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# Hypoxic tumor microenvironment and immune cell dynamics: From metabolic reprogramming to therapeutic innovation

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ABSTRACT

The tumor microenvironment (TME) comprises the cellular and non-cellular components present within and around a tumor and plays a critical role in tumor progression and development. Metabolic changes in immune cells within the TME have been reported, including alterations of glycolysis, oxidative phosphorylation, and fatty acid oxidation pathways that contribute to tumorigenesis. In the present review, we highlight the significant role of hypoxia within the TME as a primary characteristic of most solid tumors. A comprehensive search of the EMBASE, MEDLINE, and Web of Science databases was conducted, encompassing all literature published up to and including June 2025. This study emphasizes the critical role of hypoxia in the TME and its impact on immune cell function. By understanding how hypoxia affects immune cell metabolism, researchers can develop therapeutic approaches targeting immune cell metabolism in the TME. In this regard, we discussed the role of targeting hypoxia via HIF-1 for immunotherapeutic implications; targeting HIF-1 for immunotherapeutic purposes is an area of active research and holds promise for developing new and more effective cancer treatments.

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## Introduction

The immune system is fundamentally responsible for recognizing and eliminating malignant cells, serving as a key line of defense against tumor development (1). However, tumor cells have unique abilities to evade immune responses, leading them to outcompete the suppressive effects of the immune system (1). Various mechanisms, such as a high metastatic rate and loss of neoantigen expression, endow tumor cells with these abilities (2). On the other hand, during antigen recognition, immune cells undergo specific metabolic alterations. The TME modifies the metabolic profiles of both immune and tumor cells, leading to a mix of beneficial and detrimental effects, with tumor cells primarily benefiting from these changes (3).

Hypoxia has been shown to reprogram immune landscapes by recruiting immunosuppressive populations and by inducing checkpoint molecules and suppressive metabolites that inhibit effector lymphocytes. Indeed, hypoxic signaling has been described as a "hijacker" of immune surveillance, significantly impairing the ability of NK cells and cytotoxic T cells to eliminate cancer cells (4). Several metabolic changes in immune cells have been observed within the TME. These include alterations in pathways such as oxidative phosphorylation (OXPHOS), glycolysis, and fatty acid oxidation (FAO), all of which contribute to tumor progression (5). Hypoxic TME can induce the expression of hypoxia-inducible factor (HIF) and metabolic changes in immune cells (6). Given the central role of hypoxia in driving immune suppression and therapeutic resistance, there is an urgent need for deeper mechanistic and translational insights. In particular, targeting HIF-1α or its downstream pathways represents a promising strategy to reverse hypoxia-induced dysfunction. However, translating such approaches to the clinic has proven challenging: to date, many HIF-1α inhibitors lack specificity and clear pharmacodynamic markers, and single-agent efficacy has been difficult to demonstrate. A rigorous understanding of these barriers and rational combination strategies will be needed to realize the potential of hypoxia-targeted therapies (7, 8).

Accordingly, this manuscript is structured to address these gaps. We first survey the hallmarks and heterogeneity of the hypoxic TME and its relevance to cancer progression. Next, we examine how key immune subsets – including conventional and engineered T cells (such as CAR T cells), macrophages, natural killer cells, and dendritic cells – function and rewire their metabolism under low-oxygen

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stress. We then explore immune–immune metabolic crosstalk within the hypoxic niche, highlighting how reciprocal metabolic cues shape the immunosuppressive environment. Finally, we evaluate current efforts to therapeutically target HIF-1α signaling, discussing translational hurdles and future directions. By integrating these perspectives, we aim to illuminate how metabolic reprogramming in hypoxia bridges basic immunology and clinical innovation in oncology.

### *Overview of hypoxic TME*

Cancer cells have evolved to evade immune surveillance and prolong their longevity by various mechanisms. For instance, the degradation of tryptophan in the TME leads to the production of Indoleamine 2,3-dioxygenase (IDO), which inhibits T cell proliferation and negatively impacts NK cell function (9). The elevated expression of programmed death-ligand 1 (PD-L1) on tumor cells is another way to evade immune cells (10). Moreover, reduced expression of MHC class I molecules and diminished immunogenic antigens support tumor cells in evading T-cell responses (11). Since antigenicity plays a significant role in detecting antigens expressed by tumor cells, shedding these antigens leads to a decreased response by immune cells and therapeutic methods, resulting in an inherent reduction in immunogenicity that inhibits the immune response (11, 12).

