Regulatory networks of HIFs in tumor-infiltrating immune cells: From molecular mechanisms to therapeutic implications (Review)

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Received July 29, 2025; Accepted November 20, 2025

DOI: 10.3892/ijo.2026.5845

Abstract. Hypoxic tumor microenvironment (TME) is a common occurrence in the development of solid tumors, which activates hypoxia-inducible factors (HIFs) and their downstream signaling pathways in cancer cells to facilitate tumor progression and immune escape. However, among the various immune cells that constitute innate and adaptive immune systems, HIFs have a more intricate function; moreover, different isoforms of HIFs play different functions under spatial and temporal conditions. HIFs are conducive to the adaptation of various immune cells to the hypoxic TME. The stability of HIF-α can regulate metabolism and directly regulate the expression of immune genes. Additionally, the activation of HIF signaling may also inhibit the development of immune cells in some tumor environments, affecting the antigen recognition and killing processes to assist cancer cells in immune escape. Therefore, understanding the relationship between HIF signaling and immune cells more comprehensively may yield substantial benefits for the immunotherapy of various types of cancer. The present study reviewed the role of HIFs in immunity, including their role in T cells, B cells, macrophages, neutrophils, dendritic cells and natural killer cells. It also discussed the effectiveness of HIF targeted therapy in clinical application, the challenges associated with it and the development of a precise targeting drug delivery system. The present review may help researchers comprehend the tumor immune process in a hypoxic microenvironment. It aimed to offer novel strategies for cancer immunotherapy and prolonging the overall survival of patients.

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Abbreviations: HIFs, hypoxia-inducible factors; TME, tumor microenvironment; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; TGF-β, transforming growth factor-β; IL-10, interleukin 10; PI3K, phosphoinositide 3-kinase; P-gp, P-glycoprotein; PHD, prolyl hydroxylase; VHL, von Hippel-Lindau; NK cells, natural killer cells; D-2HG, D-2-hydroxyglutarate; TEBs, tumor-educated B cells; EVs, extracellular vesicles; DCs, dendritic cells; LDHA/LDHB, lactate dehydrogenase A/B; STING, stimulator of interferon genes; NF-κB, nuclear factor κ-light-chain-enhancer of activated B cells; ADAM10, A disintegrin and metalloproteinase domain 10; MICA/B, major histocompatibility complex class I chain-related gene A/B; ccRCC, clear cell renal cell carcinoma; NETs, neutrophil extracellular traps; OCT-3/4, octamer-binding transcription factor 3/4; DLBCL, diffuse large B cell lymphoma; STAT3, signal transducer and activator of transcription 3; TAMs, tumor-associated macrophages; TNF-α, tumor necrosis factor-α; IL-12/P40, interleukin 12 p40 subunit; RORγt, RAR-related orphan receptor γt; Foxp3, forkhead box P3; VEGF, vascular endothelial growth factor; GLUT1, glucose transporter 1; BNIP3, Bcl2 interacting protein 3; IFN γ, interferon γ; CLL, chronic lymphocytic leukemia; TEEB, transcription factor regulating lysosomal proteins; ATP6V0d2, ATPase H^+ transporting V0 subunit d2

Key words: hypoxia-inducible factor, immune cells; tumor immunity, tumor microenvironment, tumor immune escape

Contents

1. Introduction

The immune system serves as the primary defense mechanism in the body against external pathogens and abnormal

cells; it plays a vital role in identifying and eliminating tumor cells (1). The relationship between tumors and immune function represents a complex and intricate biological network that has emerged as the key focus in research on cancer. Hypoxia is a common characteristic of solid tumors (2). During tumor growth, cancer cells progressively form an immunosuppressive hypoxic tumor microenvironment (TME), which promotes the proliferation and metastasis of tumors by influencing processes such as metabolism, angiogenesis and immune evasion (3). In the TME, critical transcription factors, particularly hypoxia-inducible factors (HIFs) and their downstream signaling pathways, are activated. These signals regulate the differentiation, function and metabolic reprogramming of immune cells, thereby shaping the direction and strength of the tumor immune response. Ultimately, HIFs influence angiogenesis, cell proliferation and invasion in tumors, mediating the progression and development of tumors (4).

Several epidemiological studies have identified a significant correlation between HIFs and greater incidence and mortality in various types of cancer. The two primary HIF isoforms, HIF-1α and HIF-2α, serve as key regulators under hypoxic conditions and play crucial roles in tumor immune evasion by modulating the innate and adaptive immune systems (5). Hypoxia upregulates the transcription and expression of HIF-1α, which subsequently activates the immune checkpoint comprising programmed cell death protein 1 (PD-1) and its ligand PD-L1 (6). This pathway indirectly suppresses the activation and proliferation of T-cells, leading to immune evasion by tumor cells. Similarly, the interaction between CD137 expressed on T cells and its ligand CD137L can activate dendritic cells and macrophages; this, in turn, allows them to recognize and eliminate cancer cells. However, HIF-1α present in tumor cells can prevent this process, causing the tumor cells to escape from adaptive immunity (7,8). Compared with HIF-1α, HIF-2α more prominently induces the expression of genes associated with invasion and stem cell properties, such as matrix metalloproteinases and stem cell factor octamer-binding transcription factor 3/4 (OCT-3/4) (9,10). When these genes are expressed, the invasive and metastatic capabilities of tumor cells are enhanced (11). In clear cell renal cell carcinoma (ccRCC), HIF-2α promotes the secretion of immunosuppressive cytokines such as transforming growth factor-β (TGF-β) and interleukin (IL) 10 by upregulating stem cell factors, thereby fostering an immunosuppressive TME (12).

The induction of HIF-dependent genes not only improves the ability of the tumor to adapt to more hypoxic conditions but also promotes angiogenesis, cell survival, invasion and metastasis in tumors (4). Numerous preclinical and clinical studies have investigated targeted cancer therapeutic strategies aimed at inhibiting or activating HIFs. The methods available for inhibiting the response of HIF-1α to hypoxia include, but are not limited to, small interfering RNA (siRNA) therapy, blocking of the dimerization of HIF-1α and β subunits and the use of anticancer agents that directly inhibit HIF-1α by targeting the PI3K/AKT/HIF-1α pathway (13). However, in clinical trials, HIF-targeted therapeutic techniques have often failed to achieve the desired outcomes and HIF inhibitors are associated with significant dose-limiting side effects. As tumor immunity is complex, deciding whether to target all HIF isoforms or selectively target HIF-1α or HIF-2α requires careful consideration of their distinct functions, as well as the different roles HIFs play across various types of cells. Additionally, hypoxia-induced reduction in pH leads to an acidic TME, which leads to a decrease in the concentration of the drug due to ion trapping, a reduction in the apoptosis of cancer cells and an increase in the activity of multidrug transporter P-glycoprotein (P-gp) (13-15). These factors contribute to HIF-mediated therapeutic failure and/or an increase in tumor drug resistance.

The present review comprehensively examined the mechanisms and effects of HIFs on both innate and adaptive immune systems in the hypoxic TME. It evaluated the potential of HIFs as critical therapeutic targets in cancer treatment and proposed strategies for developing novel HIF inhibitors to systematically combat cancer.

2. Molecular features and functions of HIFs

HIFs is a heterodimeric transcription factor composed of α and β subunits. The α subunit exhibits oxygen-dependent expression, while the β subunit exhibits constitutive expression. A total of three α subunits (HIF-1α, HIF-2α and HIF-3α) and three β subunits (HIF-1β, HIF-2β and HIF-3β, also known as ARNT1, ARNT2 and ARNT3) are known. Although the HIF-β subunit shows excellent stability, the stability of the HIF-α subunit fluctuates in response to changes in oxygen tension, regulated by prolyl hydroxylase (PHD)1, PHD2 and PHD3 (16-18). Under normoxic conditions, oxygen is used by PHDs to hydroxylate two conserved proline residues on the HIF-α subunit. These hydroxylated proline residues are recognized by the Von Hippel-Lindau (VHL) E3 ubiquitin ligase complex, leading to proteasomal degradation of the HIF-α subunit (19). However, under hypoxic conditions, PHDs lack sufficient oxygen as a substrate to perform their dioxygenase function, thereby preventing VHL from recognizing the HIF-α subunit, resulting in its stabilization. As a result, the HIF-α subunit translocates to the nucleus, where it dimerizes with the HIF-β subunit and binds to DNA at hypoxia response elements, thereby driving HIF-dependent transcription (20,21).

Transcriptional targets dependent on HIFs spans numerous biological processes, including angiogenesis, glycolysis, chromatin remodeling, cell cycle regulation and even genes involved in the oxygen-sensing pathway. Through genome-wide analyses of hypoxic transcriptomic responses and HIF binding sites, researchers have found that, in any specific cell type, at least 500-1,000 genes are directly or indirectly regulated by HIFs (22-24). Concerning target genes, HIF-1 and HIF-2 exhibit a degree of specificity. HIF-1 generally induces genes encoding glycolytic enzymes, such as phosphofructokinase and lactate dehydrogenase A (LDHA); those involved in the regulation of pH, such as monocarboxylate transporter 4 and carbonic anhydrase IX and genes that promote apoptosis, such as Bcl2 interacting protein 3 (BNIP3) and Bcl2/Adenovirus interacting protein 3 (BNIP3L/NIX) (11,24). By contrast, HIF-2 generally induces genes associated with invasion processes, such as MMP2 and MMP13 and the stem cell factor OCT-3/4 (11). These two heterodimeric transcription factors may substitute for each other under certain circumstances, besides specifically regulating downstream target genes, HIF-1 and HIF-2 share some common targets, such as

