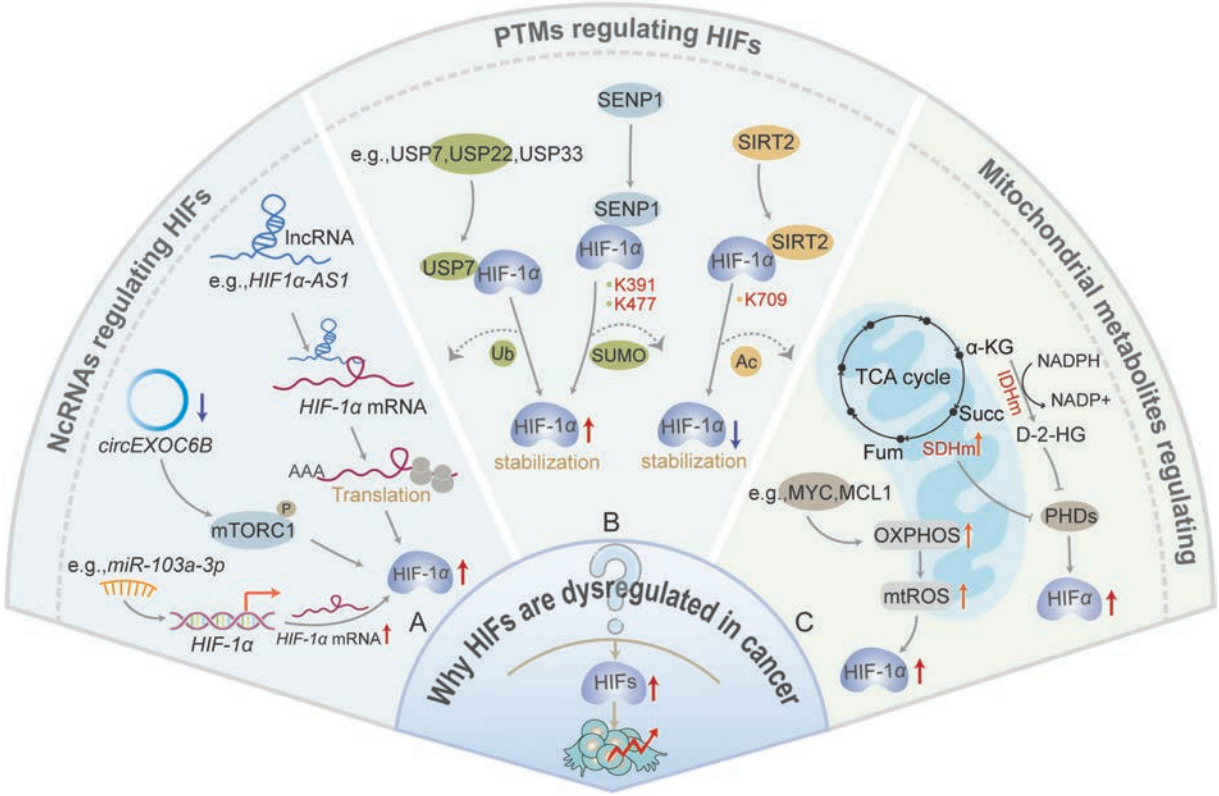

Figure 3 Multidimensional regulatory network of HIF dysregulation in tumors. (A) HIF expression regulated by ncRNAs. At the transcriptional level, miRNAs such as *miR-103a-3p* can upregulate *HIF-1α* transcription. At the protein level, ncRNAs including *circEXOC6B* and *HIF1α-AS1* promote increased HIF-1α protein levels by enhancing translational efficiency, thereby driving malignant phenotypes such as tumor proliferation. (B) HIF stability modulated by PTMs. HIFs are dynamically regulated by diverse PTMs, including ubiquitination, acetylation, and SUMOylation, with ubiquitination playing a predominant role. Deubiquitinating enzymes (DUBs) such as USP7, USP22, and USP33 significantly enhance HIF-1α stability by counteracting ubiquitin-mediated degradation pathways, consequently promoting cancer stemness maintenance and tumor growth. Furthermore, post-translational modifications intricately regulate HIF-1α stability. While SIRT2-mediated deacetylation promotes its degradation, SENP1-mediated de-SUMOylation enhances its stability. (C) HIF stability and activity are regulated by mitochondrial metabolite-mediated modulation of PHD activity. For instance, mutations in TCA cycle enzymes (*e.g.*, *IDH*-mutant, *SDH*-deficient) or accumulation of ROS inhibit the hydroxylation activity of PHDs. This leads to aberrant stabilization and accumulation of HIFα protein, ultimately promoting tumorigenesis and progression.

Overall, ncRNAs orchestrate multifaceted regulation of HIFs (particularly HIF-1α) through multi-tiered mechanisms including transcriptional activation, translational regulation, and suppression of protein degradation. This regulatory complexity not only underscores the pivotal role of ncRNAs within the HIF expression network but also reveals diverse molecular targets for intervening in HIF-mediated tumor progression *via* ncRNA-directed approaches.

3.2. HIF stability: Do post-translational modifications dictate destabilization or stabilization?

PTMs serve as fundamental mechanisms for regulating protein function, dynamically altering protein conformation and stability to play decisive roles in tumor progression and therapy resistance. Notably, the stability of HIFs is precisely regulated by diverse PTMs, including ubiquitination, acetylation, and SUMOylation[35-37]. Among these, ubiquitination exerts central control over HIF protein stability and modulates malignant tumor progression[38].

Specifically, in cholangiocarcinoma (CCA), hypoxia-induced spindle and kinetochore-associated complex subunit 3 (SKA3) stabilizes HIF-1α protein by enhancing its interaction with the deubiquitinase USP7, thereby promoting tumor proliferation and gemcitabine resistance[35]. In HCC, Shan et al.[4] demonstrated that phosphorylated non-muscle myosin heavy chain 9 (*p*-MYH9) stabilizes HIF-1α by recruiting the deubiquitinase ubiquitin-specific peptidase 22 (USP22), augmenting cancer stemness. Similarly, Zhang et al.[39] revealed that deubiquitinase USP33 stabilizes HIF-2α protein to enhance tumor angiogenesis and promote glioma stem cell growth. Integrative analysis reveals that ubiquitination-mediated stabilization represents an evolutionarily conserved mechanism through which HIFs drive therapy resistance across diverse malignancies, underscoring its pivotal regulatory role.

The stability of HIF is further fine-tuned by a dynamic balance of acetylation and SUMOylation modifications. For instance, sirtuin 2 (SIRT2) suppresses tumor cell adaptation to hypoxia by specifically deacetylating HIF-1α at K709, thereby reducing its protein stability[40]. Conversely, in HCC, the SUMO-specific protease 1 (SENP1) enhances HIF-1α stability by removing SUMOylation modifications at K391 and K477 residues, consequently promoting cancer stemness[37]. These findings demonstrate that PTMs differentially reprogram HIF stability and their mediated oncogenic processes, effectively altering the biological outcomes of HIF signaling.

Collectively, PTMs—including ubiquitination, acetylation, and SUMOylation—finely tune HIF stability to reprogram their mediated oncogenic processes. Deciphering the site specificity, enzyme dependency, and tumor-contextual regulation of these modifications not only establishes a molecular framework for understanding HIF proteostasis but also paves the way for novel therapeutic strategies targeting PTM-mediated HIF stabilization.

3.3. HIF activity and stability: Can mitochondrial metabolic derangements reprogram the PHD regulatory network?

Mitochondria, pivotal regulators in tumorigenesis and cancer progression, contribute to oncogenesis through multifaceted pathways, including energy supply and metabolic reprogramming. Substantial evidence confirms that aberrant mitochondrial metabolites serve as cornerstone modulators of both HIF activity and stability, thereby influencing the progression of diverse malignancies such as pancreatic cancer (PC), CRC, and BC[41-43]. Notably, dysregulated tricarboxylic acid (TCA) cycle metabolites and mitochondrial reactive oxygen species (mtROS) accumulation represent two central regulatory pathways that converge on inhibition of PHD activity[44]. Critically, mitochondrial metabolic reprogramming achieves differential regulation of HIF activity and stability by reconfiguring the PHD regulatory network.

The activity and stability of HIFs are precisely regulated through diverse molecular mechanisms mediated by TCA cycle metabolites[45]. In malignancies, while both isocitrate dehydrogenase (*IDH*) mutations generating D-2-hydroxyglutarate (D-2HG) and succinate dehydrogenase (*SDH*) deficiencies causing succinate accumulation represent TCA cycle abnormalities that converge on PHD inhibition to modulate HIFα, they exhibit selective divergence in regulatory outcomes: *IDH*-mutant tumors predominantly enhance HIFα activity to drive transcriptional activation of downstream targets[46], whereas *SDH*-deficient pancreatic ductal adenocarcinoma (PDAC) preferentially augments HIFα stability to promote glycolytic reprogramming[47]. Collectively, these findings demonstrate tumor-context-dependent regulation of HIFα by TCA metabolites, revealing distinct mechanistic preferences across the core dimensions of activity *versus* stability.