Hypoxia affects T cells differently based on their differentiation state: it impairs activation, reduces proliferation, and decreases CD25 expression in naïve CD8+ T cells, while promoting the differentiation of exhausted memory CD8+ T cells to cells that exhibit enhanced expression of pro-angiogenic mediators. In addition, hypoxia can decrease the antitumor activity and cytotoxic capacity of effector CD8+ T cells, and it may also increase the expression of coinhibitory molecules and reduce polyfunctional cytokine secretion (13, 14). Additionally, the hypoxic TME can affect other immune cells, such as macrophages, by increasing the secretion of specific mediators, including monocyte-activating polypeptide II (EMAPII), thrombomodulin (THBD), and Semaphorin 3A (Sema3A) (15, 16). Also, in the study of Xun *et al.*, by applying an integrated approach utilizing bulk, single-cell, and spatial transcriptomics, a hypoxia-centered intercellular communication network was identified, comprising malignant cells, exhausted CD8+ T cells, and Activated Leukocyte Cell Adhesion Molecule (ALCAM) $^{high}$ macrophages, predominantly localized at the tumor periphery. It was demonstrated that low oxygen levels promote the association of the HIF-1α complex with the promoter region of ALCAM, leading to increased ALCAM expression in macrophages. Furthermore, spatial analysis revealed that ALCAMhigh macrophages were found in close proximity to exhausted CD8+ T cells within the TME, suggesting a role in promoting T cell exhaustion (15).

Alterations in cellular metabolism also influence the polarization and functional behavior of immune cells within the TME, leading to tumor progression (17). A defining feature of cancerous cells is increased glycolysis, leading to enhanced glucose uptake at tumor sites (18). In fact, tumor cells increase glucose uptake via overexpression of GLUT1 in the hypoxic area (18). Normoxic cancer cells consume extracellular lactate through MCT-1 to use it for oxidative metabolism (19). Lactate is released by hypoxic tumor cells into the surrounding environment, transferred via the lactate transporter MCT-4 into the extracellular environment. Moreover, the increased lactic acid stimulates immunologically chronic inflammation in tumors and blocks T cell response (20). The metabolic alterations observed in cancer cells significantly impact the TME beyond merely affecting cellular proliferation. These changes, which notably involve modifications in the metabolism of amino acids, lactic acid, and lipids, have been found to strongly influence the overall dynamics of the TME (21). In the following sections, the intricate interplay between hypoxia and immune cell function within the TME will be discussed.

### *T cells under hypoxia*

Unlike naïve T cells, effector T cells up-regulate GLUT1 expression to increase their glucose uptake and promote the expression and activation of glycolytic enzymes. However, in TME, the rate of glycolysis in T cells significantly decreases, resulting in the inability to produce immune-stimulating cytokines. Finally, effector T cells are converted to anergy T cells (22, 23). It has been reported that effector T cells engage multiple ATP-generating metabolic pathways, including aerobic glycolysis, mitochondrial metabolism, the TCA cycle, and OXPHOS (Figure 1) (24). Lactate production driven



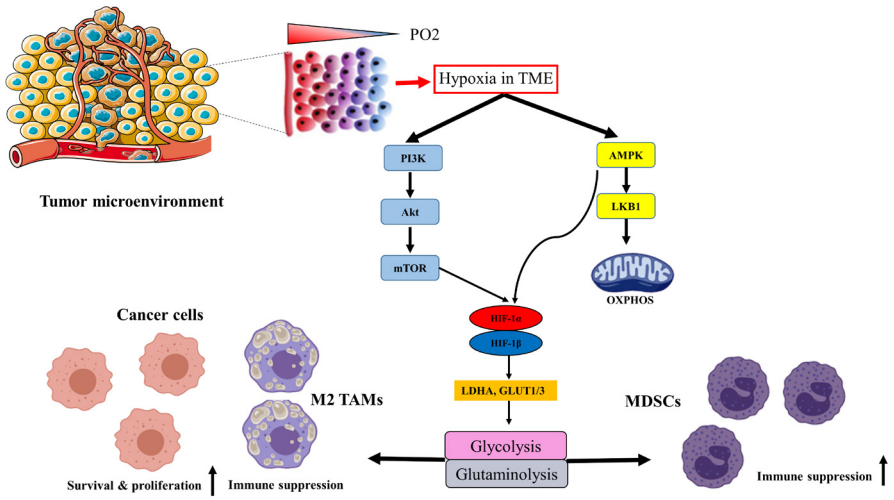


**Figure 1.** Hypoxia-induced metabolic reprogramming in the TME
Reduced oxygen tension (PO2) in the TME leads to hypoxia, activating signaling cascades such as PI3K/Akt/mTOR and AMPK/LKB1. These pathways converge on hypoxia-inducible factors (HIF-1α/β), which up-regulate key metabolic enzymes and transporters (LDHA and GLUT1/3), promoting glycolysis and glutaminolysis. This metabolic shift supports the adaptation and survival of cancer cells and immunosuppressive cells, including myeloid-derived suppressor cells (MDSCs) and M2 macrophages (TAMs), thereby facilitating tumor progression.