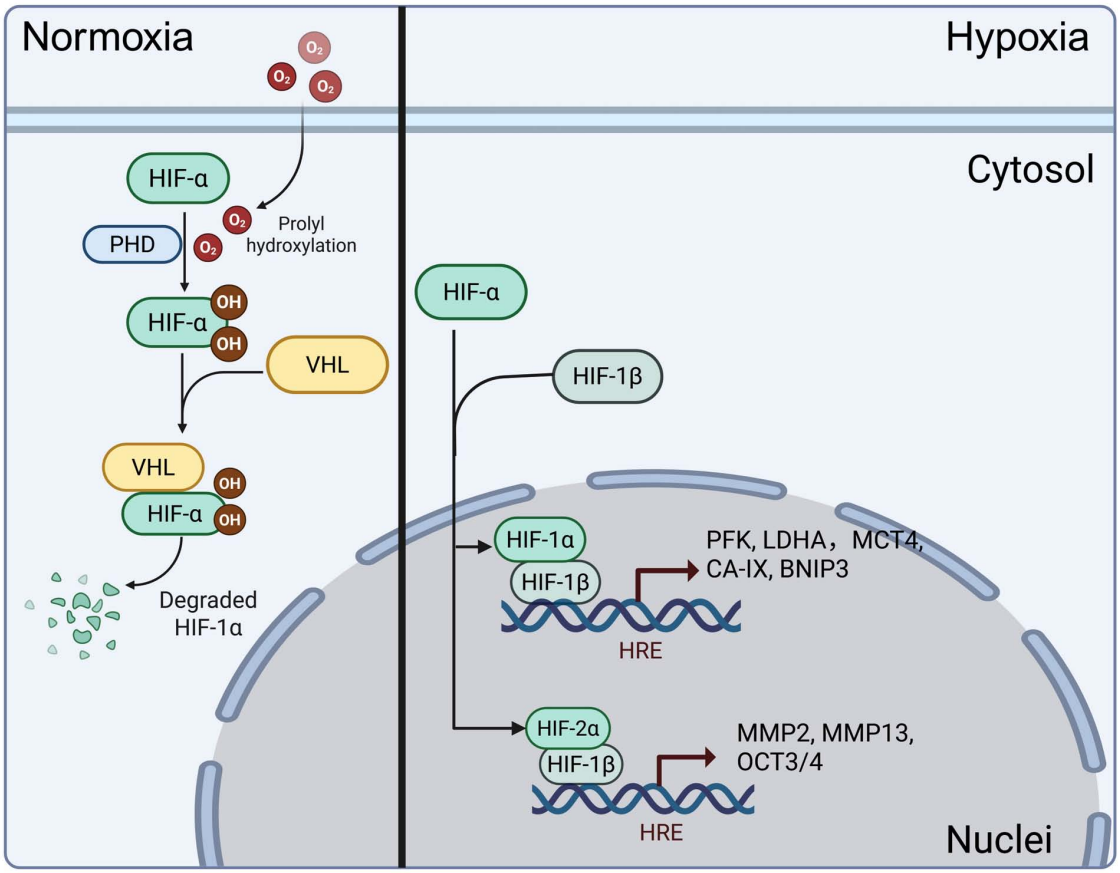


Figure 1. Regulation of HIF Proteins. Under normoxic conditions, the proline residues of HIF-α are hydroxylated by the dioxygenase PHD enzymes. Subsequently, VHL protein binds to the hydroxylated proline sites. The binding of VHL to HIF-α recruits an E3 ubiquitin ligase complex along with E2 ubiquitin-conjugating enzymes, catalyzing the ubiquitination of HIF-α and targeting it for proteasomal degradation. However, under hypoxic conditions, the activity of PHD is inhibited, leading to the stabilization of HIF-α. Stabilized HIF-α dimerizes with HIF-1β, translocates into the nucleus and binds to HREs to stimulate the transcription of target genes. HIF, hypoxia-inducible factor; PHD, prolyl hydroxylase domain VHL, von Hippel-Lindau; HREs, hypoxia response elements; PFK, phosphofructokinase; LDHA, lactate dehydrogenase A; MCT4, monocarboxylate transporter 4; CA-IX, carbonic anhydrase IX; BNIP3, Bcl2 interacting protein 3.

vascular endothelial growth factor A (VEGF-A) and glucose transporter 1 (GLUT1) (25,26). In human tissues, HIF-1α is widely expressed, while HIF-2α, initially identified as Endothelial PAS domain protein 1, was previously considered an endothelial-specific HIF-α isoform (27). However, studies have found that under hypoxic conditions, the expression of HIF-2α is not limited to the vasculature; its transcriptional response is widely activated under prolonged hypoxia, complementing rather than redundantly overlapping with the function of HIF-1α (28,29) (Fig. 1).

3. Orchestrating immune cell fate: Cell-type specific functions of HIFs in the TME

The immune system is a network that operates due to the interaction of lymphoid organs, cells, humoral factors and cytokines. It is divided into nonspecific immunity (innate immunity) and specific immunity (adaptive immunity); the two types of immunity differ in their activation times, the types of immune cells involved and their modes of action (30). HIF-1α and HIF-2α are broadly expressed and detectable in nearly all innate and adaptive immune cell populations. The unique expression patterns of HIF-1α and HIF-2α in immune cells depend on intrinsic and extrinsic factors, with the balance between them contributing to the regulation of overlapping or distinct sets of target genes. Their expression and stabilization in immune cells can be triggered not only by hypoxia but also by other factors associated with pathological stress, such as inflammation, infectious microorganisms and cancer (31-33). HIFs regulate various types of immune processes, enhancing the bactericidal capacity of phagocytes and driving the differentiation of T cells and cytotoxic activity. Additionally, HIF-mediated cellular metabolism is a critical immunoregulatory factor, influencing the development, fate and function of myeloid cells and lymphocytes (31,34).

In the hypoxic TME of solid tumors, >7,000 types of mRNAs that are regulated by the transcription of HIFs have been identified in cancer cells. These mRNAs contribute to important aspects of cancer progression, including tumor angiogenesis, metabolic reprogramming, cell motility and invasion and resistance to chemotherapy and radiotherapy (35-38). However, in the hypoxic TME of solid tumors, besides cancer cells, there are also immune cells that are either resident or recruited from oxygen-rich blood circulation (39). Therefore, compared with cancer cells, the expression of HIFs in immune cells exerts a more complex influence on tumor immunity. Depending on the type of immune cells, HIFs demonstrate varied roles and effects across different tumor models. In the

following sections, we comprehensively reviewed the roles of HIFs in various cells of the innate and adaptive immune systems within the TME.

T cells. The expression of HIFs in T cells exhibits stage-specific characteristics. While HIF-1α in cancer cells can inhibit the activation of T cells via PD-L1 interaction (40), it primarily displays an activation-promoting effect in naïve T cells (41). Studies have highlighted the upregulation of aerobic glycolysis as a hallmark of T cell activation (42,43). In response to T cell activation, the transcriptional activity of HIF-1 increases, promoting the upregulation of glycolytic enzymes, such as pyruvate kinase, hexokinase 2 (HK2) and GLUT1; these enzymes and their associated metabolic pathways are integral to the activation and function of T cells (44-46). However, in tissues, hypoxia may suppress T cell activation, with T cells exposed to higher oxygen levels exhibiting a more robust activation profile than those in hypoxic environments (47). Glycoproteomic studies on the surfaces of primary human T cells have shown that hypoxia substantially alters the $CD8^+$ T cell surface profile in a manner consistent with metabolic reprogramming and an immunosuppressive state. $CD4^+$ T cells demonstrated similar responses, indicating a common hypoxia-induced surface receptor program and suggesting that hypoxic environments pose challenges to T cell activation (48). Therefore, the levels of HIF-1 during and after activation play a critical role in adapting to the hypoxic environment and regulating the functions of T cells. The evidence from experiments has shown that preconditioning human T cells to hypoxia or activating HIF pathways before chimeric antigen receptor T-cell therapy sustainably enhance T cell cytotoxic functionality (49,50).

HIF-1α contributes to the polarization of naïve T cells into Th17 cells. Naïve T cells differentiate into various functional effector and regulatory subsets, the process being partially regulated by the cytokine environment present during antigen recognition. During the differentiation of naïve T cells, HIF-1, as a key glycolysis-promoting factor, may be an important driver of the differentiation of Th17 cells (51). HIF-1 controls cell fate decisions through glycolysis, promoting the differentiation of naïve T cells into Th17 cells rather than Treg cells. The absence of HIF-1α results in a decrease in the differentiation of Th17 cells, while Treg differentiation is enhanced (52). HIF-1 also promotes the development of Th17 cells through direct transcriptional activation of RAR-related orphan receptor C (RORC) and by forming a ternary complex with RAR-related orphan receptor γt (RORγt) and p300 to recruit the IL-17 promoter, thereby regulating the differentiation program of Th17 signature genes (53,54). Additionally, HIF-1 suppresses Treg development by binding to forkhead box P3 (Foxp3) and targeting it for proteasomal degradation (53). Evidence from patients with thymoma-associated myasthenia gravis suggests that a higher RORγt/FOXP3 ratio may provide evidence for Th17/Treg imbalance, potentially associated with an increase in HIF-1α levels (55). By contrast, in acute myeloid leukemia patients, the metabolic product D-2-hydroxyglutarate (D-2HG) affects the differentiation of T cells upon uptake. D-2HG induces the instability of the HIF-1α protein, thereby increasing the abundance of Treg subsets and reducing the differentiation of Th17 cells (56). The intrinsic expression of oxygen-sensing PHD proteins, which promote the degradation of HIFs, in T cells is necessary for sustaining immune evasion and tumor colonization in the lungs. PHD proteins limit the differentiation of Th17 cells, promote the induction of Treg cells and suppress $CD8^+$ T cell effector functions, contributing to IFN-γ-dependent tumor immune suppression (57) (Fig. 2A).

In Treg cells, HIF-1α promotes the instability and degradation of Foxp3, induces IL-17 expression, stimulates IFN-γ production and increases the fragility of Tregs (58). Through these activities, the expression of HIF-1α in Tregs imparts antitumor immunity, thereby protecting the host from tumor growth. Thus, selectively increasing the expression of HIF-1α in Tregs can be considered a therapeutic approach to cancer treatment. Despite some controversy (59), with reports suggesting that hypoxia promotes the expression of Foxp3 (60,61), a more detailed examination indicates that hypoxia inhibits the differentiation of Tregs, while HIF-1α deletion rescues the differentiation of Tregs under hypoxic conditions, providing increasing evidence of the intrinsic negative effects of HIF-1α on FOXP3 and Tregs (52,53). Hsu *et al* (62) discovered that HIF-2α and HIF-1α have opposite effects on the differentiation of Tregs. Although the development of Tregs remains normal in mice with Foxp3-cre-specific deletion of either HIF-1α or HIF-2α, Tregs lacking HIF-2α, but not HIF-1α, display functional defects in suppressing effector T cells, exhibit enhanced reprogramming toward IL-17-secreting cells and confer resistance to the growth of MC38 colon adenocarcinoma and the metastasis of B16F10 melanoma (62). This is attributed to the inhibition of HIF-1α expression by HIF-2α, considering that HIF-2α deficiency leads to upregulation of HIF-1α expression both transcriptionally and post-transcriptionally, which increases Glut1 expression and a modest increase in Pdk1; these changes increase glycolytic activity that is unfavorable for the development of Tregs (62). The cross-talk between these two isoforms may partially explain the controversy surrounding hypoxia and the function of Tregs. For example, Neildez-Nguyen *et al* (59) observed that significant Treg proliferation Compared with normoxia only occurs after prolonged culture (7 and 11 days) under hypoxic conditions, as HIF-2α is expressed predominantly during long-term hypoxia (63) (Fig. 2A).