HIF activity and stability are critically modulated by mtROS[48], with distinct regulatory emphasis on these parameters across tumor types. Specifically, in CRC, Oh et al.[49] demonstrated that c-MYC promotes mtROS accumulation, which inhibits PHD activity, thereby enhancing HIF-1α stability and upregulating glycolysis-related gene transcription. Conversely, in triple-negative breast cancer (TNBC), Lee et al.[50] revealed that MYC and MCL1 cooperatively increase mitochondrial oxidative phosphorylation (mtOXPHOS) to stimulate mtROS production, predominantly stabilizing HIF-1α protein to maintain cancer stemness and induce chemotherapy resistance. These findings collectively reveal a central theme: mtROS serves as a common regulatory node for HIF-1α, yet this node is integrated into distinct tumor-specific networks that ultimately determine critical differences in HIF signaling stability, activity, and downstream functional outputs.

Collectively, the regulatory mechanisms governing HIFs in tumors exhibit multifaceted and multilayered characteristics. The three pivotal dimensions—ncRNA-mediated expression control, PTM-dependent stability regulation, and mitochondrial metabolic reprogramming impacting both activity and stability—operate not in isolation but through dynamic interplay, collaboratively constructing the sophisticated HIF regulatory network in oncogenesis. Deciphering the molecular logic of this network holds significant implications for understanding tumor pathogenesis and identifying potential therapeutic vulnerabilities.

4. HIF-mediated regulation of tumor biological functions

In the tumor microenvironment, aberrant activation of the HIF pathway stems from extensive dysregulation of its upstream regulatory network. The abnormal accumulation and sustained activation of HIF-α subunits are directly driven by key nodes such as PHD/FIH, VHL, and deubiquitinating enzymes (DUBs), which further mediate a series of critical tumor biological processes. Therefore, as a central hub, HIFs tightly connect upstream

molecular dysregulation with downstream malignant phenotypes, and together with their related regulatory nodes, constitute highly promising therapeutic targets.

Specifically, functioning as central regulators of tumor microenvironment adaptation and malignant phenotypes, HIFs exert decisive roles across multiple pivotal stages of tumor progression through isoform-specific mechanisms. Multiple studies have confirmed that HIF-1α and HIF-2α, frequently overexpressed in diverse malignancies, serve as primary drivers of tumorigenesis and progression (Fig. 4). Although research on HIF-3α remains comparatively limited, emerging evidence demonstrates its ability to promote tumor invasion and metastasis by modulating the RhoC−ROCK1 signaling pathway[51]. Notably, HIF functions are not exclusively pro-tumorigenic: HIF-1α may exert context-dependent tumor-suppressive effects, exemplified by enhanced pancreatic cancer cell invasiveness upon its deletion[52] or accelerated acute myeloid leukemia (AML) progression[53], underscoring its functional complexity. Critically, HIFs demonstrate strong associations with tumor initiation and poor patient prognosis (Table 1[4-5,33,35,50-51,54-80]), exerting core regulatory functions spanning programmed cell death regulation, metabolic reprogramming, tumor metastasis, cancer stem cell self-renewal, immune microenvironment remodeling, and chemotherapy resistance (Fig. 5). These interconnected biological processes collectively constitute a multidimensional regulatory network that drives malignant progression.

4.1. HIFs as fate arbiters: Reprogramming the dynamic balance of cell death modalities

As fate arbiters of programmed cell death, HIFs exhibit complex, context-dependent regulatory roles in tumor progression through mediating the dynamic balance of cell death modalities, such as autophagy and ferroptosis, with their effects exhibiting marked isoform specificity.

In autophagy regulation, HIF isoforms display striking functional divergence. For example, HIF-2α promotes tumor malignancy by facilitating E3 ubiquitin ligase activity to enhance the aggregation of the autophagy receptor neighbor of BRCA1 gene 1 (NBR1), thereby triggering autophagy[75]. Conversely, HIF-2α suppresses clear cell renal cell carcinoma (ccRCC) progression through upregulation of *hsa-mir-7-5p*, which inhibits TBC1D5-mediated autophagy[81]. Research indicates that alterations in autophagy levels can reciprocally regulate HIFs. For instance, Liu et al.[82] demonstrated that loss or mutation of the autophagy-

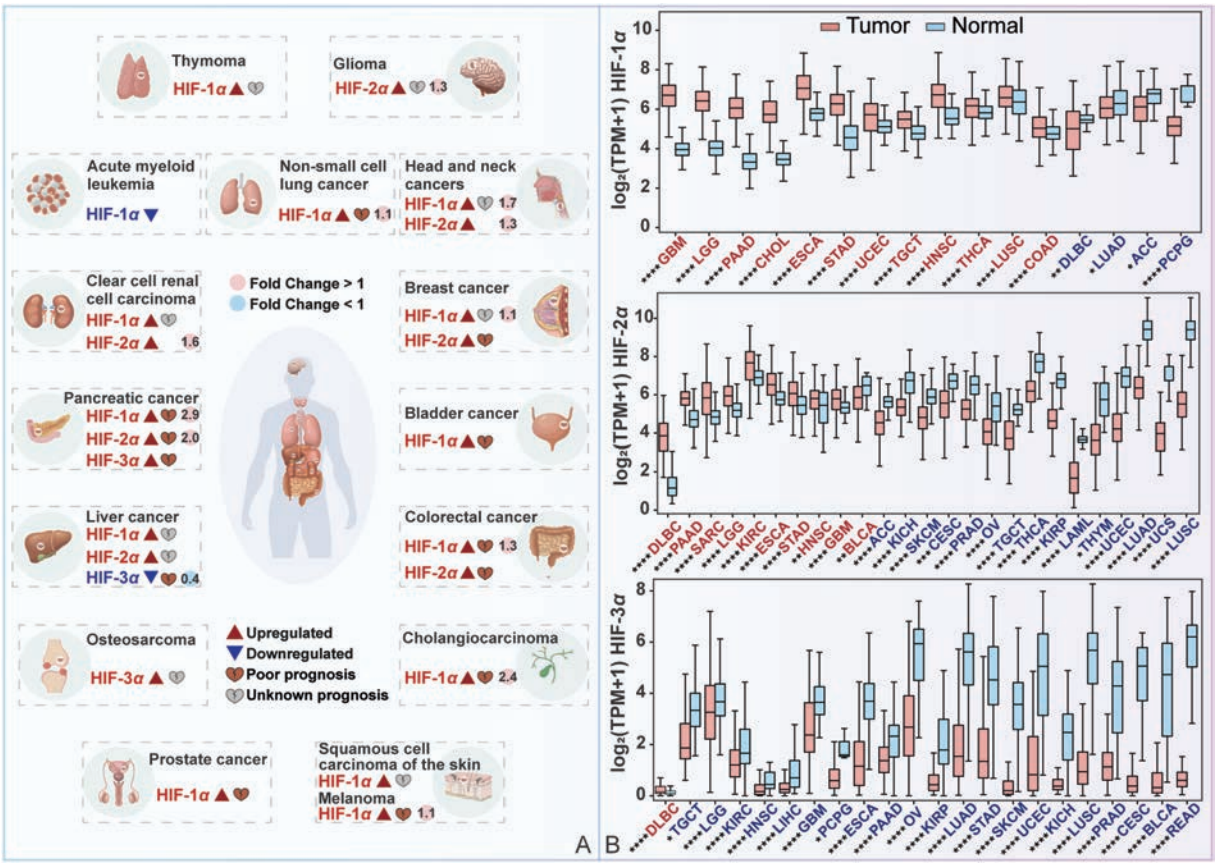

Figure 4 Dysregulation and prognostic significance of HIFs across various cancer types. (A) Dysregulation of HIFs expression and its prognostic significance in 15 cancer types. Based on analyses of the TCGA and GTEx data (https://gepia3.bioinfoliu.com/), the graphical elements are defined as follows: circles represent expression changes with statistical significance and consistent with literature reports (red: FC $>$ 1; blue: FC $<$ 1), with specific FC values labeled; triangles correspond to expression levels in cancer tissues (red: upregulation; blue: downregulation); hearts indicate prognostic associations (red: high HIF expression associated with adverse prognosis; gray: prognostic relationship remains unclear). (B) The expression landscape of HIFs across human cancers. This box plot, based on TCGA and GTEx data, illustrates the expression levels of HIF-1α, HIF-2α, and HIF-3α in tumor tissues *versus* corresponding adjacent normal tissues.

Table 1 Roles of HIFs in tumors.

