REVIEW

Hypoxia-inducible factors: A target of cancer treatment

Behnam Hasannejad-asl*[1], Azam Bolhassani[2], Farkhondeh Pooresmaeil[3], Mohammad Javad Roustaye Gourabi[4], Shahla Takamoli[5]

[1] *Student Research Committee, Department of Biotechnology, School of Advanced Technologies in Medicine, Shahid Beheshti University of Medical Science, Tehran, Iran*
[2] *Department of Hepatitis, AIDS and Blood-Borne Diseases, Pasteur Institute of Iran, Tehran, Iran*
[3] *Department of Medical Biotechnology, School of Allied Medicine, Iran University of Medical Science, Tehran, Iran*
[4] *Department of Microbiology, School of Medicine, Shahid Beheshti University of Medical Science, Tehran, Iran*
[5] *Department of Biology, Faculty of Science, University of Guilan, Rasht, Iran*

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ABSTRACT

Hypoxia, a characteristic of the tumor microenvironment caused by abnormal blood vessels and rapid cellular growth, enhances tumor aggressiveness and leads to resistance against conventional therapies. Unlike normal cells, hypoxic tumor cells activate adaptive survival mechanisms, prominently mediated by hypoxia-inducible factors (HIFs). HIF-1 is the most studied member of the HIF family, and the stability of its alpha subunit (HIF-1α) is a crucial determinant of the overall activity of the HIF-1 complex. HIF-1α stabilization under low oxygen occurs via oxygen-dependent and oxygen-independent pathways: in the oxygen-dependent pathway, HIf-1α is normally degraded by the von Hippel–Lindau protein (pVHL) when oxygen is present. Under hypoxia, hydroxylation is inhibited, allowing HIF-1α to accumulate. In the oxygen-independent pathway, growth factor signals activate cascades like PI3K/Akt/mTOR and MAPK/ERK, stabilizing HIF-1α regardless of oxygen levels. Stabilized HIF-1α translocates to the nucleus, promoting transcription of proangiogenic genes such as vascular endothelial growth factor (VEGF), thereby facilitating angiogenesis, tumor invasion, and progression. Dysregulation of these signaling pathways underpins the pathogenesis of many cancers, making HIF and its associated cascades critical targets for innovative cancer therapies. This review focuses on the pivotal role of HIF in tumor angiogenesis and emphasizes the therapeutic potential of targeting HIF signaling in cancer treatment.

Key Words: Cancer angiogenesis, Cancer therapy, Hypoxia-inducible factors, Mitogen-activated protein kinase, Phosphatidylinositol 3-kinase

1. INTRODUCTION

Mammalian cells require proper oxygen levels to perform aerobic metabolism efficiently and produce energy. Conditions such as heart disease, cancer, and chronic obstructive pulmonary disease can severely disrupt the balance of oxygen in the body, leading to hypoxia in the cells.[1,2] Hypoxia plays a critical role in tumor growth and aggressiveness, and it is a significant predictor of treatment resistance in neoplastic diseases. In vivo oxygen levels vary considerably across tissues, with normoxic conditions typically ranging between

*Correspondence: Behnam Hasannejad-asl; Email: b.hasannejad-asl@sbmu.ac.ir; Address: Student Research Committee, Department of Biotechnology, School of Advanced Technologies in Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

4% and 9% oxygen, while hypoxic tumor regions often show severe oxygen deprivation, with levels as low as 0.1% to 2% oxygen, creating an oxygen gradient within the tumor microenvironment approximately from 9% at well-perfused areas to near anoxia in necrotic zones.[3] Precise definition of "low" and "high" oxygen levels is thus essential to appropriately model and study hypoxia in cancer.[3] Detection of hypoxia in vivo and in vitro employs both direct and indirect approaches. Direct methods include oxygen-sensitive electrodes and phosphorescent probes that measure partial oxygen pressure in tissues dynamically.[3,4] Indirect methods rely on hypoxia markers such as Pimonidazole or EF5, which form adducts in hypoxic cells identifiable by immunohistochemistry, or on imaging modalities using hypoxia-specific radiotracers and near-infrared probes that reveal hypoxic tumor regions non-invasively.[5] In vitro, hypoxia is frequently modeled by culturing cells under reduced oxygen tension (typically 1%–5%) within hypoxia chambers calibrated to physiological oxygen levels. Accurate hypoxia detection is critical to validate experimental settings and to enable precise targeting of hypoxia-induced pathways in cancer therapy.

Mammalian cells stimulate a variety of genes to adapt to hypoxia. Hypoxia-inducible factor 1 (HIF-1),[6] as a regulator, controls the transcription of these genes. The stability of the alpha subunit of HIF-1 (HIF-1α) plays a critical role in modulating the overall activity of HIF-1.[6] Changes in glycolytic metabolism toward anaerobic pathways, pH modulation, prevention of normal cell death, and cell cycle interruption are a few examples of the adaptive actions mediated by HIF-1α.[7,8] The "angiogenic switch" that occurs during tumor formation is also significantly influenced by hypoxia. HIF-1α has been demonstrated to be an immediate regulator of vasculature formation by upregulating proangiogenic factors, such as vascular endothelial growth factor (VEGF).[9] These processes lead to a greater capability for invasion, more tumor development, and enhanced tumor hypoxia.[10]

HIF-1 indeed needs to bind to Hypoxia Response Elements (HREs) on DNA to initiate transcription of target genes. This binding is necessary but not sufficient. Therefore, in addition to binding HREs, HIF-1 interacts with coactivators such as CREB-binding protein (CBP),[11,12] and this relationship is regulated by oxygen tension and redox status. For HIF-1 to function at its maximum potential, it is assumed that it must interact with other transcription factors.[13]

In normoxic situations, prolyl hydroxylase domain (PHD) is responsible for hydroxylating the proline residues in HIF-1α. This post-translational modification allows for specific recognition by the von Hippel–Lindau tumor suppressor protein (pVHL). pVHL functions as the substrate-recognition component of an E3 ubiquitin ligase complex, which subsequently polyubiquitinates HIF-1α, tagging it for rapid degradation through the ubiquitin-proteasome system (UPS).[14,15] Contrarily, hypoxia significantly reduces HIF-1α prolyl hydroxylation because it inhibits PHD activity. As a result, pVHL is unable to ubiquitinate HIF-1α, so its stability and nuclear levels increase, allowing it to interact with the α subunit of HIF-1 to form an active complex that promotes the transcription of proangiogenic genes.[16,17] In addition to hypoxia, HIF-1α production and activation can also be triggered through pathways associated with normal oxygen levels (normoxia). Under normal oxygen levels, various malignancies aberrantly upregulate HIF-1α through mechanisms that are independent of hypoxia, frequently involving oncogenic signaling pathways that are commonly activated in cancer. For example, the phosphoinositide 3 kinase (PI3K)/Akt/mTOR signaling cascade can be applied to activate and stabilize HIF-1α.[18–20] Additionally, it was indicated that the Raf/MEK/Extracellular signal-regulated kinase (MAPK /ERK) pathway enhances the HIF-1α transcriptional function.[20,21] HIF-1α regulates the expression of numerous genes involved in angiogenesis and other critical processes related to cancer development.[23,24] Therefore, reducing HIF-1α function directly impacts its target genes, potentially hindering cancer development and aggressive phenotype. Consequently, a key focus of fundamental, translational, and clinical cancer research has been on identifying and blocking the factors and crucial stages of tumor angiogenesis, including pathways that are activated by hypoxia and redox states.[25,26]