HIFs facilitate the antitumor responses of cytotoxic $CD8^+$ T cells. Palazon *et al* (64) found that knocking out HIF-1α in $CD8^+$ T cells reduced tumor infiltration and tumor cell killing by cytotoxic T cells. Deleting the HIF target gene VEGF-A in $CD8^+$ T cells prevented effective tumor infiltration and accelerated subcutaneous Lewis lung carcinoma tumor growth in mice. In mouse models of transplanted colon cancer, melanoma and spontaneous breast cancer, $CD8^+$ and $CD4^+$ tumor-infiltrating lymphocytes (TILs) were positive for CD137, a critical immune checkpoint molecule that enhances antitumor immunity. Under hypoxic conditions, the expression of CD137 on T cells is upregulated, whereas HIF-1α-deficient T cells remain CD137-negative even when they became TILs (7). Therefore, inhibiting the degradation pathway to stabilize HIF-1α expression in T cells is a promising therapeutic strategy for enhancing tumor immune response. This hypothesis is supported by studies that achieved effective enhancement of T cell cytotoxicity in multiple tumor models using various methods, including PHD2/3 knockout (65,66),

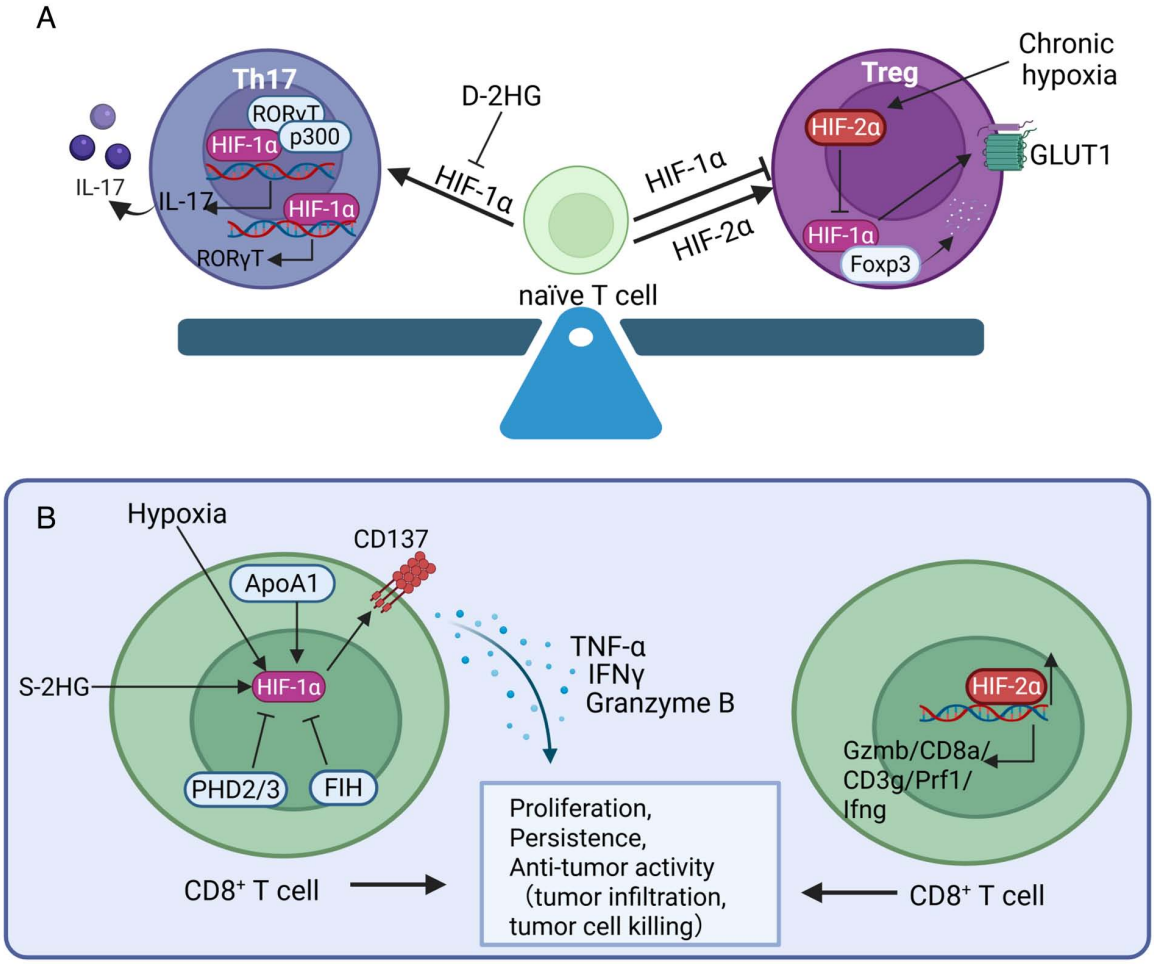


Figure 2. Regulation of T cell differentiation and function by HIFs. (A) Effects of HIFs on T cell differentiation and proliferation. In the TME, HIF-1α-induced glycolysis promotes the polarization of naïve T cells toward the Th17 phenotype. This occurs through the direct activation of RORγt, the master transcription factor of Th17 cells. HIF-1α also forms a complex with RORγt and p300, which enhances IL-17 transcription, thereby driving Th17 differentiation. Additionally, HIF-1α inhibits Treg cell development by suppressing Foxp3 signaling in a glycolysis-dependent manner. However, overexpression of HIF-2α in Treg cells antagonizes HIF-1α activity, thereby facilitating Treg differentiation and function. (B) HIFs Enhance CD8$^+$ T Cell Function. HIF-1α promotes the expression of CD127 on CD8$^+$ T cells, enhancing their capacity to secrete cytokines such as IFN-γ, TNF-α and granzyme B, thereby improving their tumor-killing efficacy. Furthermore, agents such as ApoA1 and the immunometabolite S-2-hydroxyglutarate stabilize HIF-1α, enhancing antitumor immunity. Similarly, HIF-2α strengthens the immune response of CD8$^+$ T cells by upregulating genes encoding granzyme B (Gzmb), Cd8a, Cd3g, perforin (Prf1) and IFN-γ (Ifng). Conversely, overexpression of HIF regulatory proteins such as PHD domain enzymes or FIH, which suppress HIF-1α activity, impairs tumor immunity. HIFs, hypoxia-inducible factors; TME, tumor microenvironment; RORγt, RAR-related orphan receptor γt; IL, interleukin; GLUT1, glucose transporter 1; Foxp3, forkhead box P3; IFN-γ, interferon γ; TNF-α, tumor necrosis factor-α; ApoA1, apolipoprotein A1; PHD, prolyl hydroxylase; FIH, factor-inhibiting HIF.

FIH deletion (67), treatment with HIF stabilizers (dimethyloxalylglycine or metabolite S-2-hydroxyglutarate) (68,69), or the overexpression of apolipoprotein A1 (70). Veliça *et al* (71) reported that HIF-2α plays an important role in CD8$^+$ T cells. By constructing retroviral vectors that inhibit the hydroxylation of the alanine residues of HIFs by PHD or FIH and delivering HIF-1α and HIF-2α expression vectors into mouse CD8$^+$ T cells, the researchers found that HIF-2α, rather than HIF-1α, drives a wide range of effector gene transcriptional changes in CD8$^+$ T cells, such as Gzmb, Cd8a, Cd3g, perforin 1 and interferon γ (IFN γ). Certain mutations at the FIH hydroxylation site on HIF-2α produced the most effective antitumor T cell responses after adoptive transfer *in vivo* (71). Therefore, the two isoforms of HIFs may play overlapping and complementary roles in T cell-mediated tumor immunity (Fig. 2B). Zhang *et al* (72) also suggested that when CD8$^+$ T cells are glucose-limited, HIF-1α-driven promotion of glycolysis and inhibition of OXPHOS lead to an increase in LAG-3 expression, which impairs CD8$^+$ T cell function. Improving fatty acid catabolism can improve the ability of CD8$^+$ TILs to slow melanoma progression in mice. These findings emphasize the importance of oxygenation levels in regulating immune cell metabolism. When O_2 levels decrease, HIF-1α mediates an increase in Glut1 expression in immune cells, including CD4$^+$ T cells (73), further highlighting the key role of HIF-1α in the differentiation and function of T cells.

B cells. In the blood, B cells are key cells responsible for antibody production. Specific receptors on B cells recognize harmful substances in the blood as antigens. After the antigens are processed, with the help of T cells, B cells mature and differentiate into plasma cells that secrete antibodies. B cells also play roles in antigen presentation and the secretion of cytokines (74,75). The development and selection of B lymphocytes are core processes in adaptive immunity and self-tolerance, relying on B cell receptor (BCR) signaling (76). The activity

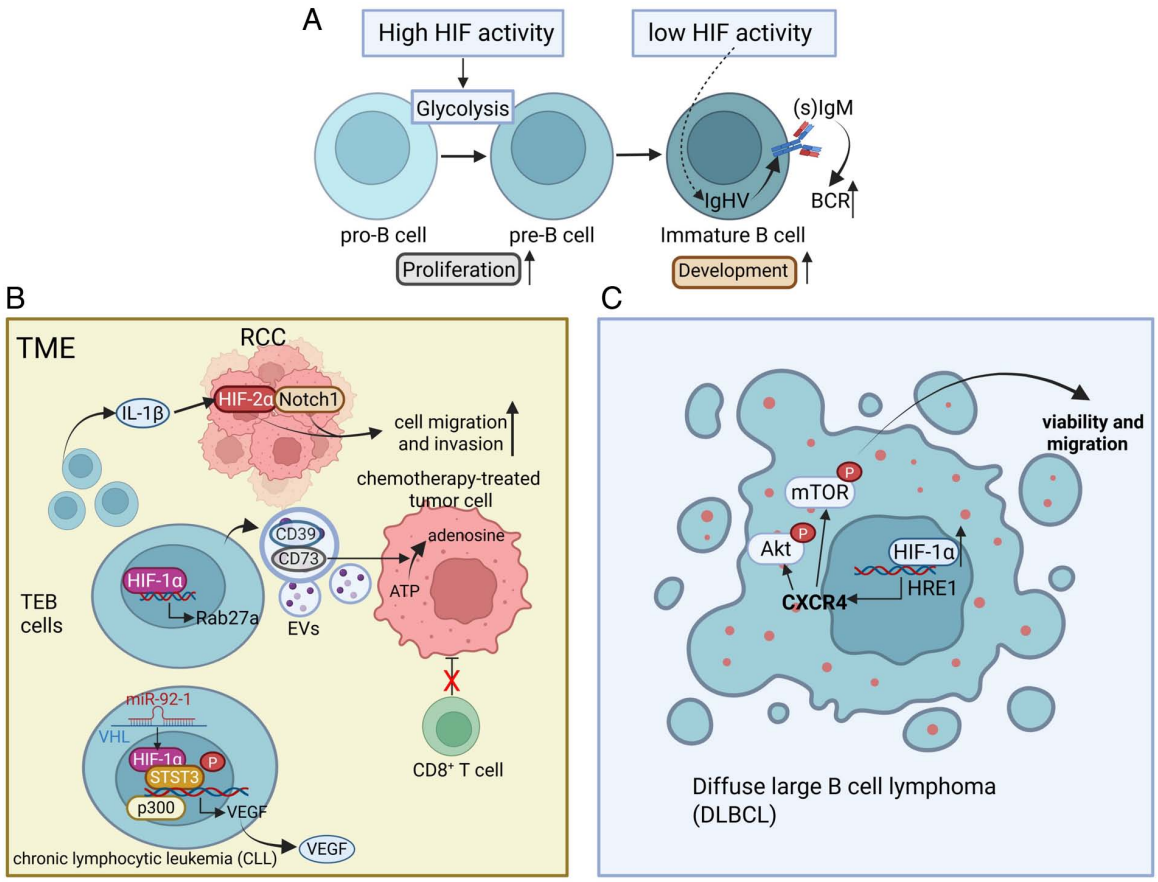


Figure 3. Regulation of B Cells by HIFs. (A) Stage-specific regulation of B cell development by HIF-1α. During early B cell development, high levels of HIF-1α activation are required to support glycolysis, facilitating the proliferation of pro-B and pre-B cells. However, in immature B cells, HIF-1α expression is downregulated. Persistent HIF-1α activity at this stage can limit IgHV editing, suppress sIgM expression and reduce BCR synthesis, ultimately impeding B cell maturation. (B) Regulation of B Cells by HIFs in the TME. TEBs play a pro-tumorigenic role by promoting cancer progression. For example, IL-1β released by TEBs can activate the HIF-2α/Notch1 signaling pathway in renal carcinoma cells, driving cancer cell migration and invasion. Additionally, HIF-1α activated by TEBs induces the transcription of *Rab27a* mRNA, facilitating the release of extracellular vesicles containing CD39 and CD73. These vesicles promote tumor immune evasion and chemoresistance. Moreover, microRNA miR-92-1, overexpressed in TEBs from CCL patients, inhibits *VHL* transcription, stabilizing HIF-1α. The stabilized HIF-1α forms a complex with p300 and phosphorylated STAT3, enhancing VEGF expression and thereby promoting angiogenesis in the TME. (C) Regulation of malignant B Cells by HIF-1α, HIF-1α promotes *CXCR4* transcription, activating the AKT and mTOR pathways to enhance migration and viability in DLBCL. HIFs, hypoxia-inducible factors; IgHV, immunoglobulin heavy chain variable region; sIgM, surface IgM; BCR, B cell receptor; TME, tumor microenvironment; TEBs, tumor-educated B cells; IL, interleukin; CCL, chronic lymphocytic leukemia; STAT3, signal transducer and activator of transcription 3; VEGF, vascular endothelial growth factor; DLBCL, diffuse large B-cell lymphoma; RCC, renal cell carcinoma.

of HIFs is high in human and mouse bone marrow, particularly in pro-B and pre-B cells and decreases at the immature B cell stage. This stage-specific inhibition of HIFs is essential for the normal development of B cells, as genetic activation of HIF-1α in mouse B cells leads to reduced repertoire diversity, decreased BCR editing and developmental arrest of immature B cells, resulting in a reduction in the number of peripheral B cells (77) (Fig. 3A).