Gene	Cancer type	Expression	Prognosis	Target genes/mechanisms axis	Biological function	Ref.
HIF-1α	Pancreatic cancer	Upregulated	Poor	AKT−YB1−HIF-1α	Metabolic reprogramming	33
	Pancreatic ductal adenocarcinoma	Upregulated	Poor	*YAP1*	EMT, metastasis	54
	Cholangiocarcinoma	Upregulated	Poor	SKA3−PARP1−HIF-1α	Proliferation, metabolic reprogramming	35
	Hepatocellular carcinoma	Upregulated	Poor	p-MYH9−USP22−HIF-1α	Stemness	4
	Hepatocellular carcinoma	Upregulated	Poor	FASN−HIF-1α−SLC7A11	Metabolic reprogramming, ferroptosis	55
	Hepatocellular carcinoma	Upregulated	/	ABCF1−KDM3A−H3K9me2−HIF-1α	Proliferation, metastasis	56
	Hepatocellular carcinoma	Upregulated	Poor	*CP*, *SLC7A11*	Ferroptosis, radioresistance	57
	Renal cell carcinoma	Upregulated	/	C11orf54−HIF-1α−RRM2	Apoptosis	58
	Renal cell carcinoma	Upregulated	Poor	Trim21−HIF-1α	Proliferation and metastasis	59
	Renal cell carcinoma	Upregulated	Poor	DEPDC1−AKT−mTOR−HIF-1α	Metabolic reprogramming	60
	Bladder cancer	Upregulated	Poor	HIF-1α−ALYREF−PKM2	Proliferation and metabolic reprogramming	61
	Cutaneous squamous cell carcinoma	Upregulated	/	*HK2*, *GLUT1*, *PDK1*	Metabolic reprogramming	62
	Prostate cancer	Upregulated	Poor	HIF-1α−TGM2	Proliferation, apoptosis	63
	Colorectal cancer	Upregulated	Poor	USP51−HIF-1α−USP51	Proliferation, migration, and stemness	64
	Colon cancer	Upregulated	/	*PFKFB3*, *PFK1*	Metabolic reprogramming, proliferation	65
	Triple-negative breast cancer	Upregulated	/	CARM1−HIF-1α	Proliferation, invasion, and stemness	66
	Triple-negative breast cancer	Upregulated	Poor	HIF-1α−HDAC1−PRC2	Immune escape	67
	Melanoma	Upregulated	Poor	HIF-1α−CCL2−CCL5	Proliferative	68
	Melanoma	Upregulated	Poor	BNIP3−HIF-1α	Metabolic reprogramming	69
	Head and neck cancer	Upregulated	/	*HIF-1α−AS2*	Immune escape	70
	Head and neck squamous cell carcinoma	Upregulated	Poor	*ATP6V1A*	Tumor microenvironment	71
	Nasopharyngeal carcinoma	Upregulated	/	HIF-1α−TfR1	Proliferative	72
	Thymoma	Upregulated	/	HIF-1α−Th17−Treg	Immune evasion	73
	Solid tumors	Upregulated	/	*MT2A*, *PDK1/3*	Cuproptosis	74
	Triple-negative breast cancer	Upregulated	Poor	MYC−MCL1−HIF-1α	Metabolic reprogramming, stemness	50
HIF-2α	Breast cancer	Upregulated	Poor	*SOD2*	Metabolic reprogramming, stemness	5
	Clear cell renal cell carcinoma	Upregulated	/	HIF-2α−NBR1−SQSTM1	Autophagy	75
	Clear cell renal cell carcinoma	Upregulated	/	*FABP5*	Metabolic reprogramming	76
	Colorectal cancer	Upregulated	Poor	NRF2−miR181a-2-3p−HIF-1α	Stemness, migration	77
	Glioblastoma	Upregulated	Poor	*SOX2*, *Klf4*	Proliferation, invasion, migration	78
HIF-3α	Pancreatic cancer	Upregulated	Poor	HIF-3α−RhoC−ROCK1	Proliferation, invasion, migration	51
	Osteosarcoma	Upregulated	/	HIF-3α−KDM3A−SOX9	Proliferation, invasion, apoptosis	79
	Hepatocellular carcinoma	Downregulated	Poor	HIF-1α−miR-210−HIF-3α	Metastasis	80

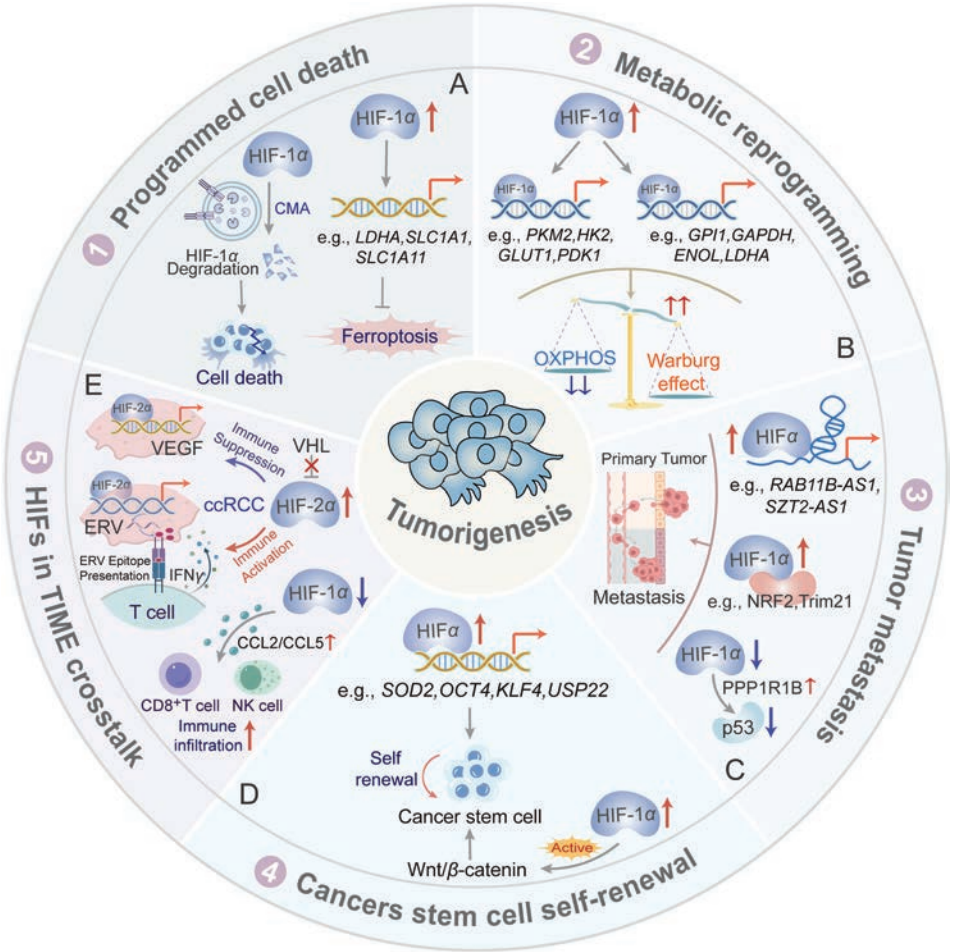

Figure 5 Biological functions of HIFs in tumor regulation. (A) HIFs regulate programmed cell death. HIF-1α promotes its own degradation *via* the CMA pathway, thereby inducing cell death. Additionally, HIF-1α promotes resistance to ferroptosis by transcriptionally upregulating key genes such as *LDHA*, *SLC1A1*, and *SLC1A11*. (B) HIFs drive metabolic reprogramming. HIF-1α significantly enhances the glycolytic capacity of tumor cells by activating the expression of glycolysis-associated genes, including *PKM2*, *HK2*, and *GLUT1*, thereby enabling metabolic reprogramming. (C) HIFs mediate tumor metastasis. HIFα drives tumor metastasis by transcriptionally activating metastasis-associated lncRNAs such as *RAB11B-AS1* and *SZT2-AS1*. Meanwhile, HIF-1α facilitates the metastatic process by interacting with key proteins like NRF2 and Trim21. Paradoxically, HIF-1α loss enhances tumor invasion and metastasis by promoting p53 degradation. (D) HIFs sustain cancer stem cell self-renewal. HIFα enhances the self-renewal capacity of CSCs by transcriptionally activating stemness-associated genes (*e.g.*, *SOD2*, *OCT4*, *KLF4*, *USP22*) or activating the Wnt/β-catenin signaling pathway. (E) HIFs Modulate the Tumor Immune Microenvironment. HIF-1α deficiency enhances the infiltration of NK cells and $CD8^+$ T cells through the upregulation of CCL2 and CCL5, resulting in suppressed tumor growth. Notably, HIF-2α exerts a dual role in ccRCC: driving VEGF-mediated immunosuppression while transactivating ERVs to generate immunogenic neoantigens that elicit anti-tumor immunity.

related gene *ATG7* in ccRCC upregulates HIF-2α expression, consequently promoting tumorigenesis. Furthermore, Tan et al.[58] revealed that HIF-1α undergoes degradation *via* the chaperone-mediated autophagy (CMA) pathway, suppressing ribonucleotide reductase regulatory subunit M2 (*RRM2*) transcription and ultimately reducing DNA damage and cell death in cancer cells. These findings collectively illustrate the distinct functional roles of HIF isoforms in autophagy regulation.