by glycolysis induces the up-regulation of monocarboxylate transporters, including MCT1 and MCT4, which remove lactate (25). Remarkably, the glycolysis pathway has more advantages for T cells than OXPHOS. For instance, in hypoxic or acidic environments, glycolysis supports higher rates of ATP synthesis, meets biosynthetic demands, and helps maintain redox balance (26). Overexpression and HIF-1α activation triggered by oxygen deprivation boost the glycolysis pathway and decrease the OXPHOS pathway by increasing the expression of both pyruvate dehydrogenase kinase (PDK1) and lactate dehydrogenase A (LDHA) (27). Additionally, HIF-1α promotes the overexpression of transporters GLUT1 and MCT4, which can increase glycolysis under hypoxic conditions (28). Alternatively, T memory (Tm) cells rely on β-oxidation of fatty acids generated from glucose consumption in the effector phase to meet their energy demands (29).

HIF-1α is crucial in regulating the Th17/Treg ratio in lymphocyte cells (Figure 1). It shifts OXPHOS activation toward the glycolysis pathway, favoring Th17 differentiation via RORγt/P300 and Foxp3 for Treg differentiation (30). The suppression of the glycolysis pathway hinders Th17 cell polarization and promotes the development of Treg cell lineages (30). HIF-1α activation in response to hypoxic conditions facilitates FOXP3 expression and drives Treg differentiation via the TGF-β signaling cascade. However, this pathway is suppressed in the presence of TGF-β and IL-6, which instead promote Th17 cell polarization through a mechanism involving hypoxia, mTORC1 activation, and HIF-1α signaling, thereby undermining the tolerance typically mediated by Tregs (31). Deletion of Von Hippel-Lindau (VHL), a tumor suppressor responsible for degrading HIFs in regulatory T cells, coupled with HIF-1α stabilization, promotes the conversion of Tregs into IFN-γ–secreting cells (32). This occurs because HIF interacts with the promoter controlling IFN-γ expression, thereby activating and proliferating Th1 cells. In the hypoxic TME, IFN-γ production was increased by HIF-1α and Tregs, leading to their fragility (33). Additionally, prolyl hydroxylases (PHD) isoforms, as a HIF regulator, restrain Th1 differentiation and promote Tregs as a result of the suppression of the glycolytic metabolism derived from HIF and the production of IFN-γ (Figure 2) (33, 34). Moreover, hypoxia can enhance infiltration and counteract the immunosuppressive activity of Tregs via HIF-1α. Hypoxia could indirectly affect T cell–directing chemokine regulation by acting on CXCL9/10-expressing cellular subsets. HIF-1α in the hypoxic TME induces CCL28 secretion to recruit Tregs (CXCR10+) into tumors, thereby enhancing tumor tolerance and angiogenesis (35). While migratory capacity derived by glycolysis and tumor-infiltrated Treg is increased by HIF-1α, immunosuppressive capacity induced by OXPHOS is reduced (35). In addition, the effect of ROS on nitrosylation revokes the CCL2 potential in T cells' recruitment to the TME (36). Moreover, hypoxia and increased Treg in TME affect T cell surface omics and function. For instance, an *in vitro* study found that TNF receptor and lymphocyte-activating 3 (LAG3) expression on T cells is increased in the presence of Treg cells and hypoxia. Besides this, the CD73/CD39 axis, which is responsible for producing immunosuppressive adenosine from ATP, undergoes changes because of Treg. The expression of CD73 decreases while that of CD39 increases (37, 38). Also, from the adhesion molecules, the expression of CD84, ALCAM, and integrin αX is increased, but neuronal cell adhesion molecule, ICAM1, and integrin α4 are down-regulated (13). It has been documented that the THBD+ macrophage subpopulation shows a strong association with hypoxic conditions in glioma. These macrophages demonstrate markedly increased infiltration in tumor tissues when compared to non-tumor areas. Furthermore, glioblastoma (GBM) patients with a high percentage of THBD+ cells tend to have a less favorable prognosis, indicating the clinical significance of this macrophage subtype in glioma