The B cells in the TME and the intracellular HIF signals may play a significant role in the progression of cancer. Renal cell carcinoma (RCC) tissues contain a higher number of B cells than the surrounding normal renal tissues and these recruited B cells are referred to as tumor-educated B cells (TEBs) (75). The IL-1β released by TEBs activates the HIF-2α/Notch1 signaling pathway in RCC, promoting the migration and invasion of RCC cells (78). The upregulation of HIF-1α in TEBs induced by the TME further promotes the release of CD19-containing extracellular vesicles (EVs) from B cells through the transcription of Rab27a mRNA. The CD39 and CD73 proteins in these EVs hydrolyze ATP in chemotherapy-treated tumor cells to adenosine, thereby impairing the responses of CD8 T cells and reducing the efficacy of tumor chemotherapy in humans and mice (79). In chronic lymphocytic leukemia (CLL), miR-92-1 expressed in TEBs targets the VHL transcript to inhibit its expression and the stabilized HIF-1α forms an active complex with the coactivator p300 and phosphorylated signal transducer and activator of transcription 3 at the promoter of VEGF, which recruits RNA polymerase II, explaining the abnormal autocrine VEGF in CLL (80) (Fig. 3B).

Additionally, HIF-1α is associated with the self-transformation of B cells, thereby contributing to the formation of diffuse large B cell lymphoma (DLBCL), which is the most common form of lymphoid malignancy. Under hypoxic conditions or upon overexpression of HIF-1α under normoxic conditions, the viability and migration of DLBCL cells increase markedly, while downregulation of HIF-1α has the opposite effect. This process involves the binding of HIF-1α to the functional site HRE1 on the CXCR4 promoter, thereby activating its transcription. The activation of CXCR4 mediated by HIF-1α

further increases the phosphorylation of AKT/mTOR under hypoxic conditions (81) (Fig. 3C).

Macrophages. Macrophages exhibit high plasticity and, in response to different stimuli, unpolarized macrophages (M0) can differentiate into cells with unique phenotypes that perform different functions. Based on phenotypic and functional characteristics, polarized macrophages are generally categorized into classically activated M1 macrophages and alternatively activated M2 macrophages. M1 macrophages are induced by Th1-type cytokines and bacterial lipopolysaccharide (LPS); they are typically pro-inflammatory and anti-tumoral, characterized by the secretion of inflammatory cytokines such as IL-1β, IL-6 and tumor necrosis factor (TNF)-α. By contrast, M2 macrophages are stimulated by Th2-type cytokines; they play key roles in tumor initiation, proliferation, metastasis and immune evasion and can secrete anti-inflammatory cytokines such as IL-10 and transforming growth factor (TGF)-β (82,83). Mantovani *et al* (84) further subdivided M2 macrophages into four subsets: M2a, M2b, M2c and M2d. Among these macrophages, M2d macrophages, activated through Toll-like receptors and characterized by the expression of VEGF and IL-10, contribute to angiogenesis and tumor progression and are thus also referred to as tumor-associated macrophages (TAMs) (85). Macrophage polarization is a dynamic process. The M1 and M2 phenotypes are not strictly antagonistic; rather, they frequently coexist and can interconvert under specific conditions. This plasticity allows macrophages to adapt to microenvironmental changes and maintain tissue homeostasis and systemic balance.

Macrophages are an important component of the immune system. As they are frequently found in hypoxic tissues (86), their functions and polarization states are strongly influenced by HIFs, as most transcriptional responses to hypoxia are mediated by HIFs. In primary macrophages from normal mice, the expression levels of HIF-1α and HIF-2α mRNAs differ between M1-polarized and M2-polarized macrophages. HIF-1α is induced by Th1-type cytokines during the polarization of macrophages to the M1 phenotype, whereas HIF-2α is induced by Th2-type cytokines during the M2 response. This differential expression becomes more prominent in macrophages after polarization. In mice specifically overexpressing HIF-1α in bone marrow cells, macrophages exhibit an exaggerated inflammatory state characterized by the upregulation of M1 markers (87,88).

The situation is more complex in the context of tumor immunity. Talks *et al* (89) examined the distribution of HIFs in a wide range of solid tumors, including bladder, brain, breast, colon, ovarian, pancreatic, prostate and renal cancers. HIF-1α and HIF-2α both exhibited nuclear expression in different subpopulations of tumor cells. High expression of HIF-2α was also detected in various subsets of TAMs, occasionally even in the absence of HIF-2α expression in the tumor cells. High HIF-2α levels in TAMs are associated with poor prognosis in patients with cervical cancer, breast cancer and other malignancies (90,91). In a study, mice lacking HIF-2α in myeloid cells displayed reduced infiltration of TAMs in independent murine hepatocellular and colitis-associated colon carcinoma models, which was associated with a decrease in tumor cell proliferation and progression, HIF-2α regulates the migration of macrophages to the TME of orthotopic liver cancer by upregulating the expression of the cytokine receptor M-CSFR and the chemokine receptor CXCR4 (92). Clinically, high HIF-2α expression in macrophages is associated with poorer survival in patients with lung adenocarcinoma. Liu *et al* (93) found that glycolytic lactate, produced and secreted by tumor cells, suppresses the activity of mTORC1 in macrophages. This inhibition reduces TFEB-mediated expression of the macrophage-specific lysosomal ATPase subunit ATP6V0d2, thereby increasing the stability of HIF-2α and promoting VEGF secretion and a pro-tumorigenic macrophage phenotype (Fig. 4A).

Some studies have found that HIF-1α promotes the polarization of TAMs. Wu *et al* (94) observed that the metabolic product succinate secreted by cancer cells activates the succinate receptor (SUCNR1) signal on macrophages, inducing the polarization of TAMs via the PI3K/HIF-1α signaling pathway. In turn, TAMs release IL-6, which promotes cancer cell metastasis through IL-6R signaling. Succinate can inhibit PHD activity, thereby stabilizing the expression of HIF-1α. Activated HIF-1α directly upregulates the levels of IL-1β proteins, enhancing the proliferation and invasiveness of tumor cells (95).

ccRCC exhibits unique features in the context of HIF signaling-mediated regulation of tumor immunity. Moreover, ccRCC is commonly associated with the inactivation of the VHL tumor suppressor gene, leading to the constitutive stabilization and activation of both HIF-1α and HIF-2α (96). In ccRCC, HIF-2α acts as a tumor promoter, whereas HIF-1α has tumor-suppressive effects. HIF-2α and other hypoxia-associated factors are predominantly expressed in tumor cells and HIF-2α is widely recognized as a key oncogenic driver and a promising therapeutic target in ccRCC (97-99). By contrast, HIF-1α is primarily expressed in TAMs. Cell-based studies have shown that the overexpression of HIF-1α in TAMs suppresses the growth of ccRCC xenografts (29). Consistent with this notion, homozygous deletion of *HIF1A* is found in ~50% of high-grade ccRCC cases, suggesting that *HIF1A* functions as a tumor suppressor gene in ccRCC (100). However, clinical studies have further revealed that HIF-1α is primarily expressed in TAMs and is associated with higher tumor grades, an increase in metastatic risk, resistance to anti-angiogenic therapy and a significant reduction in overall survival. No differences were observed between HIF-1α protein levels within TAMs compared with macrophages derived from uninvolved kidneys, suggesting that increased HIF-1α levels in high-grade ccRCC may be due to an increase in the number of immune cells rather than an increase in HIF-1α expression (101). To summarize, these studies illustrate the distinct functional roles of HIF-1α and HIF-2α in tumor immunity. The effects of these HIFs may differ based on upstream regulatory signals, providing important insights into the functions and regulatory mechanisms of TAMs in the TME.

Under hypoxic conditions, the metabolic reprogramming mediated by HIF may strongly influence the immune function and polarization of macrophages. Hypoxic stimulation induces HIF-1α, which upregulates key enzymes in the glycolytic pathway, such as Glut1. This promotes rapid conversion of glucose to pyruvate even under normoxic conditions and is known as the Warburg effect (102,103). The resultant