In the regulation of ferroptosis, HIFs also exhibit isoform-specific effects. HIF-1α primarily enhances tumor cell resistance to ferroptosis through mechanisms such as promoting lactate generation or solute carrier family 1 member 1 (*SLC1A1*) expression, and upregulating solute carrier family 7 member 11 (*SLC7A11*)[55,83]. In contrast, HIF-2α sensitizes CRC and ccRCC to ferroptosis, either by cooperating with ferroptosis activators (*e.g.*, Erastin) or by upregulating hypoxia-inducible lipid droplet-associated protein (HILPDA) to promote the accumulation of polyunsaturated fatty acids (PUFAs)[84,85]. Furthermore, Li et al.[79] revealed that HIF-3α directly inhibits osteosarcoma (OS) cell death by activating lysine demethylase 3A (KDM3A)-mediated demethylation of SRY-box transcription factor 9 (SOX9), thereby expanding the molecular dimensions of HIF family regulation in cell death.

In summary, HIFs critically influence the survival-death fate of tumor cells by fine-tuning the balance between autophagy and ferroptosis. This bidirectional and isoform-specific regulation not only underscores the central role of HIFs as essential regulators of programmed cell death but also provides a multi-tiered theoretical framework for targeting HIFs to restore tumor cell death programs and circumvent treatment resistance.

4.2. HIFs as metabolic architects: Engineering the tumor metabolic network

Functioning as architects of energy remodeling in metabolic reprogramming, HIFs fine-tune the dynamic equilibrium of glycolysis and diverse metabolic pathways, thereby sustaining tumor cell proliferation and survival under microenvironmental stresses. Their roles exhibit distinct isoform specificity and pathway selectivity.

In the regulation of glycolysis (Warburg effect), HIF-1α serves as the principal driver by transcriptionally activating pyruvate kinase muscle isozyme M2 (*PKM2*) to initiate aerobic glycolysis and promote bladder cancer (BCa) cell proliferation[61]. Concurrently, it regulates a spectrum of key glycolytic genes—including solute carrier family 2 member 1 (*SLC2A1*), *HK2*, and *LDHA*—thereby modulating glycolytic flux and proliferative capacity in cutaneous squamous cell carcinoma (cSCC) and prostate cancer (PCa)[62,63]. The core role of HIF-1α is further underscored by evidence that flavonoids counteract glycolysis-mediated therapy resistance through targeting the HIF-1α signaling pathway[86]. Notably, HIF-1α exhibits functional duality in metabolic reprogramming: beyond driving glycolytic flux, it directly suppresses oxidative metabolism. Research demonstrates that in VHL-deficient renal carcinoma cells, HIF-1α antagonizes c-MYC transcriptional activity and represses peroxisome proliferator-activated receptor gamma coactivator 1-beta (PGC-1β) expression, thereby negatively regulating mitochondrial biogenesis and oxidative phosphorylation[87]. This coordinated regulation ultimately reshapes the global energy metabolism profile of tumor cells.

The metabolic regulatory network orchestrated by HIFs extends beyond glycolysis. HIF-1α broadens its influence to encompass nucleotide and amino acid metabolism, thereby sustaining the rapid growth demands of cancer cells[88]. de Heer et al.[89] further demonstrated that HIFs drive multifaceted metabolic reprogramming in BC by modulating carbohydrate, amino acid, and lipid metabolism, while also orchestrating mitochondrial and ROS metabolism. In contrast, HIF-2α specifically promotes lipid droplet biogenesis in ccRCC by regulating fatty acid binding protein 5 (FABP5)-mediated fatty acid metabolism[76], highlighting the isoform-specific metabolic pathway selectivity of HIFs.

HIFs underpin the energy remodeling network in tumor metabolic reprogramming through the core regulation of glycolysis and involvement in diverse metabolic pathways. The broad-spectrum and subtype-specific nature of this control solidifies their role as "metabolic architects" and provides precise molecular targets for therapeutic intervention against metabolic adaptation.

4.3. HIFs as core drivers: Architects of tumor metastasis

Metastasis is the leading cause of cancer-related mortality. As core drivers of tumor metastasis, HIFs play a dominant role in this process by regulating multiple pathways, including angiogenesis, epithelial-mesenchymal transition (EMT), and metastasis-associated genes. In regulating angiogenesis, HIFs drive tumor neovascularization by activating factors such as *VEGF*, thereby promoting metastasis[90]. Studies demonstrate that HIF-2α can induce *lncRNA RAB11B-AS1* to mediate angiogenesis and breast cancer metastasis under hypoxic conditions[91], while HIF-1α transcriptionally activates *SZT2-AS1* to synergistically promote tumor growth, angiogenesis, and metastasis in HCC[92]. Although both target angiogenesis, the distinct downstream molecules they engage highlight the regulatory preferences of HIF isoforms. HIF-1α plays a particularly prominent role in EMT regulation[93]. Research reveals that HIF-1α transcriptionally activates *YAP1* in PDAC, directly driving EMT and metastasis[54]. Notably, even under normoxic conditions, minute amounts of HIF-1α can still promote EMT in breast cancer through interaction with eukaryotic translation elongation factor 1 alpha 2 (EEF1A2)[94], indicating that HIF-1α′s regulation of EMT extends beyond the hypoxic milieu, broadening the contexts for its pro-metastatic action.

The mechanisms by which HIFs regulate metastasis-associated genes reveal even greater complexity. Specifically, HIF-1α can cooperate with nuclear factor erythroid 2-related factor 2 (NRF2) to enhance the metastatic potential of HCC or interact with the E3 ubiquitin ligase Trim21 to promote renal cell carcinoma (RCC) metastasis[59,95]. In contrast, HIF-3α indirectly promotes HCC invasion by upregulating HIF-1α activity *via* negative feedback and inhibiting tissue inhibitor of metalloproteinases-2 (TIMP2) expression[80], illustrating functional crosstalk and layered regulation within the HIF family. Recently, Qiao et al.[96] reported that a synthetic transcriptional repressor (STR) blocks TNBC metastasis by suppressing HIF-1α-induced gene expression, further validating the potential of targeting HIFs as the "core drivers" of metastasis.

It is noteworthy that the pro-metastatic function of HIF-1α is not absolute but exhibits profound context dependence. In tumors with intact p53 function, HIF-1α stabilizes p53 protein through direct binding or by interfering with murine double minute 2 (MDM2), thereby establishing an HIF-1α—p53 tumor-suppressive axis[97,98]. This axis is further validated by reverse evidence from pancreatic cancer, where loss of HIF-1α promotes p53 degradation *via* upregulation of protein phosphatase 1 regulatory Inhibitor subunit 1B (PPP1R1B), thereby abolishing this tumor-suppressive function and enhancing tumor invasion and metastasis[52]. Thus, within specific genetic contexts, HIF-1α acts as a critical molecular guardian of p53 homeostasis and metastasis restraint.

In summary, while HIFs coordinate multiple pathways to form a dominant regulatory network governing tumor metastasis and solidify their role as "central drivers", their functional output is constrained by the background dependence of axes such as HIF-1α/p53. This fundamental complexity necessitates that any strategy targeting HIFs for anti-metastasis therapy must be grounded in a precise understanding of the tumor's genetic background.

4.4. HIFs as stemness engineers: Driving the molecular machinery of cancer stem cells

Self-renewal is a defining characteristic of cancer stem cells (CSCs), essential for sustaining the persistence and stability of this cellular population. HIFs act as pivotal regulators of CSC stemness maintenance by finely tuning self-renewal mechanisms, with HIF-2α and HIF-1α exhibiting context-dependent functional divergence across different tumor types.

HIF-2α serves as a core regulator of self-renewal in CSCs, and its functions demonstrate marked tumor-type specificity. In glioblastoma (GBM), sustained HIF-2α expression directly promotes stem cell self-renewal[39]. In BC, HIF-2α drives CSC self-renewal by upregulating superoxide dismutase 2 (*SOD2*), which mediates the mtROS—PDI/GRP78—UPR axis and thereby couples endoplasmic reticulum and mitochondrial metabolism[5]. In CRC, HIF-2α sustains stemness properties by regulating pluripotency genes, including octamer-binding transcription factor 4 (*OCT4*) and Krueppel-like factor 4 (*KLF4*)[77]. Collectively, these studies

demonstrate that HIF-2α operates through diversified mechanisms—termed "pluripotency gene activation coupled with metabolic reprogramming"—to serve as a critical molecular determinant of CSC stemness maintenance across tumor types.

HIF-1α similarly contributes to CSC stemness regulation, with its mechanisms relying more heavily on cooperative signaling pathways. Ling et al.[99] demonstrated that in *TP53*-mutant HCC, HIF-1α enhances CSC self-renewal capacity by inducing upregulation of the deubiquitinating enzyme USP22. In TNBC, HIF-1α interacts with coactivator-associated arginine methyltransferase 1 (CARM1) to activate the Wnt/β-catenin signaling pathway, thereby maintaining stemness[66]. These findings demonstrate that HIF-1α maintains stemness through enzyme-mediated regulatory mechanisms coupled with pathway activation.

HIFs—particularly HIF-1α and HIF-2α—function as stemness engineers that drive the molecular machinery of cancer stem cells by targeting pluripotency genes, metabolic pathways, and signaling networks. The isoform specificity and mechanistic diversity underlying this regulation not only cement the pivotal driver role of HIFs in CSC self-renewal but also provide a precise molecular rationale for targeting HIFs to disrupt CSC populations.