In this review, we concentrate on the ways that hypoxia and HIFs control the development of tumors. We also highlight recent research on the prospective effectiveness of agents to suppress HIF-1α. Different pathways that affect the stability and function of hypoxia-inducible factors are briefly illustrated in the Graphical Abstract (see Figure 1).

2. HIF-1 MOLECULAR STRUCTURE

HIF-1 is a dimeric protein composed of alpha (α) and beta (β) subunits.[27] HIF-1α is the oxygen-sensitive and regulatory subunit, which is crucial for the transactivation capabilities of HIF-1 under hypoxic conditions. It contains the transactivation domains necessary for hypoxia-induced gene expression and is subject to oxygen-dependent degradation. In contrast, HIF-1β, also known as the aryl hydrocarbon receptor nuclear translocator (ARNT), is a constitutively expressed subunit that is not regulated by oxygen levels and does not possess transactivation domains. Instead, HIF-1β acts as a stable heterodimerization partner not only for HIF-1α but also for other basic helix–loop–helix/Per–Arnt–Sim (bHLH/PAS) transcription factors.[28,29] It heterodimerizes with HIF-1α, facilitating DNA binding to hypoxia response

elements (HREs) and enabling transcriptional activation.[30] Both subunits belong to the bHLH/PAS family, possessing two PAS domains (PAS-A and PAS-B) and one bHLH domain, which are important for dimerization and DNA recognition.[31] The regions N-terminal to the HLH domain mediate binding of the heterodimer to the HRE-DNA motif in gene promoters.[32] HIF-1α uniquely contains a central oxygen-dependent degradation domain (ODD), which is hydroxylated by prolyl hydroxylases at conserved prolines, targeting it for ubiquitination and proteasomal degradation via the von Hippel-Lindau (pVHL) complex under normoxia;[33,34] Therefore, the ODD is critical for regulating the stability and activity of the alpha subunit.[35,36] HIF-1α also has two transactivation domains — the N-terminal (N-TAD, residues 531–575) and the C-terminal (C-TAD, residues 786–826) — with distinct functions: the C-TAD recruits co-activators like CBP/p300 to drive transcription of target genes, while the N-TAD, partially overlapping with the ODD, modulates HIF-1α degradation.[37] These TAD domains are localized in the C-terminal region of HIF-1α, whereas the N-terminal region contains the bHLH and PAS domains.[32] The overall structure of HIF-1 and its subunits is illustrated in Figure 2. Finally, the inhibitory domain (ID), a negative regulatory region, suppresses the activity of TADs under normoxia by spatially separating them.[38–40] Importantly, HIF-1 transcription and function are tightly regulated by multiple signaling pathways, which will be discussed in the following section.

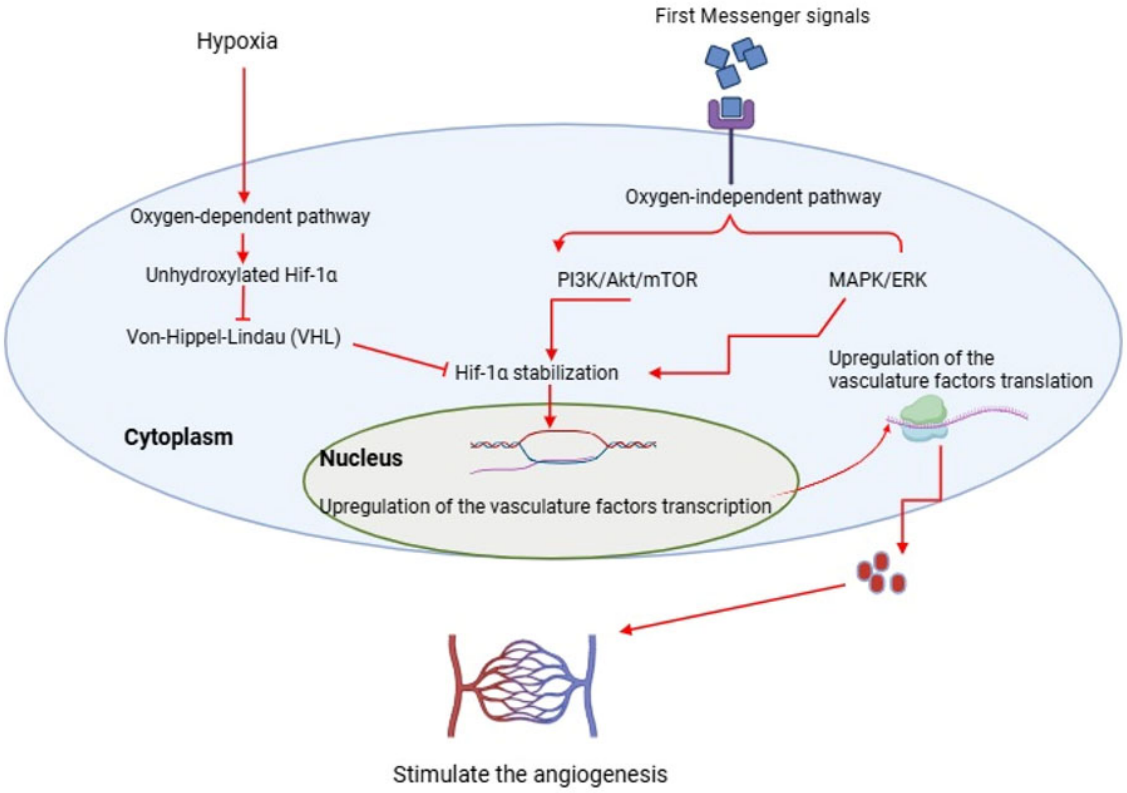

Figure 1. Graphical Abstract: Different pathways that affect the stability and function of hypoxia-inducible factors. The biorender, a web-based application, has been utilized for the Figure design

3. HIF-1α REGULATION

The accumulation and activity of HIF-1α were found to be regulated at various levels throughout the transcription-to-activity cycle within cells. Independent of oxygen level, the HIF-1α gene is transcriptionally regulated through a complex set of signaling processes involving multiple growth factors and other signaling factors.[41,42] In normoxic conditions, HIF-1α degrades quickly and typically has a relatively short half-life.[42] Conversely, it has been demonstrated that a number of mechanisms regulate the durability and transcriptional function of HIF-1α in hypoxic situations through post-translational modifications involving acetylation, hydroxylation, phosphorylation, and ubiquitination processes.[41,43] In this section, we will review the various pathways that stabilize and activate HIF-1α.