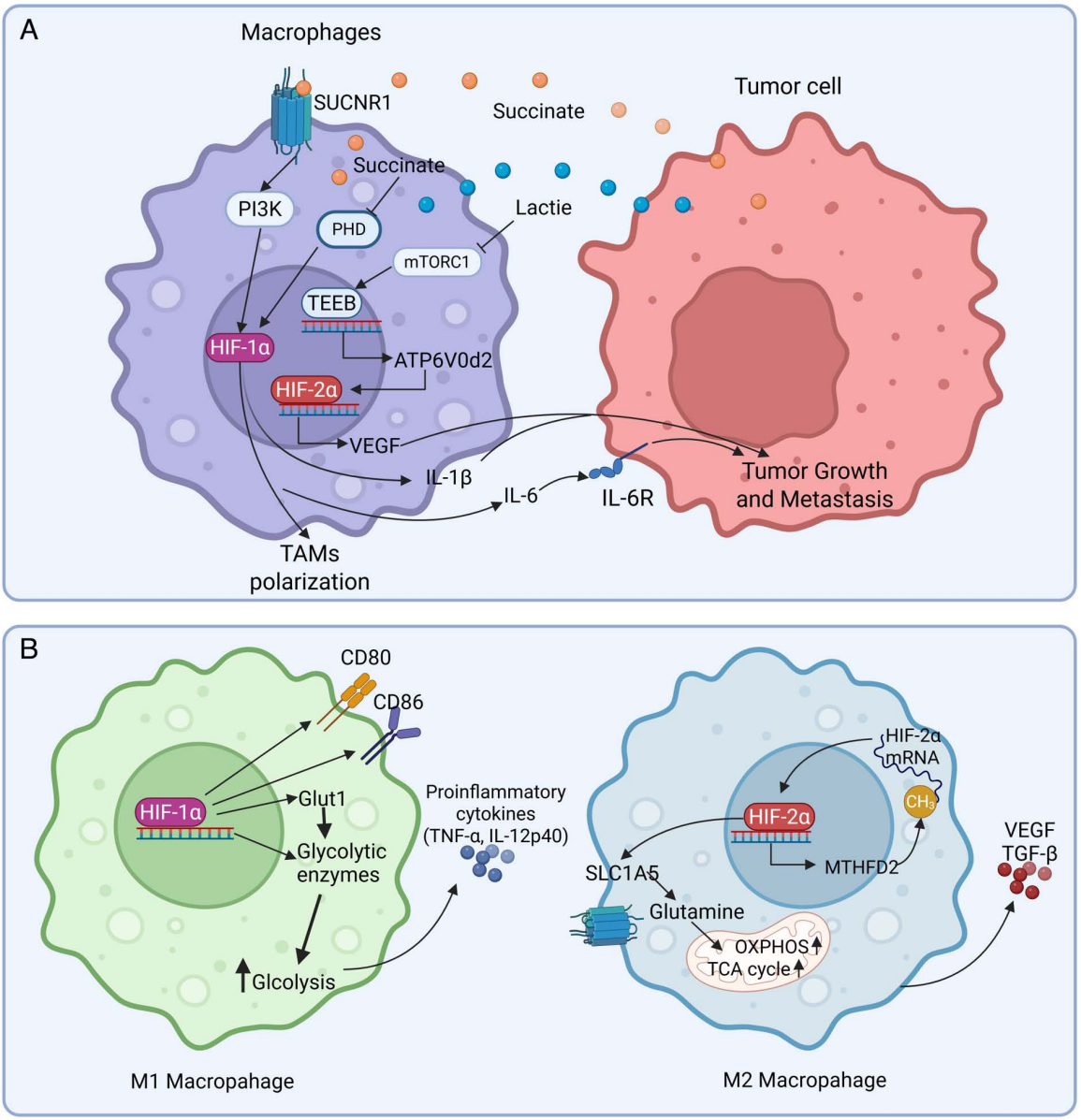


Figure 4. HIF Signaling in TAMs and its role in tumor progression. (A) In the TME, tumor cells release lactate and succinate, which act on macrophages to stabilize HIF-1α and HIF-2α. Succinate binds to SUCNR1 and activates the PI3K/mTORC1 pathway and inhibits PHD activity, both leading to HIF-1α stabilization. Lactate from tumor cells inhibit mTORC1 in TAMs, which further suppresses TEEB-mediated transcription of ATP6V0d2 and stabilizes HIF-2α protein. HIF-1α and HIF-2α promote TAM polarization, inducing the expression of pro-tumoral factors such as IL-1β, IL-6 and VEGF, which in turn enhance tumor growth and metastasis. (B) The metabolic and functional polarization of macrophages into M1 and M2 subtypes is depicted. M1 macrophages, driven by HIF-1α activation, upregulate glycolysis via GLUT1 and glycolytic enzymes, producing pro-inflammatory cytokines (such as TNF-α, IL-12p40) and expressing surface markers CD80 and CD86, which are associated with antitumor immune responses. By contrast, M2 macrophages rely on HIF-2α, which promotes glutamine metabolism via SLC1A5 and mitochondrial OXPHOS. HIF-2α also induces MTHFD2 expression, facilitating metabolic reprogramming and the secretion of VEGF and TGF-β, contributing to angiogenesis and immunosuppression in the TME. HIF, hypoxia-inducible factor; TAMs, tumor-associated macrophages; TME, tumor microenvironment; SUCNR1, succinate receptor; PHD, prolyl hydroxylase; TEEB, transcription factor regulating lysosomal proteins; ATP6V0d2, ATPase H^+ transporting V0 subunit d2; VEGF, vascular endothelial growth factor; GLUT1, glucose transporter 1; TNF-α, tumor necrosis factor-α; IL, interleukin; SLC1A5, solute carrier family 1 member 5; OXPHOS, oxidative phosphorylation; TGF-β, transforming growth factor-β.

glycolytic intermediates further drive the polarization of M1 macrophages. Concurrently, M1 macrophages exhibit greater secretion of pro-inflammatory cytokines, such as TNF-α and IL-12, along with an increase in the levels of co-stimulatory molecules CD80 and CD86 (102). This metabolic reprogramming supports the high energy demands of M1 macrophages during immune responses against tumors while establishing a positive feedback loop to reinforce their pro-inflammatory phenotype (Fig. 4B). By contrast, HIF-2α supports tumor progression through metabolic reprogramming. Under hypoxic conditions, HIF-2α is stabilized and activated in macrophages, triggering several metabolic adaptations, such as upregulation of genes and expressions related to glycolysis [methylenetetrahydrofolate dehydrogenase (NADP+ Dependent) 2, MTHFD2] and glutamine metabolism (solute carrier family 1 member 5, SLC1A5). The upregulation of SLC1A5 mediated by HIF-2α increases glutamine transport into mitochondria, which fuels the tricarboxylic acid cycle and oxidative phosphorylation (104). The upregulation of MTHFD2 by HIF-2α promotes one-carbon metabolism, which can alter RNA methylation

patterns, particularly through an increase in the m6A methylation of HIF-2α mRNA. This improves the translation efficiency of HIF-2α, forming a positive feedback loop between the expression of HIF-2α and metabolic reprogramming (105). These metabolic shifts allow macrophages to produce more energy and biosynthetic precursors, such as α-ketoglutarate, thereby supporting the rapid growth demands of tumors (Fig. 4B).

Additionally, macrophage-derived HIF extends beyond macrophages, influencing the TME by modulating other cell types, such as fibroblasts and endothelial cells. HIF-1α and HIF-2α in macrophages also exhibit antagonistic effects in regulating tumor angiogenesis. Macrophage-specific HIF-1α deletion markedly reduces the proportion of proangiogenic TME in mice, promoting tumor oxygenation and the response to chemotherapy. By contrast, in macrophage HIF-2α-deficient tumors, proangiogenic TEMs exhibit increased $CD31^+$ microvascular density. However, these tumors experience exacerbated hypoxia and necrosis, probably due to impaired adaptation to hypoxia. These findings suggest that in wild-type macrophages, HIF-2α may suppress HIF-1α-dependent TEM differentiation, thereby limiting excessive and dysfunctional angiogenesis during tumor progression (106). Eubank *et al* (107) found that HIF-2α promotes macrophage production of sVEGFR-1, a soluble decoy receptor that inhibits VEGF signaling, whereas HIF-1α induces the expression of VEGF. A lower sVEGFR-1/VEGF ratio, often seen in HIF-2α-deficient settings, favors tumor angiogenesis and is associated with poor prognosis (107). Despite its usual pro-tumorigenic characteristics, HIF-2α can inhibit the differentiation of macrophages into proangiogenic and M2-like TAMs under certain conditions (Fig. 4B).

Recent studies suggest that HIF-3α may contribute to the alternative M2-like polarization of TAMs, particularly in response to anti-inflammatory signals. Transcriptomic analyses have revealed that HIF-3α levels are higher in macrophages polarized by glucocorticoids (such as dexamethasone), a model for M2-like TAMs (108). This increase is associated with genes involved in the regulation of transcription of pluripotent stem cells, such as Klf4, implying that HIF-3α may help establish a sustained anti-inflammatory or homeostatic state in TAMs (89,108). HIF-3α is often described as a negative regulator of HIF-1α signaling, suggesting that it may inhibit the pro-inflammatory response of macrophages (109).

To summarize, during different stages of tumor progression, HIFs are regulated by complex signaling networks, which influence the functions and polarization states of macrophages. While regulating the functionality of TAMs, tumor growth and metastasis and antitumor immune responses, HIFs exhibit overlapping yet distinct roles, reflecting their nuanced contributions to the TME.

Neutrophils. Neutrophils are key effector cells of the innate immune system and play a complex dual role in tumor immunity. They exert antitumor effects by directly killing tumor cells. On the other hand, particularly under hypoxic conditions, neutrophils may facilitate the initiation and progression of tumors. The polarization, transcriptional regulation of tumor-associated neutrophils (TANs) and their interactions with tumors and other immune cells are closely associated with HIFs (110).

When the microenvironment changes, neutrophils respond by exhibiting functional plasticity. In tumors, they can be classified into antitumor N1 and pro-tumor N2 phenotypes. HIF-1α promotes the formation of N2-type neutrophils by influencing signaling in the TME. For example, HIF-1α regulates downstream effectors, such as TGF-β and IL-8, which drive the polarization of neutrophils toward the N2 phenotype and enhance their pro-tumor activity (111,112). Additionally, N2-type TANs promote the growth and invasion of tumors by secreting pro-inflammatory cytokines, such as IL-6 and angiogenic factors, such as VEGF (113). HIF-2α can also enhance the immunosuppressive properties of TANs by inhibiting their pro-inflammatory responses. Singhal *et al* (114) demonstrated that the deletion of HIF-2α in neutrophils slows the growth of colorectal cancer by reducing the secretion of pro-inflammatory cytokines (such as TNF-α and IL-1β) and immunosuppressive cytokines.

Moreover, HIF-1α facilitates the migration of neutrophils to tumor sites by regulating the expression of chemokine receptors, with the CXCR4/CXCL12 axis serving as a key pathway. By upregulating the expression of CXCR4, HIF-1α enhances the responsiveness of neutrophils to the tumor-derived chemokine CXCL12, thereby accelerating the directed migration of TANs to tumor sites (115-117). Besides directly promoting the migration of neutrophils toward tumors, HIF-1α may support tumor immune evasion by modulating the immunosuppressive functions of neutrophils. HIF-1α-activated neutrophils express PD-L1, which inhibits the activity of tumor-infiltrating T cells, thereby enhancing tumor immune escape (40,118,119). Moreover, when exposed to hypoxia and signals from cancer and stromal cells, invasive neutrophils in tumors are stimulated to form neutrophil extracellular traps (NETs). In gastric cancer, hypoxic conditions induce neutrophil infiltration and the formation of NETs via the activation of HIF-1α. During this process, high-mobility group box 1 translocates from the nucleus to the cytoplasm in gastric cancer cells and mediates NET formation through the TLR4/p38 MAPK signaling pathway. NETs exacerbate the progression of gastric cancer by promoting angiogenesis rather than directly enhancing the proliferation of cancer cells (120) (Fig. 5).

The role of HIF-3α in neutrophils is particularly understudied, but recent studies have found its involvement in stress-induced adaptation of neutrophils. In models of chronic stress, glucocorticoid signaling upregulates the expression of the *HIF3A* gene in neutrophils, linking HIF-3α to neuroendocrine-immune cross-talk in the TME. This suggests that HIF-3α may help fine-tune neutrophil responses to systemic cues, such as stress hormones, rather than direct hypoxia. For example, HIF-3α may modulate neutrophil migration (e.g., via CXCR4/CXCL12 axis), formation of NETs, or polarization toward a pro-tumor (N2) phenotype (114). However, no study has directly verified these hypotheses. As HIF-1α promotes NETs and immunosuppressive functions in TANs, HIF-3α might act as a counterbalance and is worthy of further study (120).