4.5. HIFs as microenvironment reinventors: Reprogramming the tumor immune microenvironment

The dynamic equilibrium of the tumor immune microenvironment (TIME) is a critical determinant of cancer progression. As key reinventors, HIFs shape the immunosuppressive phenotype by remodeling the TIME through multidimensional strategies, thereby significantly influencing therapeutic responses[100,101]. Among these, HIF-dominated exosome-mediated intercellular communication represents a core mechanism: studies indicate that under hypoxic stress, HIFs remodel the immune microenvironment by regulating the molecular cargo (including miRNAs, lncRNAs, and proteins) of exosomes released by cancer cells and stromal cells[102,103]. For instance, key factors carried by HIF-regulated exosomes, such as *miR-1246* and transforming growth factor beta (TGFβ), can transmit immunosuppressive signals to macrophages, driving their polarization towards the M2 phenotype, thereby establishing a positive feedback loop of immunosuppression within the TIME[104,105]. More importantly, HIFs can directly reprogram the functions of various immune cells and synergistically activate a broad immunosuppressive network, thereby remodeling the tumor immune microenvironment in multiple dimensions.

Specifically, through their complex isoform specificity and context-dependency, HIFs exert fine-tuned regulation over immune cell populations within the TIME. On one hand, HIFs drive the recruitment and functional activation of various immunosuppressive cells[29,73]. For example, HIFs can upregulate chemokines such as chemokine (C−C motif) ligand 20 (CCL20) and C−X−C motif chemokine ligand 5 (CXCL5) to enhance the recruitment of regulatory T cells (Tregs)[106]. More critically, HIF-1α serves as a central regulatory hub for the function and differentiation of myeloid-derived suppressor cells (MDSCs), promoting their differentiation into tumor-associated macrophages (TAMs) and enhancing the secretion of factors like interleukin-6 (IL-6) and interleukin-10 (IL-10), collectively consolidating the immunosuppressive niche[107,108]. However, in PDAC-associated cancer-associated fibroblasts (CAFs), specific loss of HIF-2α leads to reduced infiltration of M2-type macrophages and Tregs, further highlighting the isoform and context-specific functions of HIFs[109].

On the other hand, HIFs directly suppress the function of cytotoxic immune cells. For instance, HIF-2α dampens the activity of natural killer (NK) cells by activating the STAT3/IL-10 pathway[110]. In various tumor models, loss of HIF-1α promotes the infiltration of NK and $CD8^+$ T cells by upregulating chemokine (C−C motif) ligand 2 (CCL2) and chemokine (C−C motif) ligand 5 (CCL5), and synergizes with programmed cell death protein 1 (PD-1) blockade therapy to enhance anti-tumor immunity[68,111]. The regulatory function of HIF-1α varies by tumor type: in HNSCC, its high expression restricts $CD8^+$ T cell infiltration by downregulating human leukocyte antigen class I (HLA-ABC)[70]; whereas in liver cancer, it recruits plasmacytoid dendritic cells (pDCs) *via* the CD39/CD73−adenosine axis to directly suppress $CD8^+$ T cell function[112].

Beyond directly reprogramming immune cells, HIFs consolidate immunosuppression across multiple layers by activating broad immune evasion mechanisms[113]. Among these, the manipulation of immune checkpoints is a core strategy. Studies show that HIF-1α can directly upregulate programmed death-ligand 1 (PD-L1) expression on tumor cells and myeloid cells, while hypoxia itself can trigger PD-1 signaling on NK cells and T cells, collectively leading to functional exhaustion of immune cells[102]. Notably, Bailey et al.[114] discovered that HIF-1α differentially regulates PD-L1 in tumor *versus* normal tissues, providing a potential strategy for combining anti-cytotoxic T-lymphocyte-associated protein 4 (anti-CTLA-4) therapy to enhance efficacy and reduce toxicity. Furthermore, HIF-1α can drive the CD39/CD73−adenosine pathway, further inducing the upregulation of PD-1/PD-L1, thereby synergistically reinforcing immunosuppression across multiple dimensions[115].

It is particularly noteworthy that HIF-2α exhibits a complex "dual nature" in specific cancers, most typically in ccRCC. On one hand, HIF-2α fulfills its classic immunosuppressive role by upregulating factors like *VEGF* to drive angiogenesis and immune evasion[116]. On the other hand, HIF-2α also acts as an "activation switch" for tumor immunogenicity: in the context of VHL loss leading to stabilized HIF-2α, it can directly and transcriptionally activate multiple human endogenous retroviruses (*ERVs*)[117,118], echoing the previously observed HIF-mediated upregulation of ERVs in PBRM1-deficient models[119], collectively establishing HIFs as the upstream central hub for ERV expression. These activated *ERV* transcripts can be translated into neoantigens recognized by T cells, thereby stimulating anti-tumor immune responses[120]. This functional antagonism reveals the inherent contradiction in targeting HIF-2α: inhibiting its activity may simultaneously relieve immunosuppression and potentially weaken the natural "vaccine" effect mediated by *ERVs*.

In summary, as central coordinators of immunosuppression in the TIME, HIFs function across multiple layers, from exosome communication and cell population regulation to the activation of immune checkpoints. The "dual nature" of HIF signaling in ccRCC demonstrates the remarkable complexity of its regulatory network. Precisely this complexity provides the crucial scientific rationale and promising prospects for strategically integrating HIF inhibition with immunotherapy and translating these insights into effective clinical combination regimens.

4.6. HIFs as stealth conductors: Instigators of chemoresistance

Resistance to therapy represents a major challenge in clinical oncology. HIFs, functioning as "stealth conductors" of chemoresistance, drive tumor adaptation to diverse treatment modalities

through multiple mechanisms—including signaling pathway activation and post-translational modifications—exhibiting both pathway specificity and mechanistic interconnectivity.

At the signaling pathway level, HIF-1α directly mediates chemoresistance through downstream pathway activation. In CRC, HIF-1α is upregulated *via* ROS-induced PI3K/AKT and Wnt/β-catenin pathway activation, conferring resistance to 5-fluorouracil (5-FU). Inhibition of HIF-1α restores drug sensitivity[121]. In PCa, HIF-1α contributes to castration resistance, where its inhibition reestablishes apoptotic signaling cascades and overcomes resistance to androgen deprivation therapy (ADT)[122]. Collectively, these findings demonstrate that HIF-1α modulates resistance to diverse therapeutic modalities through signaling crosstalk.

At the post-translational modification level, HIF-mediated chemoresistance mechanisms exhibit network-like complexity. Studies confirm that multiple deubiquitinating enzymes stabilize HIF-1α to form regulatory networks underlying tumor drug resistance. In CRC, HIF-1α cooperates with USP7 to drive organoid resistance to oxaliplatin by rewiring glycolysis and angiogenesis[123]. In HCC, USP22-mediated stabilization of HIF-1α confers acquired resistance to Lenvatinib[4]. Notably, HIF-1α and USP51 form a positive feedback loop (where USP51 stabilizes HIF-1α, and HIF-1α transcriptionally activates *USP51*), driving chemoresistance in CRC through sustained HIF-1α overexpression[64]. These mechanisms depend on stabilized HIF-1α expression, demonstrating its essential intermediary role in resistance networks and further cementing HIFs' nexus position within chemoresistance circuitry.

In summary, HIFs—through isoform-specific regulation—establish an interconnected and synergistic regulatory network governing core oncogenic processes, including programmed cell death (*e.g.*, apoptosis, ferroptosis), metabolic reprogramming, metastasis, CSC stemness maintenance, TME remodeling, and chemoresistance. This multidimensional and multilayered integration not only deciphers molecular mechanisms underlying malignant progression but also underscores the potential of HIFs as central therapeutic targets in oncology.

5. Targeting HIFs: Current strategies and therapeutic potential of inhibitors

In recent years, research on HIF inhibitors has emerged as a hotspot in oncology therapeutics, driven by their potential for precise intervention in tumor microenvironment adaptation and malignant phenotypes. Development efforts focus predominantly on isoform-specific targeting, categorizing agents into HIF-1α-selective and HIF-2α-selective inhibitors based on target specificity. These compounds exert antitumor effects through multifaceted mechanisms (Fig. 6). Furthermore, the review also summarizes therapeutic agents that exert their effects by targeting the hypoxic microenvironment itself, including hypoxia-activated prodrugs (HAPs) (Table 2[5,29,63,124-151]).

Mechanisms of HIF-1α inhibitors demonstrate multifaceted characteristics, with the core action centered on blocking its function or downregulating its expression. The first category targets the transcriptional activity of HIF-1α. For instance, the novel aryl sulfonamide KCN1 and sulfonyl-γ-AA peptides (HC11-15) inhibit its transcriptional function by blocking the interaction between HIF-1α and p300/CBP[124,127]. In contrast, the nanoliposomal echinomycin impedes HIF-1α binding to DNA by binding to HREs[152]. The second category regulates HIF-1α protein levels. For example, PX-478 inhibits its translation[63], the kempanil derivative HI-104 reduces its protein expression by promoting binding between *HIF-1α* mRNA and ATP synthase subunit beta (ATP5B)[129], while IDF-11774 hinders its accumulation by inhibiting heat shock protein 70 (HSP70) function[133]. Although their action pathways differ, these inhibitors all converge on suppressing the pro-tumorigenic activity of HIF-1α and exhibit efficacy in diverse tumor models, including TNBC, PCa, and CRC.