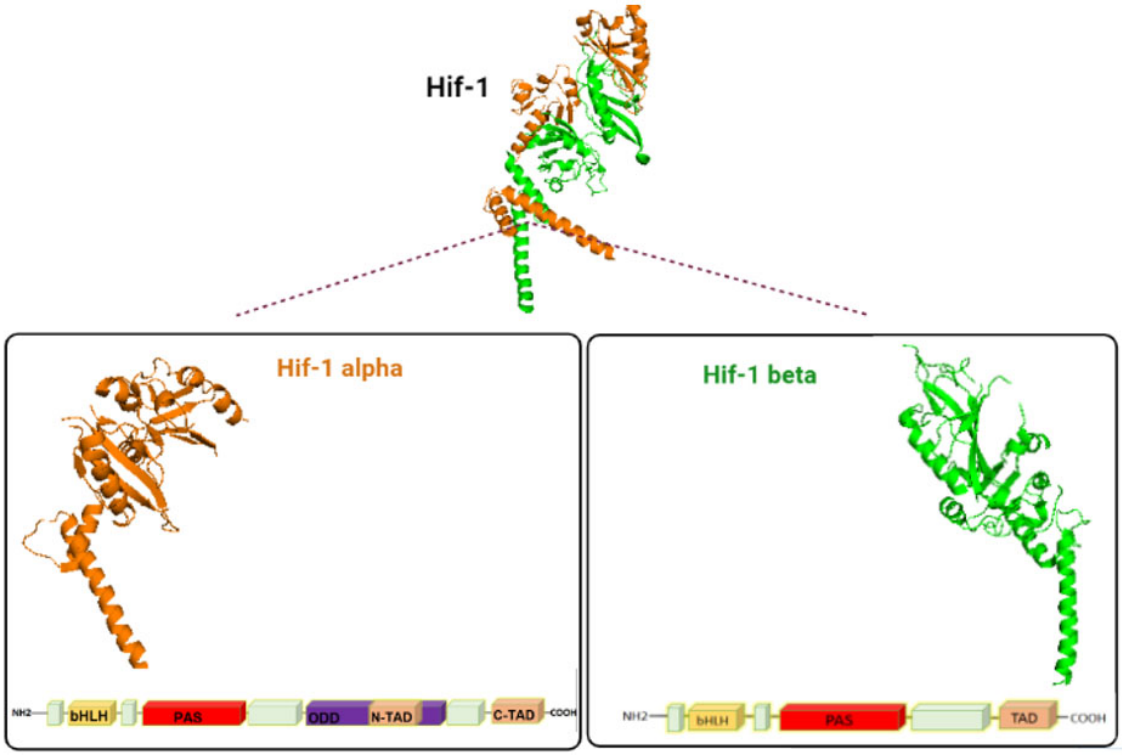

Figure 2. Human HIF-1 quaternary structural modeling (HIF-1/complex) in three dimensions

Chain A is indicated in orange next to the subunit, while chain B is indicated in green next to the subunit (HIF1). The structures of each individual chain are shown in boxes, along with illustrative protein domains. The biorender, a web-based application, has been utilized for the Figure design

3.1 Oxygen-related regulation of HIF-1α

Oxygen-related regulation of HIF-1α can be performed through both pVHL-related and pVHL-independent pathways.

3.1.1 *VHL-related pathway*

VHL is involved in a process that negatively regulates the HIF-1α protein production under normal oxygen pressure.[44,45] It was discovered that the proline residue in the LXXLAP motif of ODD served as an excellent substrate for the activity of PHD enzymes.[46] These enzymes are dependent on 2-oxoglutarate and require ascorbate, iron cofactors, and oxygen for their hydroxylation action. Therefore, PHD enzymes hydroxylate proline residues only when an adequate supply of oxygen is present.[46] Moreover, acetyltransferase arrest-defective-1 (ARD-1) may acetylate lysine residue in the ODD (K532) enhancing the binding of pVHL and further promoting HIF-1α degradation.[47,48] While ARD-1 activity is not dependent on the presence of oxygen, its expression is reduced in hypoxia.[47] As a result, hydroxylated and acetylated HIF-1α is identified by the VHL E3 ubiquitin ligase complex, which results in polyubiquitination and subsequent degradation by the proteasome.[49] In contrast, under hypoxic conditions, the hydroxylation and acetylation of HIF-1α are inhibited, stabilizing its structure. This allows HIF-1α to accumulate and translocate to the nucleus, where it initiates hypoxic gene transcription.

3.1.2 *VHL-independent pathway*

HIF-1α transactivation is regulated by another oxygen-dependent mechanism that reduces its activity under normal oxygen levels. This process occurs independently of the VHL protein and involves specific post-translational modifications in the HIF-1α transactivation domain. The coordinated binding of the HIF-1α C-TAD domain and CBP/p300 coactivators triggers the transcriptional activation of HIF-1α, leading to the transcription of target genes. Under normal oxygen levels, the oxygen-dependent asparaginyl hydroxylase factor inhibiting HIF-1 (FIH-1), hydroxylates the HIF-1α asparagine residue (N803) in the C-TAD. This prevents the interaction with p300/CBP coactivators, suppressing the transcription initiation complex and reducing HIF-1α-mediated gene transcription.[37,50–52] In contrast, hypoxic conditions inhibit the hydroxylation of N803 mediated by FIH-1, allowing the C-TAD to interact with CBP/p300 and activate transcription of target genes.[37,51–53] In summary, the regulation of HIF-1α by oxygen involves two pathways: VHL-dependent control of protein stability and VHL-independent control of transcrip-

tional activity. This mechanism ensures accurate regulation of the hypoxic response. The schematic diagram elucidating the HIF-1α regulatory pathway under both normoxic and hypoxic conditions can be found in Figure 3.