Dendritic cells. Dendritic cells (DCs) are complex antigen-presenting cells, exhibiting phenotypic heterogeneity and functional plasticity. They migrate from peripheral tissues

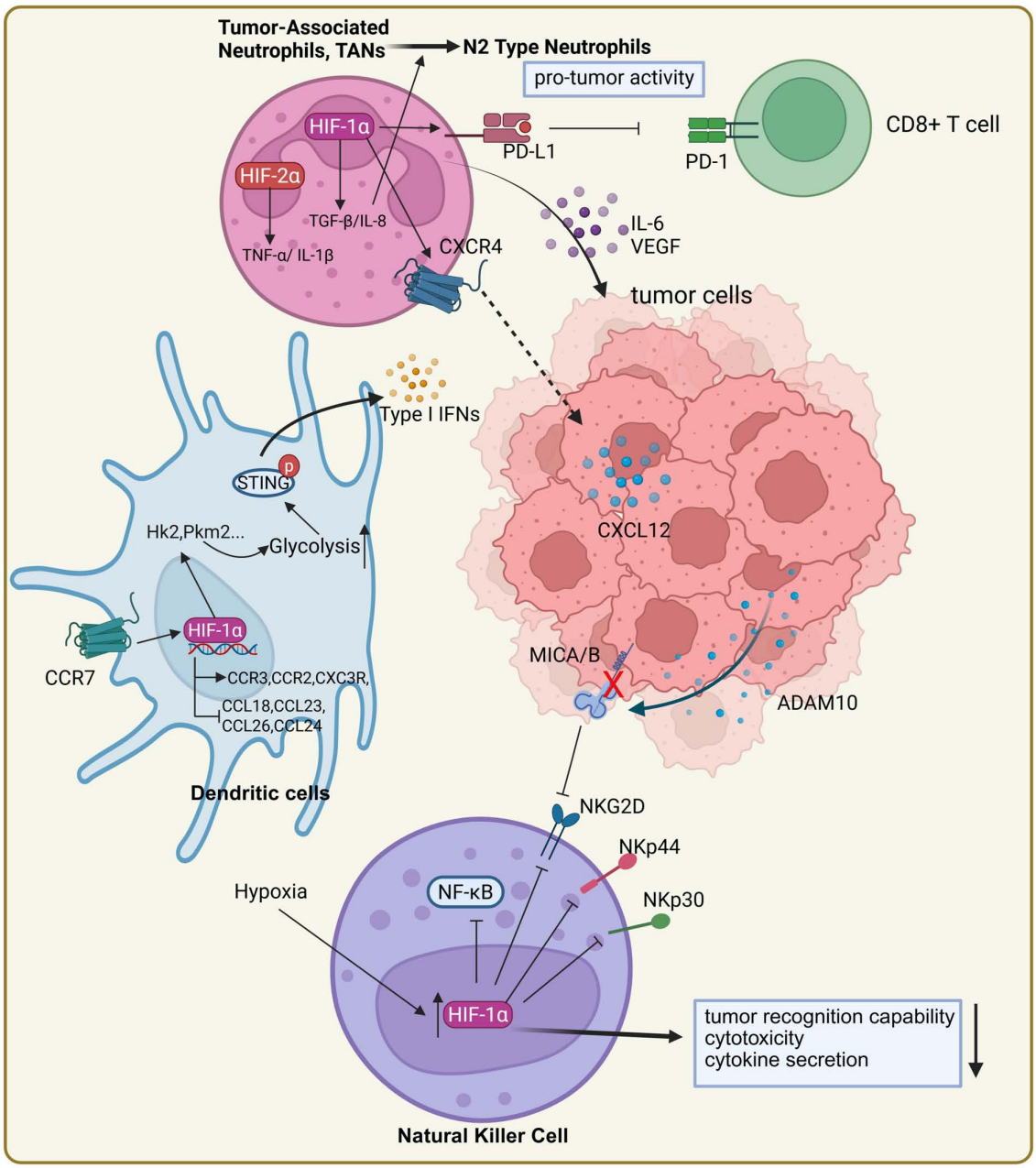


Figure 5. The role of HIFs in modulating innate immune cells in the TME. In the TME, HIF-1α in neutrophils regulates the expression of downstream molecules such as TGF-β and IL-8, while HIF-2α activates TNF-α and IL-1β. Together, these factors promote the polarization of TANs towards the pro-tumorigenic N2 phenotype. N2-type neutrophils secrete pro-inflammatory cytokines (such as IL-6) and angiogenic factors (such as VEGF), which promote tumor growth and invasion. Additionally, HIF-1α upregulates CXCR4 expression, enhancing neutrophil response to tumor-derived CXCL12, thus facilitating the directed migration of TANs to the tumor site. HIF-1α also activates PD-L1 expression, which suppresses CD8+ T cell activity, contributing to immune evasion by the tumor. In DCs, CCR7 signaling activates HIF-1α, which promotes transcription of chemokine receptors (CCR3, CCR2, CXCR3) while repressing chemokine ligands (CCL18, CCL23, CCL26, CCL24). HIF-1α also enhances transcription of glycolytic enzymes HK2 and PKM2, driving glycolysis and activating the STING pathway, leading to the production of type I IFNs. In tumor cells, hypoxia-induced CXCL12 recruits immune cells, while ADAM10 cleaves MICA/B, reducing NK cell recognition via NKG2D. NK cells under hypoxia exhibit increased HIF-1α expression, which impairs cytotoxicity and cytokine secretion by suppressing activating receptors (NKG2D, NKp30, NKp44), partially through NF-κB signaling. HIFs, hypoxia-inducible factors; TME TGF-β, transforming growth factor-β; IL, interleukin; TANs, tumor-associated neutrophils; VEGF, vascular endothelial growth factor; TME, tumor microenvironment; PD-L1, programmed cell death ligand 1; DCs, dendritic cells; CCR7, C-C motif chemokine receptor 7; STING, stimulator of interferon genes; IFNs, interferons; CXCL, C-X-C motif chemokine ligand; ADAM10, A disintegrin and metalloproteinase domain 10; MICA/B, major histocompatibility complex class I chain-related gene A/B; NK, natural killer; NF-κB, nuclear factor κ-light-chain-enhancer of activated B cells.

to lymph nodes, where they interact with T cells to trigger specific immune responses. The normal chemotaxis and migratory capacity of DCs greatly contribute to their ability to present tumor antigens (121,122). DCs generated under hypoxia display a distinguishable migratory phenotype. The migration of DCs depends on the expression of chemokine receptors on their surface. HIF-1α can regulate the expression of chemokine receptors (123). Under hypoxic conditions, the mRNA expression of chemokine receptors CCR3, CX3CR1 and CCR2 is enhanced in an HIF-1α-dependent manner; these genes are associated with the functions of DCs; their upregulation increases ligand sensitivity and migratory capacity of

DCs. Concurrently, there is a marked increase in the release of CCL17, CCL22 and IL-22. By contrast, the mRNA expression of CCL18, CCL23, CCL26 and CCL24 is decreased; these downregulated genes are involved in the recruitment of other inflammatory leukocytes and a decrease in their expression leads to impaired recruitment ability (124,125). Moreover, the most important chemotactic response for the migration of DCs is mediated by C-C motif chemokine receptor 7 (CCR7). Complex signaling pathways involving PI3K/AKT, MAPK/NF-κB, HIF-1α and IRFs are activated by CCR7 and play regulatory feedback roles in the migration of DCs in a context-dependent manner (122). CCR7 stimulation activated the HIF-1α transcription factor pathway in DCs, leading to metabolic reprogramming toward glycolysis for the migration of DCs (126).

The metabolic state of DCs plays an important role in maintaining their tumor immune function. Mature DCs primarily rely on oxidative phosphorylation, while immature DCs primarily rely on glycolysis (127). Under hypoxic conditions, activation of HIF-1α leads to metabolic reprogramming in DCs, altering their normal function. For example, HIF-1α increases the glycolytic activity of DCs by upregulating the expression of key glycolytic enzymes, such as HK2 (128,129). Hu *et al* (130) used LDHA/LDHB DC-conditional knockout mice to demonstrate that the deficiency of LDHA/LDHB inhibits glycolytic metabolism and ATP production, thereby weakening the stimulator of interferon gene (STING)-dependent type I interferon response and limiting the antitumor function of DCs. Activation of the STING signaling pathway in DCs promotes HIF-1α-mediated glycolysis, triggering a positive feedback loop centered on PI3K, which drives effector T cell responses (130-132). Clinical trials have shown that glycolysis also promotes the activity of STING-dependent DCs in tissue samples from non-small cell lung cancer patients (130). This suggests that the cross-talk between HIF-1α-mediated glycolytic metabolism and STING signaling may enhance the antitumor activity of DCs.

However, an increase in glycolysis under hypoxic conditions leads to the excessive accumulation of lactate. Lactate interacts with HIF-1α to inhibit the interaction between DCs and T cells, inducing the tumor immunosuppressive properties of DCs (133). Under hypoxic conditions, lactate produced by DCs promotes the expression of NDUFA4L2 through HIF-1α. The increase in the expression of NDUFA4L2 suppresses the pro-inflammatory response driven by mitochondrial reactive oxygen species and X-box binding protein in DCs (134). Additionally, the activation of NF-κB under hypoxia further increases HIF-1α levels stabilized by lactate (135). The positive feedback loop formed through the HIF-1α/NDUFA4L2 signaling axis limits the regulation of T cell immune responses by DCs, thereby exacerbating the immunosuppressive effect of HIF-1α in the TME (135).

Several studies have reported that the maturation and function of DCs are influenced by several HIF-1α-modulated factors, such as VEGF and IL-10, in the TME. The production of VEGF by human tumors can inhibit the functional maturation of DCs and accumulation of MDSCs that inhibit the functions of T cells (136,137). HIF-1α also induces tumor-associated DCs to express PD-L1 and other T-cell inhibitory molecules, weakening the function of $CD8^+$ T-cells and ultimately leading to tumor immune evasion (138,139).

To summarize, HIF-1α regulates the function of DCs in the TME through multiple mechanisms, markedly influencing DC maturation, metabolism, migration and the formation of immunosuppressive phenotypes. Activation of HIF-1α not only affects the antigen-presenting capability of DCs but also plays a key role in tumor initiation and progression by driving metabolic reprogramming and immune evasion pathways (Fig. 5).

Natural killer (NK) cells. NK cells are crucial effector cells in innate immunity, capable of directly killing tumor cells. The activity of NK cells is regulated by their surface receptors, which include both activating and inhibitory receptors. The hypoxic conditions in the TME and the activation of HIF negatively affect the activity of NK cells. *In vitro* studies have shown that hypoxic stimulation and activation of HIF-1α markedly reduce the expression of activating receptors on the surface of NK cells, such as NKp30, NKp44 and NKG2D. This weakens the ability of NK cells to recognize tumor cells, which decreases their cytotoxicity and ability to secrete cytokines (140). Moreover, HIF-1α induces tumor cells to release A disintegrin and metalloproteinase domain 10 (ADAM10), which cleaves surface MICA/B ligands. This shedding decreases the level of NKG2D on the surface of NK cells, ultimately facilitating immune evasion (141). Some researchers found that conditional knockout of HIF-1α in NK cells of mice inhibited the growth of tumor cells and upregulated activation markers such as CD69, while promoting the activation of the NF-κB pathway, thus enhancing antitumor responses (142). Clinically, low HIF-1α expression in infiltrating NK cells is markedly associated with high NF-κB/IFN-γ expression profiles and this characteristic is associated with markedly higher survival rates in cancer patients (142). A similar result was found by Nakazawa *et al* (143), who observed that in glioblastoma (GBM), overexpression of HIF-1α impaired the function of NK cells, reducing their cytotoxicity against tumor cells. Knocking out HIF-1α in NK cells markedly enhanced the cytotoxicity of NK cells under hypoxic conditions and induced apoptosis in GBM cells (143). These studies suggest that HIF-1α directly participates in the negative regulation of the tumor-killing functions of NK cells.