The development of HIF-2α inhibitors represents a breakthrough journey from mechanistic elucidation to clinical translation: early conformational studies on the HIF-2α PAS-B domain laid the groundwork for developing allosteric inhibitors that block HIF-2α—HIF-1β heterodimerization[153,154]. Building upon this foundation, the first-in-class allosteric inhibitor Belzutifan (PT2977) was approved in 2021 for the treatment of VHL syndrome-associated renal cell carcinoma[155], validating the feasibility of HIF-2α-targeted therapy. Concurrently, parallel research efforts have further expanded intervention strategies: both DFF332 and cyclane[*c*]thiophene-based compounds target the HIF-2α PAS-B domain to exert antitumor effects, with DFF332 demonstrating dose-dependent antitumor efficacy in preclinical studies, and the cyclane[*c*]thiophene analogues inhibiting tumor progression through multipronged mechanisms[139,140]. Taking a distinct approach, ARO-HIF2 degrades *HIF-2α* mRNA specifically through siRNA technology, thereby suppressing HIF-2α-dependent tumor growth, and has currently entered Phase 1 clinical trials[142]. Although their modes of intervention differ, these inhibitors all share the goal of specifically inhibiting HIF-2α function, collectively advancing its exploration for applications across diverse cancers.

Beyond direct HIF inhibition, explorations leveraging tumor hypoxia have spawned multiple complementary strategies[156,157]. HAPs achieve targeted cytotoxicity in hypoxic regions through specific activation, with evofosfamide demonstrating combinatorial potential in pancreatic cancer and glioblastoma[145,146], while PR-104 has shown preliminary activity in acute leukemia[147]. However, tirapazamine failed to improve survival in phase III trials for head and neck cancer and cervical cancer[148,149], indicating that its clinical translation requires further optimization. Concurrently, novel technologies are opening new avenues to overcome hypoxia-mediated resistance: intelligent chimeric antigen receptor-modified T cells (CAR-T) therapy engineered with hypoxia-inducible designs enhances its functional persistence within the tumor microenvironment[158,159]; microenvironment remodeling strategies modulate physical barriers or synergistically reverse hypoxia and immunosuppression to improve therapeutic infiltration[160-162]; the proteolysis-targeting chimera (PROTAC) platform establishes a foundation for degrading HIF-α[163,164]; and clustered regularly interspaced short palindromic repeats (CRISPR) screening systematically uncovers resistance mechanisms and identifies cooperative targets[165].

In summary, current research is addressing the tumor hypoxic microenvironment through coordinated multi-pathway approaches. The development of HIF-1α and HIF-2α inhibitors has achieved substantial progress from mechanistic exploration to clinical translation; HAPs have validated their potential as targeted delivery strategies in specific cancer types; while novel technologies such as cell engineering, microenvironment modulation, and high-throughput screening further expand the dimensions of intervention. In contrast, targeted therapy for HIF-3α remains an unexplored

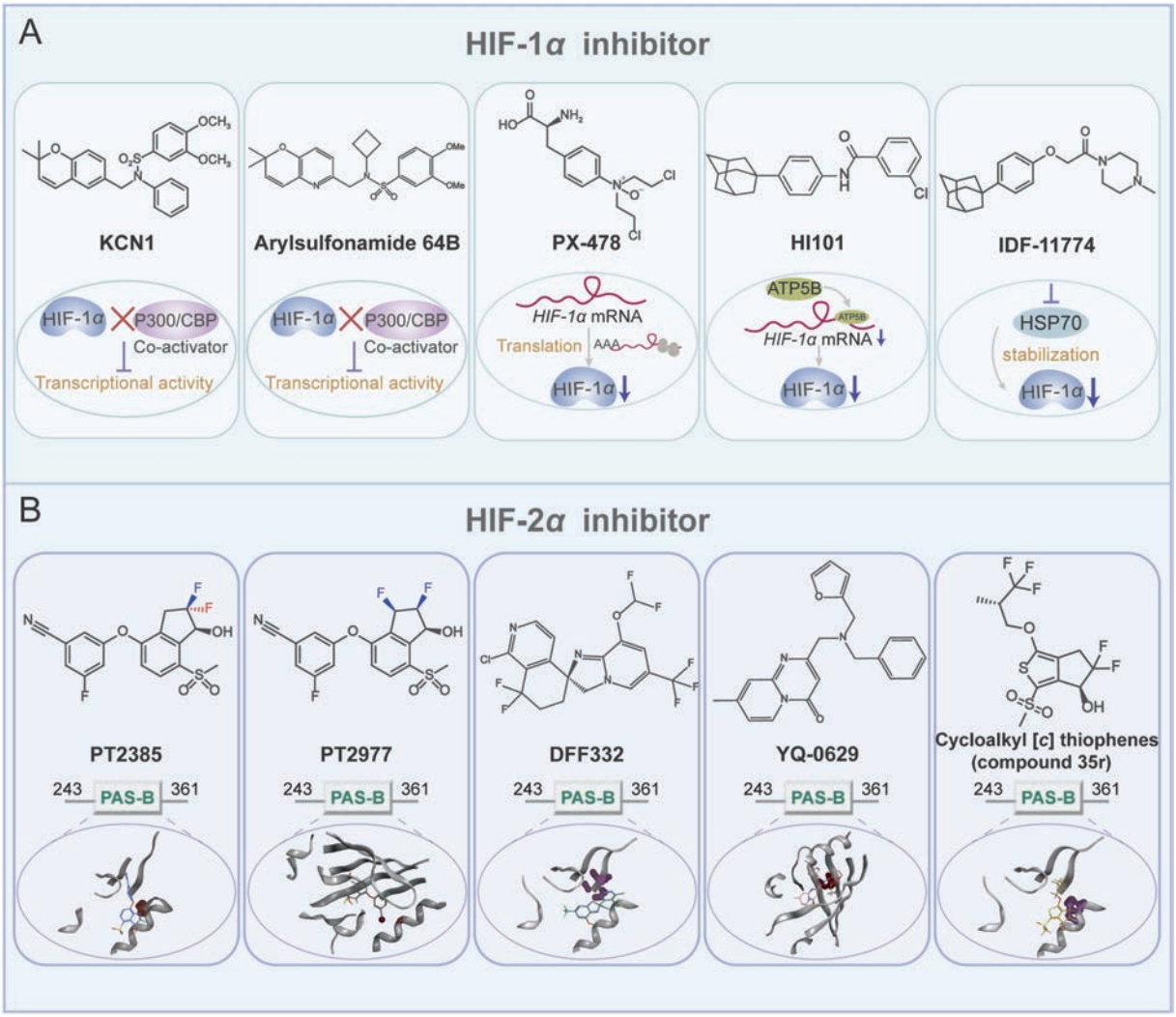

Figure 6 HIF inhibitors. (A) HIF-1α Inhibitors. KCN1 and Arylsulfonamide 64B inhibit HIF-1α transcriptional activity by blocking its interaction with the coactivators p300/CBP. PX-478 suppresses HIF-1α protein levels by inhibiting its translation. HI101 inhibits HIF-1α protein expression by promoting binding between *HIF-1α* mRNA and ATP5B. IDF-11774 downregulates HIF-1α protein stability by inhibiting HSP70 chaperone function. (B) HIF-2α inhibitors. Currently developed small-molecule inhibitors—including PT2385, PT2977 (Belzutifan), DFF332, YQ-0629, and the cyclane[*c*]thiophene derivative **35r**—allosterically inhibit HIF-2α by specifically targeting its PAS-B domain.

frontier. Future integration of multi-level strategies with artificial intelligence and multi-omics data will provide systematic solutions for achieving comprehensive and precise targeting to overcome tumor hypoxia-associated resistance.

6. Summary and prospect

HIFs, which serve as central transcriptional regulators orchestrating tumor adaptation to hypoxic microenvironments and malignant progression, have undergone a paradigm shift in research focus. This evolution has shifted from traditional investigations of oxygen-sensing mechanisms to a new era focusing on multi-dimensional network regulation. Substantial evidence implicates HIFs as crucial players in tumorigenesis and cancer progression. This review systematically delineates the subcellular localization patterns and structural/functional motifs of HIFs, with a primary emphasis on dissecting their multi-layered regulatory networks and biological functions within tumors. It further elaborates on the mechanisms of HIF-mediated tumor drug resistance and the current advances in inhibitor development. At the molecular regulation level, ncRNAs significantly influence malignant cellular phenotypes—such as cell proliferation and invasive/metastatic capabilities—by modulating HIF transcription and post-transcriptional processes. Simultaneously, PTMs and mitochondrial metabolism reshape the aggressive behaviors mediated by tumor cells during hypoxic adaptation through their regulation of HIF activity and stability. At the biological function level, HIFs drive malignant progression through multifaceted pathways. These include orchestrating programmed cell death, driving metabolic reprogramming, promoting metastasis, maintaining CSC traits, and remodeling the tumor microenvironment into an immunosuppressive state. Therefore, comprehensively deciphering the pivotal roles HIFs play in tumors represents a critical breakthrough point for advancing cancer therapy.