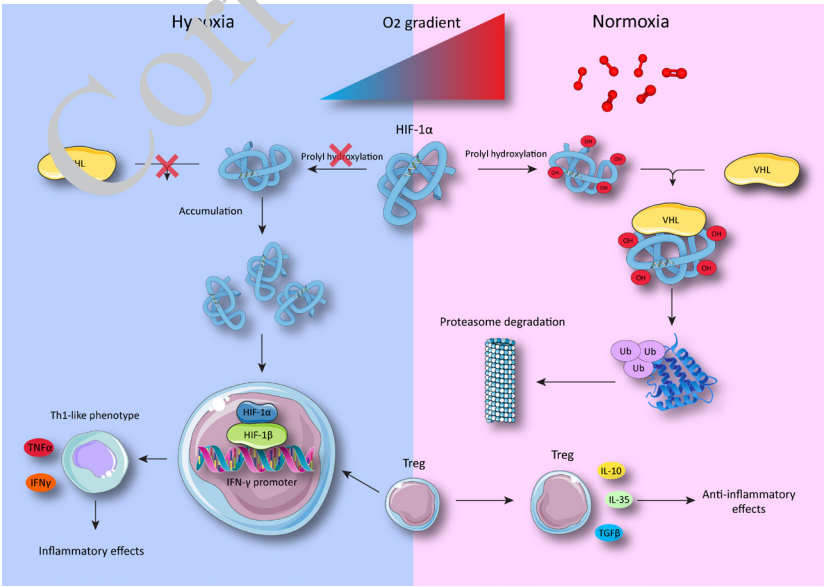


**Figure 2.** Oxygen-dependent control of HIF-1α stability and its effects on immune function

The figure illustrates the oxygen-dependent regulation of HIF-1α and its impact on immune cell phenotypes. In hypoxic environments (left), oxygen deficiency blocks the hydroxylation of HIF-1α, which is essential for its degradation by the VHL ubiquitin ligase complex. Consequently, stabilized HIF-1α accumulates in the cell, moves into the nucleus, and forms a complex with HIF-1β to drive the transcription of genes such as IFN-γ. This shifts T cell polarization toward a Th1-like pro-inflammatory phenotype characterized by IFN-γ and TNF-α production. Under normoxic conditions (right), however, HIF-1α is hydroxylated and promptly degraded by the proteasome via the VHL pathway, promoting the differentiation of regulatory T cells (Tregs) that produce anti-inflammatory cytokines, including IL-10, IL-35, and TGF-β. The central $O_2$ gradient highlights the dynamic regulation of immune responses by tissue oxygenation.

progression and patient outcomes (15).

HIFs are critically involved in directing the differentiation of CTLs, which are characterized by elevated glycolytic activity and reduced OXPHOS. CD8+ T-cells' function is impacted by ROS through the modulation of lymphocyte expansion molecule (LEM), a crucial component in the expansion of CTLs and development of memory T-cells. Nevertheless, high levels of ROS can be toxic and impair T cells (39). Within the TME, oxygen-deprived cancer cells and CTLs compete for the uptake of glucose and amino acids as essential nutrients. T cells' starvation in TME prevents T cell differentiation and expansion into tumor-specific effector T cells and promotes Treg differentiation by increasing fatty acid oxidation (FAO) (40). HIF-1α directly inhibits the TCA cycle, leading to deactivation of the pyruvate dehydrogenase complex (PDC). This inhibition leads to reduced pyruvate oxidation by activating the gene encoding PDK1 (27). The absence of VHL in CD8+ T cells increases both their survival and their ability to function as effector cells through enhanced HIF activity that induces glycolytic metabolism and regulates molecules and both activating and inhibitory receptors (41). Hypoxic TMEs can influence CD8+ T cell abundance, facilitating immunosuppressive mechanisms that enable tumor growth and spread. Additionally, lactate release contributes to an acidic TME, which impairs T cell cytotoxicity by disrupting mTOR and glycolysis (42). Besides, hypoxia negatively affects the anti-tumor functions of CTLs through HIF-1α, which induces the up-regulation of PD-L1 on cancer and myeloid cells, promoting evasion of immune surveillance (43, 44). The expression of VEGF-A can also cause the expression of inhibitory checkpoint molecules, such as PD-1, on tumor-infiltrating CTLs, thereby promoting T cell exhaustion and functional impairment within the TME (45). The effect of the hypoxic TME on the T cell population is presented in Figure 1.

***Macrophages under hypoxia:***

The TME heavily relies on macrophages, both in their presence and in their diverse functions. When macrophages reach the tumor site, they undergo a transformation into TAMs. These TAMs can be categorized into two groups: M1 macrophages or M2 macrophages (46). The distinction between macrophage polarization states can be blurred, as polarization can occur anywhere along a continuum between these two distinct phenotypes (46). In early neoplasia or in vascularized regions, M1 macrophages are typically present (47). On the other hand, M2 macrophages are commonly detected as tumors progress. The presence of the M2 subset is often an indicator of a poor prognosis (47). Exosomes isolated from tumor cells under hypoxia derive macrophages toward the M2 cell, which enhances tumor growth in animal models and *in vitro* studies (48). The TAM population in hypoxic areas exhibits low MHC-II expression (MHC-II$^{lo}$) (49). The accumulation of HIF1 and HIF2 in hypoxia affects the polarization of the MHC-II$^{lo}$ macrophage phenotype (50, 51). This attraction results in a greater number of M2 or M2-like tumor-associated macrophages, which then promote the shift from M1 to M2 macrophage phenotype through the activity of HIF-2α (52). The activation of the M1 phenotype enhances glycolysis and disrupts the Krebs cycle, whereas the M2 activation relies on FAO and OXPHOS (53). Hypoxia inhibits efferocytosis and lipid digestion, thereby regulating macrophage differentiation toward an anti-inflammatory and prohomeostatic state (53). The high glucose consumption, as a central feature of tumor cells, leads to starvation and lactate accumulation at tumor sites, affecting macrophage phenotype and function (54). HIF-1α and activation of downstream arginase-1 contribute to the differentiation of the pro-tumor M2-like macrophage phenotype resulting from the accumulation of lactate in TME (Figure 2) (55). Additionally, hypoxia and low pH can affect bone marrow-derived macrophages and TAMs, leading them to express genes associated with anti-inflammatory macrophages, orchestrated via HIF-1α-dependent processes (56). However, hypoxic cycles stabilize HIF-1α, which can recruit the inflammasome components and activate inflammatory macrophages (56). HIF induces a shift from OXPHOS to glycolytic metabolism under hypoxic conditions, worsening inflammatory responses (Figure 3).