The role of HIF-1α in regulating NK cells is complex and context-dependent. Under hypoxic conditions, human NK cell lines stimulated with IL-2 exhibit enhanced expression of HIF-1α, which in turn improves the antitumor cytotoxicity and IFN-γ secretion capacity of NK cells (144). In this process, the stability of HIF-1α is important for maximizing the effector function of NK cells.

Moreover, based on its behavior in other cell types, HIF-3α may inhibit HIF-1α-driven pathways in NK cells, thereby attenuating their antitumor activity. Alternatively, HIF-3α may support the metabolic adaptation of NK cells under prolonged hypoxia, similar to its role in some epithelial cells (145). Future studies need to verify whether HIF-3α is expressed in NK cells, how it is regulated and whether it affects key functions such as target cell killing and IFN-γ secretion.

To summarize, the effects of HIF-1α on NK cells in tumors or cancer are multifaceted, complex and highly dynamic. HIF-1α impairs the function of NK cells in the TME through various mechanisms, including its effect on the activity of

Table I. HIF-related inhibitors and effects.

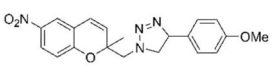
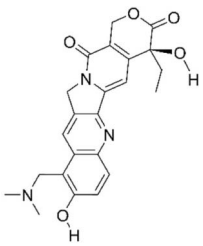
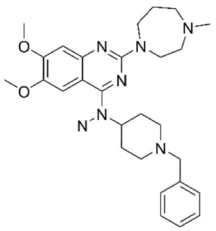
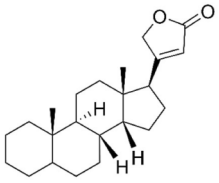
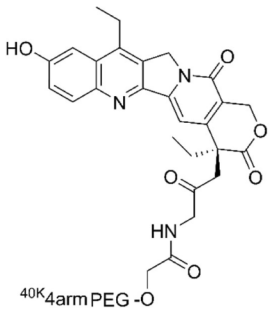
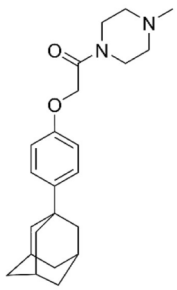
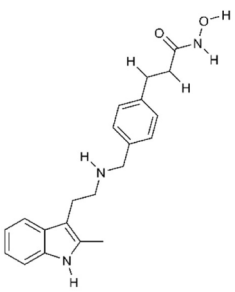
First author/s, year	Inhibitor	Structure	Type of cancer	IC_{50} (μM)	Effect	(Refs.)
Park *et al*, 2017	Benzopyranyl 1,2, 3-triazole (HIF-1α inhibitor)		Lung carcinoma	0.002	Inhibition of tumor growth and angiogenesis.	(154)
Kummar *et al*, 2011	Topotecan (HIF-1α inhibitor)		Adenocarcinoma	0.026	Enhanced tumor cell killing.	(146)
Wang *et al*, 2018	BIX01294 (HIF-1α inhibitor)		Lung carcinoma	2.5	Cancer cells. transformation	(155)
Spera *et al*, 2007	Cardenolides (HIF-1α inhibitor)		Prostate cancer cells	0.6	Inhibition of cancer cell proliferation.	(156)
Sapra *et al*, 2009, 2008	EZN-2208 (HIF-1α inhibitor)		Lymphatic carcinoma	0.003	Inhibition of tumor proliferation and angiogenesis.	(157,158)
Ban *et al*, 2017	IDF-11774 (HIF-1α inhibitor)		Intestinal cancer	3.650	Inhibition of tumor growth.	(159)
Wang *et al*, 2018, Lee *et al*, 2017	Panobinostat (HIF-1α inhibitor)		Non-small cell lung cancer	5.000	Promotes the apoptosis of cancer cells.	(160,161)

Table I. Continued.

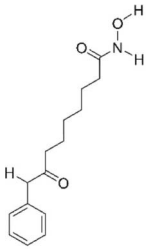
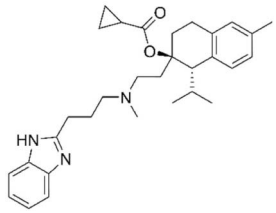
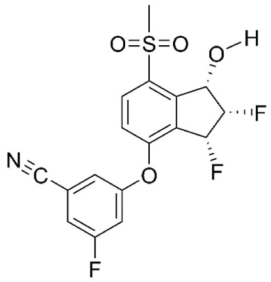
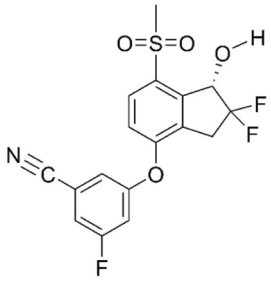
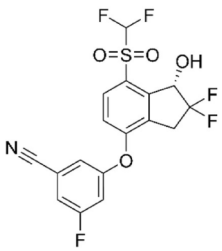
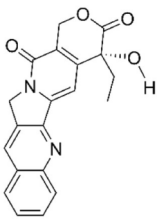
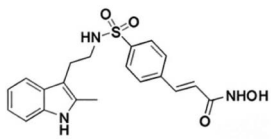
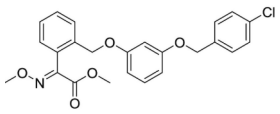
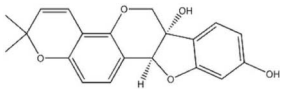
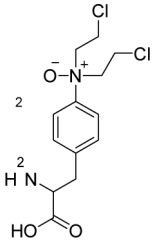
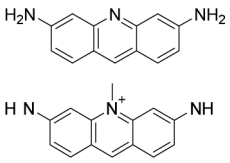
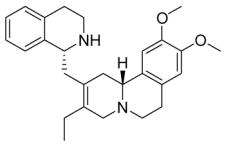
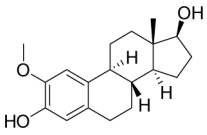
First author/s, year	Inhibitor	Structure	Type of cancer	IC_{50} (μM)	Effect	(Refs.)
Bali *et al*, 2005	Vorinostat (HIF-1α inhibitor)		Breast cancer	1.000	Promotes the apoptosis of cancer cells.	(162)
Kim *et al*, 2015	NNC 55-0396 (HIF-1α inhibitor)		Gastric cancer	4.17	Inhibition of tumor proliferation.	(163)
Jonasch *et al*, 2021	Belzutifan (HIF-2α inhibitor)		Renal Cell Carcinoma	Unclear	Inhibition of tumor cell proliferation.	(147)
Courtney *et al*, 2018, 2020	PT2385 (HIF-2α inhibitor)		Clear cell renal cell carcinomas	Unclear	Inhibition of. tumor growth	(164,165)
Ma *et al*, 2022	PT2399 (HIF-2α inhibitor)		Clear cell renal cell carcinomas	Unclear	Inhibition of tumor growth.	(166)
Keefe *et al*, 2016	CRLX101 (Combination inhibitor of HIF-1α and HIF-2α)		Non-small-cell lung carcinoma	0.251	Induces apoptosis of tumor cells and inhibits tumor growth.	(167)
Huang *et al*, 2015	MPT0G157 (HIF-1α inhibitor)		Human colorectal cancer	0.029	Inhibits tumor volume and reduces Matrigel-induced angiogenesis.	(168)

Table I. Continued.

First author/s, year	Inhibitor	Structure	Type of cancer	IC_{50} (μM)	Effect	(Refs.)
Lee *et al*, 2017	Kresoxim-methyl analogues (HIF-1α inhibitor)		Human colorectal cancer	0.60	Inhibits HIF-1α activation and cell proliferation.	(169)
Lecomte *et al*, 2017	Glyceollins (Combination inhibitor of HIF-1α and HIF-2α)		Breast cancer	Unclear	Inhibits tumor cell proliferation.	(170)
Palayoor *et al*, 2008	PX-478 (HIF-1α inhibitor)		Prostate carcinoma cells	20-30	Causes tumor cell apoptosis.	(171)
Piorecka *et al*, 2022	Acriflavine (HIF-1α inhibitor)		Human hepatocellular carcinoma cells	1	Inhibits tumor cell proliferation.	(172)
Baker *et al*, 2012	NSC-134754 (HIF-1α inhibitor)		Human prostate cancer cells	Unclear	Induces tumor necrosis.	(173)
Mabjeesh *et al*, 2003	2-Methoxy-estradiol		Breast neoplasms	0.4	Inhibits tumor cell growth.	(174)

HIF, hypoxia-inducible factor.

NK cells, receptor expression and secretion functions. These combined effects contribute to tumor immune evasion (Fig. 5).

4. Therapeutic targeting of the HIF pathway: Challenges and emerging strategies

Several studies have reported that HIFs not only regulate tumor cell proliferation, metabolism and angiogenesis but also play a complex role in immune regulation within the TME. Numerous natural and synthetic compounds have been identified as potential inhibitors of HIFs (Table I), which can specifically regulate the function of HIFs and be used in cancer treatment. The available therapeutic strategies targeting HIFs primarily include siRNA therapy, blocking the upstream regulators of HIFs, or directly inhibiting HIF-1α with anticancer drugs (13). For example, a phase I clinical study demonstrated that the topoisomerase inhibitor topotecan could inhibit the translation of the HIF-1α protein, thereby reducing tumor angiogenesis and growth (146). The selective HIF-2α inhibitor belzutifan has demonstrated significant therapeutic advancement in clinical trials (147). Belzutifan binds to the PAS-B domain of HIF-2α, blocking its dimerization with ARNT, thus inhibiting the transcriptional activation of downstream genes (147). In patients with RCC, belzutifan showed significant antitumor activity, with an objective response rate of 49% (147). On the other hand, its clinical application has health hazards, such as anemia, which is a targeted adverse effect (147). The existing HIF inhibitors still face significant challenges in clinical application. The primary concern is dose-limiting adverse effects due to different pharmacokinetic characteristics (148). This limits the long-term use of these drugs in cancer treatment. Additionally, the acidic TME may reduce drug concentrations, impair the tissue-specific delivery of HIF inhibitors and increase the activity of the multidrug transporter P-gp, leading to enhanced tumor resistance, all of which interfere with the therapeutic effectiveness of HIF inhibitors (14,15).

Table II. Molecular targets and functions of HIFs in immune cells of the tumor microenvironment.