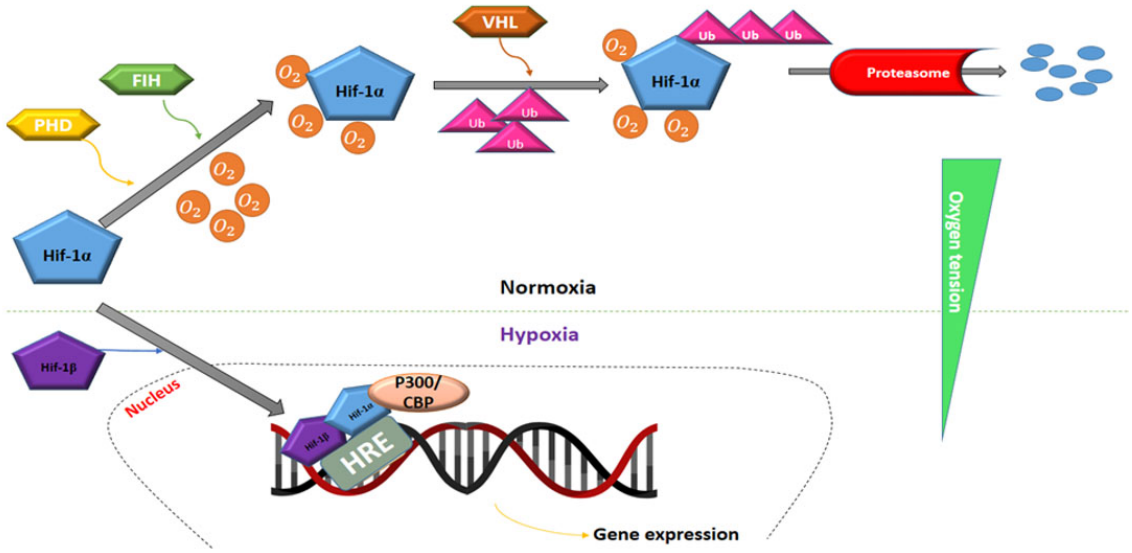

Figure 3. Regulation of HIF-1α stability and transcriptional activity by oxygen-dependent enzymes

In normoxia, enzymes such as PHD and FIH are actively engaged. These enzymes post-translationally modify HIF-1α, thereby inhibiting its capacity to activate target genes. Under hypoxia, enzyme inhibition stabilizes HIF-1α, which dimerizes with HIF-1β and recruits coactivators p300 and CBP. The active complex then moves to the nucleus to bind HREs and activate target genes. PHD = prolyl-hydroxylases Domain enzymes; FIH = factor-inhibiting; = HIF-1α = Hypoxia-Inducible Factor 1-alpha; HIF-1β = Hypoxia-Inducible Factor 1-beta; CBP = CREB-Binding Protein; HREs = hypoxia-response elements. The biorender, a web-based application, has been utilized for the Figure design

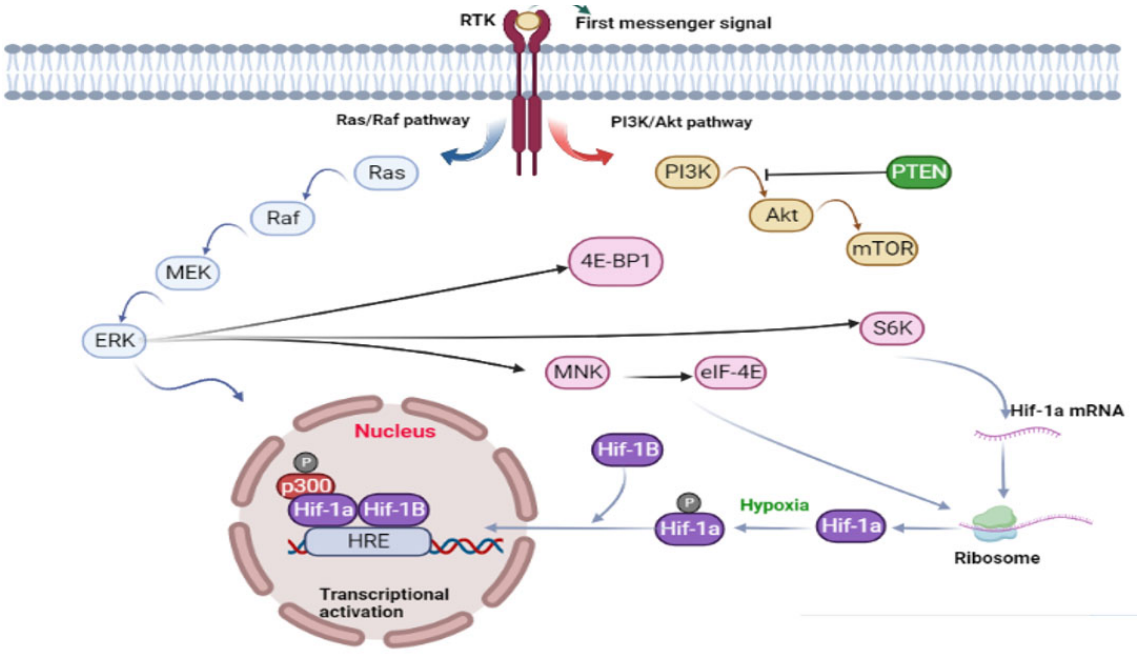

Figure 4. HIF-1 regulation by oxygen-independent mechanisms

First messenger signals (i.e., growth factors and cytokines) activate HIF-1 via the PI3K/Akt (brown) and MAPK signaling pathways (blue); The biorender, a web-based application, has been utilized for the Figure design

3.2 Oxygen independent regulation of HIF-1α pathways

HIF-1α stability is primarily regulated through oxygen-dependent pathways; however, other mechanisms also play a role in controlling its stability, production, and transcriptional activity. Various growth factors, cytokines, and signaling molecules can independently induce HIF-1α expression and activity, regardless of oxygen levels. The oxygen-independent regulation of HIF-1α mainly involves key intracellular signaling pathways, including the PI3K/Akt/mTOR signaling cascade and the MAPK/ERK signaling pathway (see Figure 4).

3.2.1 *PI3K/Akt/mTOR signaling cascade*

Numerous biological processes, including cell survival, proliferation, metabolism, neural function, motility, and cancer development, are regulated by the PI3K/Akt signaling system.[54] PI3K is a member of a phospholipid kinase family that is defined by its capacity to phosphorylate the 3'-OH group of the inositol in inositol phospholipids in the cell membrane.[55,56] The Class I and Class II are two categories for PI3Ks. Class I PI3Ks transform phosphatidylinositol 4,5-bisphosphate (PIP2) into the second messenger phosphatidylinositol 3,4,5-trisphosphate (PIP3).[57] PIP3 plays a crucial role in regulating various physiological processes that are downstream of PI3K signaling through its specific interactions with Akt, a serine/threonine kinase that contains a PH domain.[58,59] Therefore, the PI3K/Akt signaling pathway primarily depends on Akt as the key effector kinase, which mediates cellular responses by phosphorylating several important downstream targets.[60] One crucial downstream target of Akt is the mechanistic target of rapamycin (mTOR), which senses hypoxic conditions and regulates glycogen metabolism, protein synthesis, and cell cycle progression through phosphorylation of key substrates such as eukaryotic translation initiation factor 4E-binding protein 1 (4E-BP1) and ribosomal protein S6 kinase (S6K).[61] Additionally, mTOR is an upstream modulator of HIF-1α activation.[62,63] It was indicated that both HIF-1α and p-Akt levels rise in response to hypoxia. So, the PI3K/Akt pathway may regulate HIF-1α and affect its protein level.[64–66] Furthermore, the PI3K/Akt signaling pathway is inhibited by several negative factors such as phosphatase and tensin homolog (PTEN). PTEN is a lipid phosphatase that inhibits the PI3K/Akt signaling pathway via dephosphorylation of PIP-3 to PIP-2, preventing the production of p-Akt.[67] Studies have indicated that the upregulation of positive regulators like receptor tyrosine kinases (RTKs)[68] and Ras[68] or the downregulation of negative regulators like PTEN and tuberous sclerosis complex proteins (TSC 1 or 2) result in increased HIF-1α activity through sustained PI3K/Akt signaling.[69]