Current research on HIF-targeted cancer therapy faces several critical bottlenecks. First, the functions of individual HIF isoforms exhibit significant tumor-specific and context-dependent

Table 2 HIFs inhibitors.

Target/pathway	Inhibitor	Cancer type	Mode of action	Combination therapy strategy	*In vitro* activity	Evidence source	Research model	Primary finding	Safety evaluation	Research and development stage	Ref.
HIF-1α	KCN1	Glioma	Blockade of the HIF-1α −p300/CBP interaction	/	$IC_{50} \approx 593$ nmol/L (LN229-HRE-Luc)	Animal	Nude mouse subcutaneous/ intracranial models; 60 mg/ kg, intraperitoneally (i.p.), 5 times/week	Significant tumor growth inhibition; transient benefit in intracranial glioma models, but no efficacy in melanoma	Well-tolerated	Preclinical	124
HIF-1α	Eudistidine A	Solid tumors	Blockade of the HIF-1α −p300/CBP interaction	/	$IC_{50} = 75$ μmol/L (p300/ HIF-1α binding assay)	/	/	/	/	Early drug discovery	125
HIF-1α	Arylsulfonamide 64B	Uveal melanoma	Blockade of the HIF-1α −p300/CBP interaction	/	$IC_{50} \approx 0.3$ μmol/L (Mel290-V6R-HRE-luc)	Animal	Orthotopic uveal melanoma model (intraocular) with spontaneous liver metastasis; 120 mg/kg (i.p., 5 times/ week)	Potent inhibition of primary tumor growth (70% reduction) and liver metastasis (50% reduction), with a significant extension in survival	Well-tolerated with no significant toxicity	Preclinical	126
HIF-1α	Sulfonyl-γ-AApeptide (HC11-15)	Solid tumors	Blockade of the HIF-1α −p300/CBP interaction	/	$K_d = 97$ nmol/L (HC13/p300 binding assay) $IC_{50} = 3.43$ μmol/L (FP competition assay)	/		/	/	Early drug discovery	127
HIF-1α	Chetomin	Multiple myeloma	Blockade of the HIF-1α −p300/CBP interaction	Therapeutic enhancement with lenalidomide and melphalan	$IC_{50} = 2.29-6.89$ nmol/L (10 types of multiple myeloma cell lines)	Cell line	Human multiple myeloma cell lines and patient-derived primary cell models	Significant inhibition of cell proliferation	No significant toxicity to normal bone marrow cells or hematopoietic progenitors	Preclinical	128
HIF-1α	KC7F2	Prostate cancer	Inhibition of HIF-1α translation	/	Effective dose: 40 μmol/L	Cell line	In prostate cancer models	KC7F2 effectively reversed the EMT process, invasive capabilities, and M2-type macrophage infiltration in tumor cells	/	Preclinical	29
HIF-1α	Adamantaniline derivatives (HI101-105)	Liver cancer	Inhibition of HIF-1α translation	/	$IC_{50} = 26$ nmol/L (HI-105); $K_d = 2.6$ nmol/L (HI-103/F1 −ATP synthase complex binding)	Animal	MHCC97-L hepatocellular carcinoma (HCC) cell line xenograft model in nude mice; HI-104 (100 mg/kg, i. p.)	Significant inhibition of tumor growth	No apparent toxicity	Preclinical	129
HIF-1α	Everolimus (mTOR inhibitor)	Breast cancer	Inhibition of HIF-1α translation	Overcoming endocrine resistance with letrozole and goserelin	/	Patient	A randomized controlled trial involving 199 premenopausal patients with advanced, SERM-resistant breast cancer, Everolimus (10 mg/ day, *p.o.*) + Letrozole (2.5 mg/day, *p.o.*) + Goserelin (3.6 mg/ 28d, s.c.)	The median progression-free survival (PFS) in the combination therapy group was significantly superior to that of the control group	/	Phase II clinical trial (NCT02313051)	130
HIF-1α	PX-478	Prostate cancer	Inhibition of HIF-1α translation	/	/	Animal	Pten(i)pe$^{-/-}$ genetically engineered mouse model of prostate cancer	At 20 mg/kg, the treatment induced apoptosis in the precancerous stage and potently inhibited proliferation and reduced tumor weight in the late stage	No effect on normal prostate cells	Phase I clinical trial (NCT00522652)	63
HIF-1α	LW6	Colon cancer	Reduction in HIF-1α protein stability	/	Effective dose: 15 μmol/L	Animal	HCT116 colon cancer xenograft model in nude mice; LW6 (10/20 mg/kg, i. p., once daily/qd)	The 20 mg/kg dose resulted in significant tumor growth inhibition (TGI) of 53.6%	Well-tolerated	Preclinical	131
HIF-1α	EZN-2208	Acute promyelocytic leukemia	Reduction in HIF-1α protein stability	Enhancing APL treatment efficacy in combination with all-*trans* retinoic acid (ATRA)	Effective dose: 5−10 nmol/L	Animal	APL mouse models driven by PML−RARα or PLZF −RARα; EZN-2208 (5 −10 mg/kg, i.v., q2d)	Monotherapy can slow the progression of leukemia; combined with ATRA, it shows remarkable synergistic effects	/	Phase I clinical trial (NCT01251926)	132
HIF-1α	IDF-11774	Colorectal cancer	Reduction in HIF-1α protein stability	When combined with sunitinib and other drugs, the efficacy is better than that of monotherapy	$IC_{50} = 3.65$ μmol/L (HCT116-HRE-Luc)	Animal	HCT116 xenograft model in nude mice; IDF-11774 (10, 30, 60 mg/kg, *p.o.*, qd)	Dose-dependent inhibition of tumor growth; TGI in other mutant models ranged from 32% to 62%	Well-tolerated	Preclinical	133
HIF-1α	DMA	Colorectal cancer	Reduction in HIF-1α protein stability/Inhibition of HIF-1α transcriptional activation	/	Effective dose: 10 μmol/L (HCT116)	Animal	Zebrafish model; DMA (1.25 −10 μmol/L)	Significant anti-angiogenic effect	No apparent toxicity	Preclinical	134
HIF-1α	Deguelin analogues (Hsp90 inhibitor)	Non-small cell lung cancer	Reduction in HIF-1α protein stability	/	$IC_{50} = 140$ nmol/L (Analogues54,H1299)	Animal	Zebrafish model	Dose-dependent inhibition of angiogenesis at concentrations of 0.25 −1.25 μmol/L	/	Preclinical	135
HIF-1α	Luminespib (Hsp90 inhibitor)	Non-small cell lung cancer	Reduction in HIF-1α protein stability	/	/	Patient	29 pre-treated patients with EGFR ex20ins NSCLC, Luminespib (70 mg/m^2, i.v.,	Objective response rate (ORR): 17%; disease control rate (DCR): 38%; PFS: 2.9	Common adverse events included diarrhea, nausea, and fatigue	Phase II clinical trial (NCT01854034)	136

(*continued on next page*)

Table 2 (*continued*)