First author/s, year	Immune cell type	HIFs	Molecular target	Regulation by HIF	Functions	(Refs.)
Dang *et al*, 2011	T cells	HIF-1α	RORC/ RORγt	Upregulated	Promotes differentiation of naïve T cells into pro-inflammatory Th17 cells.	(53)
Altınönder *et al*, 2024			FOXP3	Downregulated	Inhibits the development and function of immunosuppressive Treg cells.	(55)
Palazón *et al*, 2012, Labiano *et al*, 2016			CD137	Upregulated	Enhances T cell activation, survival and anti-tumor cytotoxicity.	(7,8)
Palazon *et al*, 2017			VEGF-A	Upregulated	Promotes T cell tumor infiltration, but can also lead to tumor angiogenesis.	(64)
You *et al*, 2021			PD-1/ PD-L1	Upregulated	Inhibit T cell activation and promote immune escape.	(6)
Hsu *et al*, 2020		HIF-2α	FOXP3	Upregulated	Promotes the differentiation and enhances the suppressive function of Treg cells.	(62)
Zhang *et al*, 2019	B cells	HIF-1α	Rab27a	Upregulated	Facilitates the release of $CD19^+$ extracellular vesicles.	(79)
Ghosh *et al*, 2009			miR-92-1/ VHL	Downregulated	Leads to HIF-1α stabilization and autocrine VEGF signaling, promoting angiogenesis in chronic lymphocytic leukemia.	(80)
Jin *et al*, 2023			HRE1/ CXCR4	Upregulated	Activate the AKT/mTOR pathway to enhance cell migration and survival.	(81)
Li *et al*, 2020		HIF-2α	Notch1	Upregulated	Promotes renal cell carcinoma cell migration and invasion.	(78)
Talks *et al*, 2000	Macro-phages	HIF-1α	GLUT1	Upregulated	Drives metabolic reprogramming (Warburg effect) towards an M1-like, pro-inflammatory phenotype.	(89)
Wu *et al*, 2020			SUCNR1/ PI3K	Activated	Stabilizes HIF-1α, promoting a pro-tumoral TAM phenotype.	(94)
Tannahill *et al*, 2013			IL-1β	Upregulated	Enhances pro-inflammatory responses and promotes tumor progression.	(95)
Yoo *et al*, 2020		HIF-2α	SLC1A5	Upregulated	Enhances glutamine uptake, fueling mitochondrial metabolism in M2-like TAMs.	(104)
Green *et al*, 2019			MTHFD2	Upregulated	Promotes one-carbon meta-bolism, supporting biosynthetic processes in tumors.	(105)
Imtiyaz *et al*, 2010			M-CSFR	Upregulated	Promotes the migration of macrophages to the TME and enhance tumor progression.	(92)
Eubank *et al*, 2011			sVEGFR-1	Upregulated	Inhibits VEGF signaling and angiogenesis.	(107)

Table II. Continued.

First author/s, year	Immune cell type	HIFs	Molecular target	Regulation by HIF	Functions	(Refs.)
Qiu *et al*, 2023, Masucci *et al*, 2019	Neutrophils	HIF-1α	TGF-β	Upregulated	Drives neutrophils to polarize towards the pro-tumor N2 phenotype, enhance their secretion of pro-inflammatory factors and promote tumor growth and metastasis.	(111,112)
LaGory *et al*, 2016, Santagata *et al*, 2021			CXCR4	Upregulated	Enhances directional migration to the tumor site, increase TANs infiltration and promote tumor progression.	(115,116)
Noman *et al*, 2014, Du *et al*, 2022			PD-L1	Upregulated	Inhibits the activation and cytotoxicity of tumor-infiltrating $CD8^+$ T cells and promote immune escape.	(40,118)
Li *et al*, 2023			HMGB1/ TLR4	Upregulated	Induces the formation of extracellular traps, which exacerbate tumor progression by promoting angiogenesis rather than direct proliferation.	(120)
Singhal *et al*, 2024		HIF-2α	TNF-α	Downregulated	Deficiency of HIF-2α reduces the secretion of pro-inflammatory cytokines (TNF-α), weakens the tumor-promoting function of neutrophils and retards the growth of colorectal cancer.	(114)
Curiel *et al*, 2003, Noman *et al*, 2015	Dendritic cells	HIF-1α	PD-L1	Upregulated	Induces an immunosuppressive phenotype in dendritic cells, weakening $CD8^+$ T-cell function.	(138,139)
Sanmarco *et al*, 2023			NDUFA4L2	Upregulated	Limits ROS production and T cell immune responses, exacerbating immuno-suppression.	(135)
McGettrick *et al*, 2020; Ricciardi *et al*, 2008			CCR3	Upregulated	Enhances the sensitivity of dendritic cells to chemokines and promote the migration of dendritic cells from peripheral tissues to lymph nodes.	(123,124)
Cao *et al*, 2020, Hu *et al*, 2023			PKM2	Upregulated	Enhance glycolytic flux, support the energy requirements of dendritic cells, induce the production of type I interferons and improve anti-tumor immunity.	(129,130)
O'Neill *et al*, 2016, Sanmarco *et al*, 2023			NDUFA4L2	Upregulated	Inhibit the production of mitochondrial reactive oxygen species, weaken the T cell activation ability of dendritic cells and promote immunosuppression.	(134,135)

Table II. Continued.

First author/s, year	Immune cell type	HIFs	Molecular target	Regulation by HIF	Functions	(Refs.)
Barsoum *et al*, 2011	Natural killer cells	HIF-1α	NKG2D	Downregulated	Impairs natural killer cell recognition and cytotoxicity against tumor cells.	(141)
Barsoum *et al*, 2011			ADAM10	Upregulated	Cleaves MICA/B on tumor cells, reducing NKG2D ligand expression and enabling immune evasion.	(141)

HIFs, hypoxia-inducible factors; RORC, RAR-related orphan receptor C; RORγt, RAR-related orphan receptor γt; FOXP3, forkhead box P3; VHL, Von Hippel-Lindau; VRGF, vascular endothelial growth factor; SUCNR1, succinate receptor 1; PI3K, phosphoinositide 3-kinase; SLC1A5, solute carrier family 1 member 5; MTHFD2, methylenetetrahydrofolate dehydrogenase (NADP+ dependent) 2, methenyltetrahydrofolate cyclohydrolase; PD-L1, programmed death-ligand 1; NKG2D, natural killer group 2; MICA/B, human leukocyte antigen (HLA) class I-related chain A/B; ADAM10, ADAM metallopeptidase domain 10; NDUFA4L2, NDUFA4, mitochondrial complex associated like 2; sVEGFR-1, soluble vascular endothelial growth factor receptor 1; HMGB1, high mobility group box 1 protein; TLR4, Toll-like receptor 4; CCR3, C-C chemokine receptor 3; PKM2, pyruvate kinase M2; NDUFA4L2, NADH dehydrogenase (ubiquinone) 1 α subcomplex, 4-like 2.

Precision-targeted drug delivery systems can overcome these challenges and can be used to develop effective therapeutic strategies: i) HIF-activating immunotherapeutic agents can be coupled with molecules that specifically recognize tumor cells or stromal components to increase drug concentration at the targeted site. ii) Stimuli-responsive lipid-based microparticles or nanovesicle carriers can be used to allow AI-optimized drug release kinetics and spatiotemporally controlled tissue-specific distribution; iii) Prodrugs that can be selectively activated under specific conditions in the TME (such as low pH, high ATP concentration, or overexpression of certain proteases) need to be developed; iv) By fusing mitochondrial targeting sequences with functional domains (such as HIF-inhibitory domains and succinate dehydrogenase-activating domains), chimeric peptides with specific mitochondrial-tumor targeting properties can be developed to selectively inhibit the cross-talk between HIF and mitochondrial metabolism in cancer cells, ultimately reversing the Warburg effect and the immunosuppressive TME (149-151). Preliminary investigation into these strategies has been conducted. For example, a recent study demonstrated that PX478 (an HIF inhibitor) conjugated with silk fibroin nanoparticles reverses multidrug resistance by enhancing the efficacy of doxorubicin in MCF-7/ADR cells (152,153). Wu *et al* (149) found that the chimeric peptide Mito-HIF-1α effectively decreased lactate production in cancer cells by 70% in a pancreatic cancer model, while restoring mitochondrial respiratory function in $CD8^+$ T cells. Designing and developing emerging therapeutic strategies, including active targeted delivery (immunoconjugate), intelligent material design (lipid carriers), microenvironment-responsive mechanisms (prodrug activation) and precise organelle intervention (mitochondrial chimeric peptides), may increase therapeutic efficacy while minimizing systemic adverse effects. These approaches can overcome the limitations of current drug development strategies, providing more effective options for treating cancer patients. However, further interdisciplinary research and clinical validation are needed to develop and optimize these therapeutic strategies.

5. Concluding remarks

Over the past three decades, research on HIFs has considerably advanced our understanding of cellular adaptation to hypoxia, particularly in the field of cancer biology. These studies have revealed the central regulatory functions of the HIF pathway in the proliferation of tumor cells, metabolic reprogramming and angiogenesis, while also highlighting its complex role in immune regulation. The distinct and often opposing functions of HIF-1α and HIF-2α in the TME highlight the context-dependent nature of this signaling pathway. This is especially evident in immune cells, where HIFs orchestrate a delicate balance between metabolic adaptation and functional responses across diverse populations, including T cells, B cells, macrophages, neutrophils, DCs and NK cells, directly influencing their antitumor efficacy and persistence (Table II).

Although HIF-targeted therapeutic techniques have achieved preliminary clinical success, their broader application faces significant challenges. Dose-limiting toxicities, drug resistance and the complicating effects of the acidic TME on drug delivery remain major obstacles. The available strategies to overcome these limitations include the development of precision-targeted drug delivery systems, such as nanoparticle-based platforms and the optimization of combination therapy. Future studies should further assess the multifaceted roles of HIF signaling in complex immune environments, with an emphasis on understanding the cell-type-specific functions of different HIF isoforms and their interaction networks. By integrating HIF biology with emerging technologies in drug delivery, single-cell multi-omics and spatial transcriptomics, researchers can advance the rational design of next-generation immunotherapeutic strategies. Finally, targeted manipulation of the HIF pathway is highly promising for developing more precise and effective cancer treatments that

modulate both metabolism and immunity while preserving immune function.

6. Strengths and limitations

The main strength of the present review lies in its systematic synthesis of recent discoveries concerning HIF-driven regulation of the immune system, integrating mechanistic insights with translational relevance. Unlike previous reviews that have focused on tumor cell metabolism or angiogenesis, the present review emphasized the cell-type-specific roles of HIFs across major immune populations. By highlighting the metabolic and immunologic duality of HIF signaling, it provided a nuanced perspective on how hypoxia influences tumor-immune dynamics and identifies potential targets for combined HIF and immunotherapy.

However, the present review had several limitations. i) Most of the mechanistic insights summarized here are derived from preclinical or *in vitro* models and their physiological relevance in human tumors requires further validation. ii) The spatial and temporal heterogeneity of oxygen gradients, metabolic states and immune cell composition in the TME makes it difficult to extrapolate experimental findings across different types of cancer. iii) Unlike HIF-1α and HIF-2α, HIF-3α has important functions in macrophage polarization, neutrophil activation and NK cytotoxicity; moreover, HIF-3α plays a more subtle and environment-dependent role. However, research on the regulatory effect of HIF-3α on tumor-infiltrating immune cells is still lacking and further studies are needed. Moreover, existing HIF-targeted therapeutic interventions are hampered by contextual efficacy and off-target toxicity. Future studies should use single-cell multi-omics, metabolic imaging and spatial transcriptomic technologies to elucidate cell-specific regulatory networks and prioritize well-designed clinical trials to confirm the immunomodulatory effect of HIF inhibition.

To summarize, while the current understanding of HIFs in tumor-infiltrating immune cells provides a solid conceptual foundation, translating these insights into clinically actionable strategies will require continued interdisciplinary effort.

Acknowledgements

Not applicable.

Funding

The present study was supported by the Shandong Province Natural Science Foundation (grant no. ZR2025QC326), Taishan Scholars (grant no. TSQN 202312181) and Youth Innovation Team Project of Shandong province (grant no. 2023RW102).

Availability of data and materials

Not applicable.

Authors' contributions

QS, CL and YL conceived and designed the research. CL and CQ drafted the manuscript. YL revised the manuscript. JW and XL collated the literature. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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