3.2.2 *MAPK/ERK signaling pathway*

The mitogen-activated protein kinase (MAPK) signaling pathways create a complex system that governs numerous physiological functions, including cell development, differentiation, and programmed cell death.[70] Among the mammalian MAPK subfamilies, extracellular signal-regulated kinases (ERK), c-Jun N-terminal kinases (JNK), and p38 kinases each contribute to distinct signaling pathways.[71] Among these, the Ras/Raf/MEK/ERK (or ERK1/2) pathway is the primary cascade transducing mitogenic and growth factor signals. Members of the Ras family including K-Ras, H-Ras, and N-Ras essentially deliver extracellular signals into cells. Various growth factors commonly initiate activation of Ras through most notably receptor tyrosine kinases (RTKs), and additional upstream activators include G-protein coupled receptors (GPCRs), cytokine receptors and integrins. In this cascade, GTP-bound active Ras recruits Raf isoforms (A-Raf, B-Raf, C-Raf) to the plasma membrane, triggering phosphorylation and activation of MEK1/2. MEK, a dual-specificity kinase, phosphorylates ERK1/2 on both threonine and tyrosine residues within a conserved activation loop.[72–76] Once activated, ERK translocates to the nucleus to phosphorylate various TFs, thereby modulating gene expression.[77] For instance, 4E-BP1 and MAP kinase-interacting kinase (MNK) are phosphorylated by activated ERK. MNK directly phosphorylates eukaryotic initiation factor 4E (eIF-4E).[78,79] These events collectively enhance translation of HIF-1α mRNA. Moreover, ERK regulates both the transcriptional activation of HIF-1α and its functional activity by phosphorylating CBP/p300, promoting the formation of the HIF-1α/p300 transcriptional complex.[78,80]

4. ANGIOGENESIS AND CELLULAR TARGETS OF HIF-1α IN TUMORS

Angiogenesis is a critical process that enables tumors to overcome limitations of oxygen and nutrient deficiency as they grow. The initiation and maintenance of neoangiogenesis are driven by an "angiogenic switch," where pro-angiogenic factors overcome inhibitory mechanisms, allowing tumor expansion.[81] HIF-1α plays a central role in orchestrating this process by regulating a wide array of genes involved in vascular remodeling and endothelial cell (EC) behavior. Under hypoxic conditions, HIF-1α directly upregulates key angiogenic factors such as vascular endothelial growth factor-A (VEGF-A), platelet-derived growth factor B (PDGF-B), angiopoietins (ANGPT1, ANGPT2), and matrix metalloproteinases (MMPs), as well as their receptors (FLT-1, KDR/FLK-1, TIE-2). VEGF-A, a potent mitogen for ECs, drives proliferation, migration, and survival of these cells, thereby facilitating new vessel sprouting and capillary forma-

tion.[82,83] HIF-1α impacts nearly every step of angiogenesis: it stimulates ECs proliferation through cell cycle gene regulation, promotes extracellular matrix degradation via MMP induction, and enhances EC adhesion and migration by regulating integrins and other adhesion molecules.[84]

Importantly, ECs are major targets affected by HIF-1α in the tumor microenvironment. HIF-1α influences crosstalk between ECs and other stromal components, including macrophages, which contribute to angiogenesis and vascular remodeling through paracrine signaling pathways.[85] While HIF-1α enhances EC proliferation and tube formation, it does not directly induce endothelial differentiation from progenitor or mesenchymal cells, indicating its role is primarily regulatory rather than lineage-directing.[86] The interplay between hypoxia, HIF-1α, ECs, and other components of the tumor microenvironment underscores the complexity of targeting angiogenesis therapeutically. While VEGF-A is a prominent mediator, other factors including placental growth factor (PlGF), PDGF, and angiopoietins contribute to vessel maturation and stability, often regulated in part by HIF-2α.[84]

4.1 Role of pVHL in angiogenesis

As mentioned above, normal variations in tissue oxygen levels control VEGF-A production. VHL can physically bind to the proline-hydroxylated form of HIF-1α in normoxic conditions, causing proteasome-mediated degradation of the protein.[87–90] In hypoxic tumor microenvironments, the hydroxylation of HIF-1α is inhibited, preventing pVHL binding and consequent degradation of HIF-1α. As a result, stabilized HIF-1α translocates to the nucleus and activates transcription of target genes, including VEGF-A. This transcriptional activation drives the secretion of VEGF-A by tumor cells, which binds to receptors on ECs to promote angiogenesis, sustain tumor growth, and facilitate metastasis.[91,92] Importantly, vascular tumors such as renal cell carcinoma (RCC), phaeochromocytomas, and central nervous system (CNS) hemangioblastomas that overproduce VEGF-A have been shown to have functional inactivation of the VHL protein due to germline mutations.[93] Studies on VHL-deficient RCC cell lines have demonstrated constitutive stabilization of HIF-1α in the absence of functional pVHL, and reintroduction of wild-type VHL restores oxygen-dependent degradation of HIF-1α.[48] This highlights the essential role of pVHL as a key regulator in oxygen sensing and angiogenesis within tumor cells.