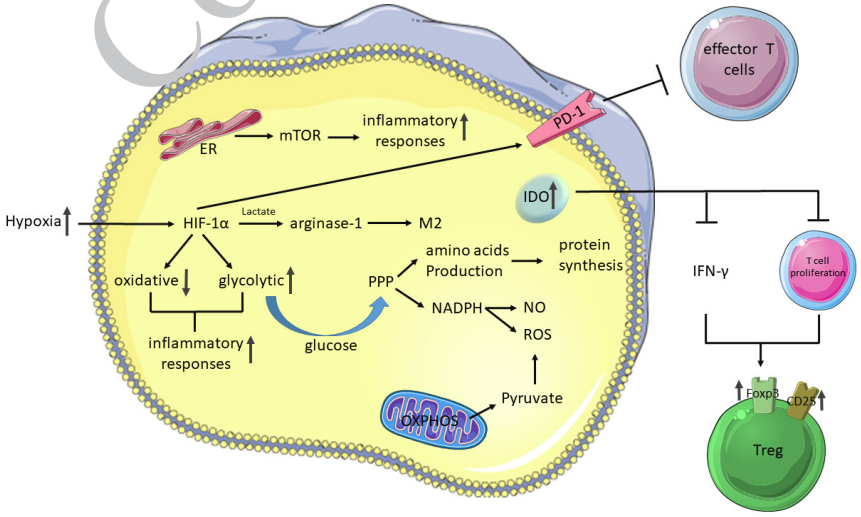


**Figure 3.** Schematic representation of the metabolic and immunoregulatory pathways in a hypoxic immune cell microenvironment

Hypoxia induces HIF-1α activation, shifting cellular metabolism toward glycolysis and enhancing inflammatory responses. mTOR signaling, endoplasmic reticulum (ER) activity, and increased arginase-1 expression promote M2 macrophage polarization and amino acid production, supporting protein synthesis. Glucose metabolism via the pentose phosphate pathway (PPP) generates NADPH, influencing NO and ROS production through the OXPHOS pathway. Up-regulation of PD-1 and IDO suppresses effector T cell activity and IFN-γ production, thereby inhibiting T cell proliferation and promoting Treg expansion (Foxp3+, CD25+), contributing to an immunosuppressive microenvironment. Nitric oxide (NO), indoleamine 2,3-dioxygenase (IDO).

The rapid induction of glycolysis provides the energy source in inflammatory macrophages. Glucose separates from the glycolysis pathway and enters the pentose phosphate pathway to supply amino acids that are necessary for protein synthesis, such as ribose in the structure of nucleotides. NADPH is required for the production of NO and ROS (Figure 3) (57).

Inflammatory macrophages utilize the TCA cycle metabolic pathway. Pyruvate produced by the OXPHOS pathway is repurposed for ROS synthesis, thereby driving further inflammatory responses in macrophages (58). microRNA (miR)-193a-3p and phosphatase PTC7 homolog (PPTC7) act oppositely in macrophages to promote glycolysis (59). Blocking PPTC7 through miR-193a-3p leads to an induction in Akt phosphorylation. This activation of Akt is crucial for the phosphorylation of 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3 (PFKFB3), an essential regulatory enzyme involved in glycolysis (59). Also, the interaction between hypoxia and ER stress is vital for macrophage metabolism and inflammatory responses, which are regulated by the mechanistic target of rapamycin (mTOR) as a regulator of anabolic pathways and energy consumption during cell growth (Figure 2) (60). In the TAMs situated within the hypoxic environment of the tumor, there is a rise in the expression of the stress-responsive protein called "regulated in DNA damage and development 1" (REDD1). This increase in REDD1 hinders glycolysis by inhibiting the mTOR (61).