Target/pathway	Inhibitor	Cancer type	Mode of action	Combination therapy strategy	*In vitro* activity	Evidence source	Research model	Primary finding	Safety evaluation	Research and development stage	Ref.
							q.w.)	months; overall survival (OS): 13 months.			
HIF-2α	PT2385	Clear cell renal cell carcinoma	Inhibition of HIF-2α−HIF-1β dimerization	/	/	Patient	51 pre-treated patients with advanced ccRCC receiving PT2385 (100−1800 mg, bid)	ORR: 14%; DCR: 66%; patients with stable disease (SD) ≥4 months: 42%	The primary adverse events were anemia, peripheral edema, and fatigue. The recommended phase 2 dose (RP2D) was determined to be 800 mg bid	Phase I clinical trial (NCT02293980)	137
HIF-2α	Belzutifan (PT2977)	Renal cell carcinoma in von Hippel-Lindau disease	Inhibition of HIF-2α−HIF-1β dimerization	/	/	Patient	61 patients with VHL disease-associated localized tumors, Belzutifan (120 mg, *p.o.*, qd)	ORR was 49% for RCC, 77% for pancreatic lesions, 30% for central nervous system (CNS) tumors, and 100% for retinal lesions	The primary adverse events were anemia and fatigue	Phase II clinical trial (NCT03401788)	138
HIF-2α	YQ-0629	Breast cancer	Inhibition of HIF-2α−HIF-1β dimerization	Sensitization to paclitaxel when used in combination	Effective dose; 15 μmol/L (MCF-7 MS); K_d = 57.5 μmol/L (SPR)	Animal	Breast cancer patient-derived xenograft (PDX) model; YQ-0629 (100 mg/kg, i.p., every other day/qod) + Paclitaxel (5 mg/kg, i.p., qod)	Demonstrated potent synergistic anti-tumor activity and significantly prolonged host survival	/	Preclinical	5
HIF-2α	DFF332	Clear cell renal cell carcinoma	Inhibition of HIF-2α−HIF-1β dimerization	/	/	Patient	40 patients with advanced ccRCC, DFF332 administered orally (50/100 mg, qw or 25/50/100/150 mg, qd)	ORR: 5%; DCR: 48%	Well-tolerated, with a 13% incidence of treatment-related anemia	Phase I clinical trial (NCT04895748)	139
HIF-2α	Cycloalkyl[*c*]thiophene (compound 35r)	Clear cell renal cell carcinoma	Inhibition of HIF-2α−HIF-1β dimerization	/	IC_{50} = 305 nmol/L (VEGF-A ELASA); K_d = 42 nmol/L (ITC)	Animal	786-O clear cell renal cell carcinoma (ccRCC) xenograft model; treated with 35r (50 & 200 mg/kg, s.c.)	A single dose significantly downregulated the mRNA expression of HIF-2α target genes in tumor tissue	/	Preclinical	140
HIF-2α	Casdatifan (AB521)	Clear cell renal cell carcinoma	Inhibition of HIF-2α−HIF-1β dimerization	Synergistic anti-tumor effects were observed in combination with Cabozantinib or the anti-PD-1 antibody	IC_{50} = 28.9 nmol/L (786-O VEGF secretion Assay)	Animal	786-O/A-498 ccRCC xenograft models; AB521 (10−100 mg/kg, *p.o.*, qd)	Single-drug administration causes dose-dependent tumor regression; combination with anti-PD-1 shows remarkable effects	Good oral bioavailability	Preclinical	141
HIF-2α	ARO-HIF2	Clear cell renal cell carcinoma	Specifically degrades HIF2α mRNA	/	/	Patient	26 pre-treated patients with advanced ccRCC, ARO-HIF2 (225−1050 mg, qw)	ORR: 7.7%; DCR: 38.5%	The primary adverse events were fatigue and dizziness; further development was hindered due to neurotoxicity	Phase I clinical trial (NCT04169711)	142
HIF-1α/HIF-2α	Cyclic peptide inhibitors	Solid tumors	Inhibition of HIFα−HIF-1β dimerization	/	EC_{50} = 30.7 μmol/L (T-Rex-293 HRE-Luc); K_d = 821 ± 147 nmol/L (HIF-1α PAS-B); K_d = 1.7 ± 0.7 μmol/L (HIF-2α PAS-B)	Cell line	In various cancer cell lines, including MCF-7, Panc-1, and 786-O	Inhibited the mRNA expression of HIF downstream target genes	/	Early drug discovery	143
HIF-1α/HIF-2α	CRLX101	Metastatic renal cell carcinoma	Nanoparticle−drug conjugate: By inhibiting topoisomerase I-mediated degradation of HIF-1α/HIF-2α	Overcome its resistance when combined with bevacizumab	/	Patient	22 pre-treated patients with mRCC CRLX101 (12, 15 mg/m^2, i.v., q2w) + bevacizumab (10 mg/kg, i.v., q2w)	ORR: 23%; patients with PFS >4 months: 55%	Common adverse events included non-infectious cystitis, fatigue, and anemia	Phase I−IIa clinical trial (NCT02187302)	144
Hypoxia	Evofosfamide (TH-302)	Advanced pancreatic cancer	HAP: targeted cytotoxicity in the hypoxic tumor microenvironment	Overcome its resistance when combined with gemcitabine	/	Patient	214 patients randomized to gemcitabine monotherapy, gemcitabine plus TH-302 240 mg/m^2 (G + T240), or G + T340	Combination therapy significantly improved median PFS; the ORR in the G + T340 group reached 26%	Manageable myelosuppression and skin/mucosal toxicity	Phase II clinical trial (NCT01746979)	145
Hypoxia	Evofosfamide (TH-302)	Glioblastoma	HAP: targeted cytotoxicity in the hypoxic tumor microenvironment	Overcome its resistance when combined with bevacizumab	/	Patient	Dose-escalation study in 28 patients with bevacizumab-refractory glioblastoma multiforme (GBM) receiving Evofosfamide (240−670 mg/m^2, i.v., q2w) combined with bevacizumab	ORR: 17.4%, DCR: 60.9%, indicating preliminary signs of activity	Well-tolerated	Phase I clinical trial	146
Hypoxia	PR-104	Acute myeloid leukemia (AML) and acute lymphoblastic	HAP: targeted cytotoxicity in the hypoxic tumor microenvironment	/	/	Patient	50 patients with R/R AML/ALL receiving PR104 (1.1−4 g/m^2).	In dose cohorts ≥3 g/m^2, the ORR for AML and ALL was 32% and 20%, respectively,	The primary toxicities were myelosuppression and gastrointestinal	Phase I/II clinical trial (NCT01037556)	147

		leukemia (ALL)o					showing preliminary anti-leukemic activity	reactions		
Hypoxia	Tirapazamine (TPZ)	Advanced head and neck squamous cell carcinoma (HNSCC)	HAP: targeted cytotoxicity in the hypoxic tumor microenvironment	In combination with cisplatin and radiotherapy	/	Patient	861 patients with advanced head and neck squamous cell carcinoma, randomized to cisplatin + radiotherapy or TPZ/cisplatin + radiotherapy	No significant difference in OS between the two groups; the result was negative	/	Phase III clinical trial (NCT00094081)	148
Hypoxia	Tirapazamine (TPZ)	Locally advanced cervical cancer	HAP: targeted cytotoxicity in the hypoxic tumor microenvironment	In combination with cisplatin and radiotherapy	/	Patient	402 patients with locally advanced cervical cancer, randomized to cisplatin + radiotherapy or TPZ/cisplatin + radiotherapy	No significant differences in 3-year PFS or OS; the result was negative	/	Phase III clinical trial (NCT00263821)	149
Hypoxia	Myo-inositol trispyrophosphate (ITPP, OXY111A)	Hepatopancreatobiliary (HPB) tumors	Hypoxia regulator: Improves oxygenation levels in tumor tissue	Used sequentially with standard chemotherapy	/	Patient	28 patients with advanced hepatopancreatobiliary (HPB) tumors received ITPP (1866–14,500 mg/m^2) sequentially followed by chemotherapy	The maximum tolerated dose (MTD) was 12,390 mg/m^2; DCR for ITPP monotherapy and sequential chemotherapy were 52% and 70%, respectively	The primary adverse event was reversible hypercalcemia	Phase Ib clinical trial (NCT02528526)	150
Hypoxia	Vorinostat	Pediatric embryonal brain tumors	HDAC inhibitor: Downregulates the HIF signaling pathway indirectly	In combination with isotretinoin and a high-intensity chemotherapy regimen	/	Patient	31 patients (<4 years old) with embryonal brain tumors received Vorinostat + isotretinoin combined with intensive chemotherapy	The 5-year PFS and OS were 55% and 61%, respectively	The regimen was feasible, with toxicity profiles as expected	Phase II clinical trial (NCT00867178)	151

variations. For instance, HIF-1α can display inhibitory effects in certain cancers. Furthermore, functional compensation or antagonism exists between isoforms, undoubtedly complicating single-isoform targeting. More crucially, tumor heterogeneity poses a major challenge: significant differences in hypoxia levels and metabolic environments exist across distinct regions within the same tumor. This results in "spatial heterogeneity" in HIF expression levels, activation status, and the spectrum of activated downstream target genes. Consequently, therapeutics employing a single dose or targeting a single entity struggle to eradicate all malignant clones. Simultaneously, variations in the genetic background of tumor cells—such as *TP53* mutational status and differential expression of metabolic enzymes—further intensify the heterogeneity within the HIF regulatory network. This, in turn, leads to marked variability in the therapeutic efficacy of identical HIF inhibitors across different patients, and even at different treatment stages within the same patient. Additionally, current inhibitors predominantly focus on HIF-1α and HIF-2α, with a notable lack of breakthrough progress in specifically targeting HIF-3α.

Future research can achieve breakthroughs through several avenues: leveraging isoform-specific structural and functional differences to develop highly selective inhibitors; integrating single-cell sequencing with spatial transcriptomics to decode the heterogeneity of HIFs within distinct TMEs, enabling precision matching guided by "isoform−spatial−patient" triomics; employing multi-omics technologies to map the dynamic HIF regulatory network and identify synergistic targets with immune checkpoints or metabolic enzymes; and designing hypoxia-responsive smart drug delivery systems to enhance inhibitor enrichment within hypoxic tumor regions, coupled with exploring combination therapy strategies to overcome resistance driven by heterogeneity. As research deepens, HIF-targeted therapy holds promise for overcoming the constraints imposed by the complex TME and tumor heterogeneity through precise modulation of this "molecular switch", thereby offering novel perspectives for clinical translation.

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Author contributions

Huizhe Wu, Minjie Wei, and Xiaoyun Hu conceived the structure of the manuscript. Yi Peng, Ying Che, Yingqi Zhao, and Zheng Wang wrote the manuscript. Huizhe Wu, Minjie Wei, Xiaoyun Hu, Zhanlei Pei, Yanyun Hu, Yuhang Yin, and Xiaolong Pan provided the guidance throughout the revision of this manuscript. Yi Peng, Ying Che, Yingqi Zhao, Zheng Wang, and Zhanlei Pei prepared the figures. All authors read and approved the final manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

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