4.2 MAPK and PI3K signaling pathways in angiogenesis

Growth factors upregulating the HIF-1α in non-hypoxic conditions by activating protein tyrosine kinases (PTKs). This activation can occur through growth factor binding or mutations that keep PTKs constantly active. Once activated, PTKs trigger signaling pathways, such as PI3K/AKT or MAPK/ERK, leading to increased HIF-1α production, which varies by cell type. The tumor microenvironment influences two pathways by promoting the selection of cells with somatic mutations that activate oncogenes and inactivate tumor suppressor genes (TSGs), thereby preventing apoptosis and allowing cells to progress uncontrollably through the cell cycle. Activation of PI3K leads to the phosphorylation of AKT, which subsequently activates mTOR, primarily mTORC1 and mTORC2. mTOR then phosphorylates two key downstream targets, p70 ribosomal S6 kinase (P70S6K) and eukaryotic translation initiation factor 4E-binding protein 1 (4E-BP1), resulting in increased translation of the HIF-1α protein. 4E-BP1 Phosphorylation interrupts its inhibitory association with eIF-4E while phosphorylation of p70S6K causes the phosphorylation of its substrate, the rpS6,[94] and these phosphorylation processes eventually lead to improved HIF-1α mRNA translation to protein. The mTORC1 and mTORC2 are separate signaling complexes that consist of mTOR. The mTORC1 is responsible for phosphorylating both 4E-BP1 and p70S6K, whereas the mTORC2 phosphorylates AKT. Growth factors such as IGF-1, IGF-2, FGF-2, and EGF, along with the autocrine activation of IGF-1 and IGF-2 receptors, stimulate the transcription of HIF-1α[95,96] and translation through activation both of the MAPK and PI3K/AKT pathways.[95,97] HIF-1 is a key transcriptional activator of IGF-2, a gene that shows significantly increased transcription levels in colon cancer.[98] In breast cancer, the human epidermal growth factor receptor 2 (HER-2) directly activates the PI3K/AKT pathway, which subsequently increases levels of HIF-1α and VEGF-A, promoting angiogenesis.[99] PTEN inactivation in glioblastoma and prostate carcinoma similarly increases HIF-1α levels. Additionally, the activation of the RAS/RAF/MEK/ERK pathway causes ERK1/2 to phosphorylate eIF4E, enhancing its activity and further boosting HIF-1α translation.[100,101] Together, the MAPK and PI3K pathways coordinate angiogenesis by modulating HIF-1α through various molecular mechanisms. This integration of extracellular signals promotes tumor vascularization and growth.

4.3 Other factors in angiogenesis

In addition to PTEN and VHL, loss-of-function mutations in the tumor suppressor p53 contribute to elevated HIF-1α expression. Normally, p53 promotes the degradation of HIF-1α by activating the E3 ubiquitin ligase Mdm2, which targets HIF-1α for proteasomal degradation.[102] This degradation is antagonized by COP9 signalosome subunit 5 (CSN5), which directly binds to the ODD of HIF-1α, competing with p53

for binding. This interaction promotes HIF-1α stabilization and enhances its transcriptional activity by preventing p53-mediated degradation, especially under hypoxic conditions.[103]

Oncogenic activation also significantly regulates HIF-1α and VEGF-A, consequently promoting tumor angiogenesis. In pancreatic cancer, the overexpression of the metastasis-associated protein MTA1 is associated with elevated levels of HIF-1α and VEGF-A, which contribute to tumor growth and metastasis. Similarly, the V-Src, an oncogenic form of the Src kinase, upregulates HIF-1α independently of its transactivation domain, thereby enhancing the transcription of angiogenic targets such as VEGF-A.[104] This effect results from the cooperative activation of both the HIF-1α pathway and the PI3K/AKT signaling pathway, which together enhance the expression of target genes involved in tumor angiogenesis and progression.[105]

5. Inhibition of HIF-1α and its signaling pathways: Progress and clinical challenges

Targeting HIF-1α and its related signaling pathways, including MAPK/ERK and PI3K/Akt/mTOR, presents a promising strategy for cancer therapy. However, despite extensive preclinical research over the last decades and the identification of several compounds that inhibit HIF-1α activity in vitro and in animal models (see Table 1), the transition of these inhibitors into effective clinical anti-cancer treatments has largely been unsuccessful. The early-stage inhibitors, which were developed and tested in the early 2000s, did not progress due to several issues, including a lack of specificity, poor pharmacokinetics, toxicity, and an incomplete understanding of the complex roles that HIFs play in tumor biology. Additionally, the tumor microenvironment, characterized by heterogeneous hypoxia, high interstitial pressure, and intricate metabolic adaptations, creates significant barriers to effective drug delivery and therapeutic success. Importantly, the lack of rigorous quantitative analysis and standardized metrics in preclinical studies of HIF-1α inhibitors may contribute to the translational failure observed clinically. Effective tumor suppression requires a clear understanding of the extent to which compounds inhibit cancer cell proliferation, migration, and survival. Recent studies emphasize that statistical significance alone does not guarantee clinical relevance; rather, inhibitors demonstrating high levels of inhibition (e.g., > 70%-90%) in physiologically relevant models are more likely to have translational potential. For example, a 2024 study employing chitosan nanoparticle-mediated delivery of HIF-1α siRNA in triple-negative breast cancer models reported over 80% inhibition of tumor growth and proliferation with robust statistical validation ($p < .0001$) compared to controls, highlighting the importance of quantitative effect size alongside significance in evaluating therapeutic promise.[106] Other investigations in colon and thyroid cancer models similarly demonstrated quantitatively substantial reductions in tumor volume and angiogenesis following targeted HIF-1α suppression, reinforcing that both magnitude and reproducibility of effects must inform clinical candidate selection.[107,108] Establishing standardized quantitative benchmarks and integrating comprehensive dose-response and time-course analyses in preclinical workflows are therefore essential to accurately gauge inhibitor efficacy and prioritize candidates with genuine clinical utility.

5.1 Molecules inhibiting the HIF-1α

Numerous small compounds have been identified as inhibitors of HIF-1α, acting through diverse mechanisms. Analogues of Camptothecin (CPTs), which have an inhibitory effect against topoisomerase I (TopI), can prevent the accumulation of HIF-1α protein in hypoxic U251 human glioma cells. By stabilizing TopI-DNA cleavage complexes, CPT induces double-strand DNA breaks, indirectly disrupting HIF-1α synthesis.[109] Topotecan (Hycamtin-TPT, 3a), a CPT that was initially found in a high-throughput screening (HTS) platform at the National Cancer Institute (NCI), was used to evaluate inhibition of HIF-1 transcriptional activity in vitro and subsequently validated as an inhibitor of HIF-1 transcriptional activity in vitro.[110] Various compounds function by directly inhibiting the transcription of the HIF1A gene. One specific anti-sense oligonucleotide, referred to as EZN-2698, acts as an RNA antagonist, particularly binding to and suppressing the transcription of HIF-1α and its target genes. Research conducted in vitro using human glioblastoma and prostate cancer cell lines, as well as in vivo studies, has demonstrated that EZN-2698 reduces HIF-1α levels and slows down tumor growth.[111] However, early clinical development of EZN-2698 was limited to Phase I trials focused on safety and pharmacokinetics in patients with advanced solid tumors.[111] Aminoflavone (AF) is another compound that lowers HIF-1α transcription. While it is known to be an aryl hydrocarbon receptor (AhR) ligand, the precise mechanism by which it inhibits HIF-1α expression remains unclear.[112] Recently, acriflavin was identified via in vitro screening assays as a novel inhibitor of HIF-1α. By attaching directly to the PAS-B domain of HIF-1α and HIF-2α, acriflavin prevents HIF-1 dimerization. Its favorable safety profile combined with its unique capacity to bind to both HIF-1α and HIF-2α, positions it as a promising candidate for clinical testing, particularly in cancers that are predominantly driven by elevated activity of HIF-1α and HIF-2α.[113]