There is a significant correlation between infiltration of TAM in hypoxic tumor niches and more unfavorable predictive results (62). Tumor-associated macrophages are commonly found in hypoxic zones, areas with low oxygen levels (63). This is often observed in solid tumors that produce increased levels of tumor growth elements such as glucose transporter 1 and VEGF (64). Hypoxic macrophages exhibit a proangiogenic response by up-regulating angiogenic molecules and modulators, such as PDGF, FGF2, IL1β, IL-8, CXCL8, angiopoietin, COX2, iNOS, and MMP7, via pathways reliant on HIF-1α (65). Furthermore, the expression of CXCL12/CXCR4, which is mainly associated with angiogenesis and cancer metastasis, was elevated by HIF-1 activity (66). Furthermore, macrophages limit the effectiveness of tumor-targeting T cells by displaying PD-L1 on their surface, via a pathway involving HIF-1α (67). In addition, Macrophages in hypoxic tumor niches suppress IFN-γ production and T cell proliferation by up-regulating IDO, thereby increasing $CD25^{+}Foxp3^{+}$ Tregs (Figure 2) (56). In the hypoxic TME, TAMs up-regulate ARG1 and iNOS to use up arginine and produce NO in response to the augmented presence of HIF-1α and HIF-2α(68). Several migratory factors, including CSF1, CCL2, and CCL5, are involved in macrophage migration to tumor hypoxic niches (69). They play a key role in guiding macrophages to hypoxic zones inside the TME. Various mechanisms, including the down-regulation of CCR2 and CCR5, increased expression of neuropilin-1 (NRP1), up-regulation of MAPK phosphatase 1 (MKP1), and the dephosphorylation of MEK, ERK1/2, and p38, are implicated in trapping TAM in the hypoxic niche (70, 71).

***Natural killer (NK) cells under hypoxia***

Although NK cells efficiently suppress tumor cells, some metabolic constraints, such as tumor-derived metabolites, impair their activation in the TME (72). The impact of hypoxic stress on NK cell phenotype is slight, whereas its effects on the NK cells' properties and functions are relatively different (72). Low oxygen levels decrease NK cell sensitivity to malignant target cells and increase cancer cell escape (73). Tumor cells are usually identified and destroyed by NK cells via NKG2D receptor engagement, with stress-regulated ligands such as Hsp70 and MICA/B on the cell surface of neoplastic cells (73). Hypoxia, by inducing down-regulation of Hsp70 and MICA/B and shedding MICA/B from the tumor surface, impairs NK cells' recognition and lysis (74). Moreover, MIC shedding from the tumor surface is accompanied by soluble MICA, leading to down-regulation of the NKG2D and CXC1 chemokine receptors (CXCR1) on NK cells (75).

NK cells are fundamental regulators of angiogenesis and have been identified as a source of intratumoral soluble VEGF receptor 1 (sVEGFR1) (76). sVEGFR1 has multifaceted function in tumor biology, with both pro- and anti-angiogenic functions. sVEGFR1 is a truncated form of the membrane-bound VEGFR1 receptor, lacking the transmembrane and tyrosine kinase domains. sVEGFR1 exhibits dual roles in tumor progression(77): Although sVEGFR1-i13 acts as a suppressor of new blood vessel formation, thereby hindering tumor progression and metastasis in mouse models, it also facilitates endothelial cell adhesion and migration by interacting with α5β1 integrin (77). Interestingly, HIF-1α-dependent NK cell inhibits the expression of NK cell-derived sVEGFR1 and aberrant angiogenesis under hypoxic conditions (78).

Under hypoxic conditions, tumor cells often release immunosuppressive cytokines, such as TGF-β, into the TME. Subsequently, it fosters the proliferation and presence of regulatory T cells in the TME. TGF-β interaction with its receptor on Tregs suppresses NK cell activity by inducing an anergic state, thereby decreasing NK cell NKG2D receptor activity (79, 80). In the hypoxic TME, NK cells can adapt and survive by up-regulating HIF-1α; however, they are no longer able to up-regulate NKp44, NKp35, NKp95, and NKG2D receptors in response to activating cytokines, including IL-12, IL-15, IL-2, and IL-21 (81).

Experimental findings have confirmed that NK cells can overcome hypoxia-induced impairments through a specific pre-activation process and metabolic adaptation. By exposing NK cells to normal oxygen levels for 7-9 days before subjecting them to hypoxic conditions (1.5% pO2), Lim *et al.* (82) showed a significant enhancement in NK cells' effector capabilities. This process triggers HIF-1α stabilization and up-regulates its downstream targets, including LDHA, VEGF, BNIP3, PDK1, and PKM2, shifting the cells' metabolism from OXPHOS to glycolysis. Moreover, the hypoxic environment induced up-regulation of the NKp44 receptor in natural killer cells through HIF-1α signaling. *In vitro* and *in vivo* studies demonstrated that this adjustment enhanced cytotoxicity against a range of tumor cell lines, including A375, K562, and CEM (82).