Table 1. Inhibitors of HIF-1α and PI3K/Akt/mTOR and MAPK/ERK signaling pathways

Inhibitor	Target molecule	Effect	Cancer of study	Reference
HIF-1α inhibition				
Benzopyranyl triazole	HIF-1α	↑ HIF-1α hydroxylation	Lung carcinoma	[151]
CRLX-101		↓ HIF-1α protein accumulation	Solid tumors	[152]
EZN-2698		↓ HIF-1α protein expression and transcriptional activity	Prostate cancer	[111]
NNC 55–0396		↓ HIF-1α protein expression/translation ↑ HIF-1α hydroxylation	Glioblastoma	[153]
MPT0G157		↑ HIF-1α degradation	Colorectal cancer	[154]
LBH589		↑ HIF-1α degradation	Glioblastoma	[155]
PI3K/Akt/mTOR pathway inhibition				
Wortmannin	PI3K	↓ Translation of HIF-1α mRNA	Prostate cancer	[156]
LY294002		↓ Translation of HIF-1α mRNA	Prostate cancer	[156]
FARA-A	Akt	↓ HIF-1α and VEGF expression	Ovarian cancer	[121]
Sirolimus	mTOR	↓ HIF-1α translation	Solid tumors	[127]
RAD001		↓ HIF-1α and GLUT-1 translation	Prostate cancer	[127]
Rapamycin		↓ HIF-1α translation	Prostate cancer	[127]
Ras/Raf/MEK/ERK/MAPK pathway inhibition				
Tipifarnib	Ras	↓ Cellular HIF-1α levels	Glioblastoma	[157]
Vemurafenib (PLX4032)	Raf	Inhibition of the signaling pathway, No effect on the protein expression levels of HIF-1α	Melanoma cancer	[158]
Encorafenib (LGX818)		Inhibition of the signaling pathway and reduce HIF-1α level	Pancreas, melanoma, and colorectal cancer	[159]
Ulixertinib (BVD-523)	ERK	Inhibition of ERK1 and ERK2	Solid tumors	[160]
Trametinib (GSK1120212)	MEK	Inhibition of MEK1 and MEK2	Melanoma, colorectal cancer, and leukemia	[161]

5.2 Oxygen-independent signaling pathways and their therapeutic targeting

RTKs initiate pivotal signaling cascades, predominantly the PI3K/AKT/mTOR and RAS/RAF/MEK/ERK pathways, which are fundamental to tumorigenesis through their roles in promoting cellular growth, survival, and metastasis.[114] In the following, we review critical molecular regulators that modulate these pathways and their therapeutic implications.

5.2.1 *MAPK/ERK pathway-targeting therapies*

The RAS/RAF/MEK/ERK (MAPK) pathway is vital in cancer development and frequently altered in human cancers. RAS acts as a key switch that activates RAF kinases in response to signals from RTKs, stimulating MEK and ERK to promote cellular proliferation and transformation. According to studies, BAY 43-9006 (sorafenib) is a RAF kinase inhibitor that targets both RTKs and RAF/MEK/ERK pathways.[115] BAY 43-9006 inhibits phosphorylation of ERK1/2 and is regarded as a typical MAPK signaling pathway blocker in various tumor cell lines, but does not affect the suppression of the protein kinase B (AKT) pathway.[116] Studies showed that BAY 43-9006 also exerts potent anti-angiogenic effects by inhibiting RTKs such as vascular endothelial growth factor receptors 2 and 3 (VEGFR2 and VEGFR3), platelet-derived growth factor receptor (PDGFR), Flt3, and c-KIT from becoming autophosphorylated. Additionally, research has demonstrated that BAY 43-9006 inhibits the phosphorylation of ERK1/2 and VEGFR-2 autophosphorylation in human umbilical vein ECs.[116] Since VEGF-A stimulates angiogenesis, which involves RAS activation, VEGF-A signaling can be suppressed at the level of the VEGFR2 receptor and fur-

ther reduced through the inhibition of the RAF/MEK/ERK signaling pathway.[115] Additional MAPK signaling pathway suppressors include SB 203580 and PD 98059, which target distinct components of this signaling cascade. SB 203580 is a pyridinyl imidazole compound that selectively inhibits p38 MAP kinase (also called SAPK2a), a MAPK family member activated by cellular stress, bacterial lipopolysaccharide (LPS), and proinflammatory cytokines.[117] PD 98059 is a specific inhibitor of MEK1 activation, a critical kinase that is activated by growth factors and phorbol esters, promoting tumor progression.[118]

5.2.2 *PI3K pathway-targeting therapies*

In addition to MAPK/ERK signaling pathway inhibitors, several agents can inhibit the PI3K/Akt pathway to downregulate HIF-1α. LY294002 is a PI3K synthetic suppressor that decreases the balance of HIF-1α in vitro, resulting in a decrease in the transcription of HIF-1α target genes.[119,120] However, due to its restricted therapeutic utility, LY294002 is not recommended for clinical use. The nucleoside analog, 9-b-D-arabinofuranosyl-2-fluoroadenine (FARA-A), induces DNA damage during the S-phase of the cell cycle. By inhibiting Akt activation, FARA-A decreases the production of VEGF-A and HIF-1α in ovarian cancer cells, although it does not influence cell viability.[121] Semaxanib® is a potent and precise inhibitor of the VEGFR. This compound enhances the antiangiogenic effects of radiotherapy.[122,123] Clinical trials have investigated Semaxanib both as a standalone treatment and in combination with chemotherapy. In ovarian cancer cell lines, it reduces HIF-1α protein levels and VEGF-A mRNA expression through the PI3K/Akt pathway.[124]

In vivo evidence indicates that mTOR is essential for the full process of Akt-dependent activation of HIF-1α.[125] In hypoxic cancer cells, the mTOR inhibitor rapamycin reduces the stability and transcriptional activity of HIF-1α[61] by impairment of mTOR-mediated signaling. Moreover, mTOR is inhibited by the TSC2 tumor suppressor, and overexpression of HIF-1 occurs in TSC2-deficient cells due to elevated mTOR activity. Treatment with rapamycin restores HIF-1α levels to normal in cells lacking TSC2.[126] For the treatment of solid tumors, mTOR inhibitors such as temsirolimus (Torisels-CCI-779), everolimus (RAD001, Afinitors), and sirolimus (Rapamycins) have been studied extensively. While early preclinical studies utilized tumor cell lines and mouse models,[127] subsequent clinical trials have focused primarily on temsirolimus and everolimus rather than sirolimus for cancer treatment. Notably, everolimus has received FDA approval for hormone receptor-positive, HER2-negative advanced breast cancer, often in combination therapies, supporting its clinical relevance in this setting.[128,129] Furthermore, the transgenic Akt-driven prostate cancer model treated with RAD001 showed reduced transcription of HIF-1α and lower expression of downstream targets such as Glucose transporter 1 (GLUT-1).[125] Temsirolimus is FDA approved for RCC but has limited direct application in breast cancer.[130,131]