While hypoxic conditions drive NK cells to shift from OXPHOS to glycolysis, the FC-γ receptor III (CD16) does not undergo extensive alteration under hypoxic stress (81). Furthermore, the activation of the NKG2D receptor, as well as the amount of intracellular granular components (perforin and granzyme B), decreased (83). In addition, hypoxia induces autophagy, which has a detrimental effect on GzmB formation via autophagosomes (84). Also, hypoxia can stimulate the production of a protein called

matrix metalloproteinase (MMP)-7. In this condition, cancer cells in the hypoxic tumor microenvironment lose Fas ligand expression due to MMP-7-mediated cleavage, thereby suppressing NK cell-mediated lysis (85).

Increased lactate levels under hypoxic conditions affect the NK cells' function directly and indirectly. Enhanced lactate levels directly down-regulate the expression of both NKp46 and perforin/granzyme B (86). Moreover, increased lactate in TME promotes the development and expansion of myeloid-derived suppressor cells (MDSCs), which can hinder NK cell function (87). *In vitro* study showed that the co-culture of NK cells with IL-18, IL-15, and IL-12 promotes IFNγ production by metabolic reprogramming to glycolysis (88). In a transgenic model, TGF-β decreased IFN-γ secretion at the post-transcriptional level by destabilizing IFN-γ mRNA. The lack of IFN-γ can reduce NK cell-mediated cytotoxicity (89).

To enhance NK cell resilience in challenging metabolic environments, metabolic reprogramming is essential, either before administration or within the TME. This necessitates a deep understanding of the metabolic processes that influence NK cell cytotoxicity in the TME. One promising approach relies on antigen-presenting cells bearing surface-bound IL-21for ex vivo NK cell expansion (90). This method activates STAT3 signaling, which promotes a Warburg-like metabolic profile in NK cells, enhances their resistance to oxidative stress, and increases their metabolic adaptability (90). Further analysis has revealed that metabolically optimized NK cells exhibit reduced Type I and II interferon responses (91). This metabolic reprogramming strategy could overcome limitations imposed by the TME, thereby boosting the success rate of NK cell immunotherapy for cancer.

### *Dendritic cells (DCs) under hypoxia*

DCs are an essential component of anti-tumor immunity that gather tumor antigens, process them, and activate T cells through antigen presentation in tumor-draining lymph nodes. These processes activate and induce DC differentiation, maturation, and migration to secondary lymphoid organs. [136]. Cancer cells possess the ability to manipulate plasmacytoid dendritic cells (pDCs) within the TME, altering their immunogenic to tolerogenic functions to suppress immune responses (92). One crucial pathway involved in this process is hypoxia, which exerts complex effects on DCs (93). The cellular response to hypoxic conditions is intricately linked to the severity and duration of oxygen deprivation. Moderate hypoxia may allow cells to adapt and survive, while prolonged oxygen deficiency can lead to cellular death. Furthermore, hypoxia can influence DCs through both direct and indirect mechanisms, modulating the nature and strength of immune responses (93).

Hypoxic conditions can significantly alter DC behavior, affecting their maturation, migration, and T-cell priming. Chronic hypoxia during monocyte differentiation into immature DCs can result in a unique migratory phenotype, characterized by changes in chemokine receptor expression and genes involved in cell adhesion (94). Additionally, DC activity under hypoxic conditions is critically modulated by HIF-1α. HIF-1α activation in classical DCs has been shown to regulate lipid metabolism and the synthesis of lipid mediators, thereby impacting inflammation and atherosclerosis in obesity models (95). In hypoxic TME, ROS significantly affects DC function and plays a fundamental role in modulating anti-tumor immune activity. DCs can absorb ROS via various pathways, and the interplay between oxygen deprivation and oxidative stress can have a nuanced impact on DC functionality, capable of both stimulating and inhibiting the maturation of immature DCs (96). Oxidative stress has a bifunctional role in managing antigen processing and its subsequent presentation. It can enhance this process by creating an alkaline environment within phagosomes, which helps preserve antigens by deactivating protein-degrading enzymes (97). Additionally, ROS can directly modify these enzymes through oxidation, further affecting antigen processing. Low oxygen conditions induce changes in DC behavior, promoting increased mobility and inflammatory characteristics (97). Moreover, oxygen-deprived environments cause DCs to modulate T-cell responses, steering them towards a specific subset (Th17) that can potentially suppress tumor growth (97). These complex interactions between oxygen levels, oxidative stress, and DC function highlight the intricate nature of immune responses within the tumor microenvironment (TME).