6. Challenges and lessons from targeting HIF-1α in cancer therapy

Despite the longstanding interest in HIF-1α as a pivotal regulator of the hypoxic tumor microenvironment, accumulating evidence suggests that its role and expression in human cancers may be more nuanced and context-dependent than widely assumed. Analysis from the Human Protein Atlas, a comprehensive resource of immunostained human tissues, indicates variable and at times limited HIF-1α protein expression across many tumor types, challenging the simplistic view of its ubiquitous and high-level presence in human cancers.[132] Moreover, recent studies have revealed discrepancies in reports of HIF-1α expression correlating with tumor aggressiveness or stage, with some aggressive tumors even showing reduced HIF-1α protein levels compared to less advanced disease.[133]

Another critical limitation arises from the prevalent use of in vitro models to study hypoxia, where standard cell culture conditions expose cells to ambient air (approximately 21% oxygen), far exceeding physiological tissue oxygen levels. In vivo, even oxygen-rich organs like the lung typically exhibit a maximum of around 9% oxygen, while tumor regions may vary between 1%–2% or display spatial heterogeneity.[134] This discrepancy casts doubt on the relevance of many in vitro hypoxia experiments that compare 'hypoxic' conditions to hyperoxic controls, potentially leading to misleading conclusions and overestimation of therapeutic responses.

Pharmacologically, existing HIF-1α inhibitors suffer from insufficient affinity and specificity for effective in vivo targeting, limiting their ability to achieve durable inhibition in tumor tissues.[134] Compounding this is the considerable challenge that many inhibitors fail to adequately penetrate the tumor microenvironment (TME), where dense stroma, abnormal vasculature, and high interstitial pressure impede drug delivery. This "push-back" from the TME is often overlooked in preclinical evaluations, yet crucially affects clinical outcomes. Toxicity also remains a significant barrier; several compounds tested in clinical trials exhibited unacceptable adverse effect profiles that precluded further development. Collectively, these factors contribute to the disappointing lack of clinically approved HIF-1α inhibitors despite decades of research and investment.

These considerations highlight that targeting hypoxia and HIF-1α in cancer is more complex than initial models suggested. Going forward, the development of inhibitors must incorporate improved tumor-targeting strategies that overcome microenvironmental barriers, utilize clinically relevant oxygen models in vitro, and apply patient stratification to identify subsets likely to benefit from HIF pathway modulation. While hypoxia remains an essential hallmark of cancer, the nuanced biology and practical challenges warrant a more tempered and rational approach to drug development in this area.

Recent progress has shifted the focus towards more selective second-generation HIF inhibitors, particularly those targeting HIF-2α. These inhibitors have shown promising clinical benefits in specific cancers, such as clear cell renal cell carcinoma.[135] For instance, Belzutifan, a first-in-class oral HIF-2α inhibitor, has demonstrated improved progression-free survival in patients with advanced kidney cancer and has been approved for treating cancers associated with von Hippel-Lindau disease.[136] This breakthrough underscores the importance of selectively targeting HIF isoforms and tailoring therapies to the specific contexts of tumors. Similarly, Casdatifan (AIT), a next-generation selective HIF-2α inhibitor, has shown best-in-class potential with encouraging monotherapy efficacy and tolerability in patients with metastatic clear cell renal cell carcinoma as evidenced in recent Phase 1/1b trials.[137] Casdatifan is currently under advanced clinical investigation, including combination therapy trials with cabozantinib, aiming to improve treatment outcomes in heavily pretreated patient populations.[138]

7. Future implications

As tumor cells grow rapidly and form large solid masses, hypoxia often occurs in various solid tumors. Tumor cells respond to hypoxic stress by selectively upregulating heat shock proteins (HSPs). Hypoxia significantly affects various HSPs, thereby contributing to tumor progression.[139–142] In hypoxic area, tumor cells start to adapt to the low oxygen tension by turning on a number of survival mechanisms. The most well-known strategy used by hypoxic cells in this challenging microenvironment is activation of HIFs.[143–146] Given the multifaceted role of HIF-1 in promoting tumor growth and metastasis, targeting this factor has long been considered a promising cancer treatment approach. Indeed, a number of investigational drugs have been developed to inhibit HIF-1α synthesis or activity by disrupting key signaling pathways. Some approved drugs, such as Vorinostat, an HDAC inhibitor, also indirectly impact HIF-1α expression. However, despite considerable research efforts and substantial investment over the past decades, no drug specifically targeting HIF-1α has yet received clinical approval for cancer therapy. Early promising in vitro and in vivo results have not translated into effective clinical outcomes. This persistent clinical translation gap calls for a reconsideration of hypoxia and HIF signaling as viable therapeutic targets. Some progress has been made with more selective second-generation HIF inhibitors, particularly those targeting the HIF-2α isoform, which has distinct roles in specific tumor types like clear cell renal carcinoma. In conclusion, while hypoxia remains an attractive target in cancer therapy, the failures of HIF-1α inhibitors in clinical settings highlight the complexity of translating molecular insights into effective drugs. A critical analysis of past failures and emerging approaches provides a roadmap for the rational development of future anti-HIF therapeutics.[147, 150]

8. Conclusion

Hypoxia is a critical feature of solid tumors that drives malignant progression. The cellular response to hypoxia is carefully regulated by HIF, which promotes tumor survival and growth through several processes, including stimulating angiogenesis, enhancing glycolytic metabolism, and inhibiting apoptosis. Additionally, HIF interacts with various oncogenic signaling pathways, including those influenced by p53, highlighting its significant role in cancer delevopment. Interestingly, many compounds known to inhibit the HIF pathway have demonstrated strong anti-cancer efficacy in clinical trials. However, the challenge of translating selective HIF inhibitors into clinical practice remains substantial. Future research is crucial to clarify the mechanisms of HIF signaling in cancer entirely and to apply these insights into effective therapeutic strategies.

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Authors contributions

BHA and AB contributed equally and are co-first authors. BHA and AB contributed to the study conception. BHA, FP, MJRG, and ST did the search for the published papers, and prepared the figures. BHA wrote the first draft of the manuscript. AB revised the first draft. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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