Under hypoxic conditions in the TME, an elevated influx of immature dendritic cells into the tumor area occurs, accompanied by reduced migration of mature DCs to lymph nodes, driven by altered chemokine receptor expression (96). Furthermore, the hypoxia-triggered PI3K/AKT signaling cascade induces RNASET2 secretion in DCs and promotes anti-tumor immunity (98). Hypoxia can also enhance immune tolerance by recruiting immature DCs to lymph nodes (99). In contrast, the movement of fully developed DCs towards the lymph nodes is hindered by the inhibition of CCR7, CCL26, CCL24, and CCL14 expression. At the same time, there is up-regulation of CCR2, CCR3, CCR5, and C5R1 (100). Furthermore, the secretion of prostaglandin E2, a migration stimulator, is enhanced by various tumor types (101). Long-term hypoxia leads to the expression of CCL20, CCL3, and CCL5 in mature DCs, which can activate monocytes, T cells, and immature DCs (102). Reports suggest that dendritic cells exhibit elevated PD-L1 levels under hypoxic conditions, which increases interaction between Treg and DCs. Treg can reduce HLA-DR expression on type 2 conventional dendritic cell (cDC2) subset surface under hypoxic conditions (94). Furthermore, hypoxia up-regulates TLR4 expression and alters TNF-α secretion in monocyte-derived DCs, and increased TLR4 in LPS-treated DCs leads to increased autophagy (103). Hypoxia in DCs also stimulates a Th2 phenotype by converting IFN-γ secretion to IL-4, which can secrete IL-10 and suppress DC activation (104). At hypoxia, DCs release a lot of osteopontins as an enhancer of IFN-α production for up-regulation of the MHC-I expression by TLR9 signaling in plasmacytoid DCs (105).

Taken together, the impact of hypoxia on dendritic cells is multifaceted, involving complex changes in differentiation, maturation, and functional capacities. While hypoxic conditions can enhance certain aspects of DC functionality—such as migration and pro-inflammatory signaling—they may also inhibit critical immune functions like antigen uptake.

### *CAR-T cells under hypoxia*

Adoption of CAR-T cell approaches for treatment has received approval for treating malignant B-cell lymphomas in patients who have been given anti-CD19 CAR T cells.

Recently, five generations of CARs have been tested in clinical trials for a range of cancer types (106). The CAR ectodomain is created using an antibody designed via recombinant scFv technology to specifically bind tumor-associated antigens (107). Intracellular portions are taken from co-stimulatory and immune receptors that participate in the activation process of T cells (108). Second-generation CAR-T therapies are defined by the inclusion of co-stimulatory domains like 4-1BB and CD28, leading to significant improvements in treating malignant B-cell lymphomas and overcoming inhibitory factors (108). The other generations have also been developed using variant domains, such as OX40 (TNFRSF4) and ICOS, or gene editing, which can lead to potential lysis (108). The CAR receptor is engineered to specifically target surface tumor antigens, independent of the MHC molecule, which are often impaired in tumor cells (108). CAR T therapy has been implemented by reprogramming the patient´s T cells to express the CAR transgene using a retroviral vector (a replication-incompetent virus) (108, 109).

Interestingly, the primary distinction among the different generations of CAR T cells lies in the type of co-stimulatory molecule used, which exerts distinct effects on metabolic pathways in the TME (108). The primary features of the TME are inadequate nutrition, hypoxia, and immunosuppressive factors, which impact the physiological properties of armored CAR-T cells (110). Recent studies indicate that hypoxic conditions decrease both the proliferation and the production and discharge of cytokines, as well as the secretion of granzyme B, from engineered T cells (110). Additionally, while the total CAR T cell frequency remains unchanged, a rise in the CD4/CD8 ratio implies greater survival of CD4+ CAR T cells compared to CD8+ cells in hypoxia (111). Although hypoxia may impair CAR-correctors, using the 5H1P-CEA CAR design, Zhu et al. created CAR-T cells that respond to the hypoxic environment of tumors. These cells showed improved metabolic function, reduced differentiation, and less exhaustion compared to conventional CAR-T cells, potentially enhancing antitumor efficacy (112).

CAR-T cells incorporating the 4-1BB co-stimulatory region not only promote mitochondrial biogenesis, leading to a central memory and less-exhausted phenotype, but are also involved in extended longevity, lasting up to 5 years and often exceeding 6 months in many instances (113). IL-12 secreted by DCs has accompanied the fourth generation of CAR-T cells. Also, IL-18 is another secretory cytokine of CAR-T cells, reinforcing the proliferation and antitumor activity in TME (114). It has been reported that the development of Delta-like protein 3 (DLL3)-specific CAR T cells capable of IL-18 production has opened promising avenues for cancer treatment (114).

In hypoxic tumor settings, CAR T-cell function is compromised due to metabolic stress and depleted energy reserves. Addressing specific metabolic vulnerabilities could inform next-generation CAR T-cell engineering strategies (115). In 2021, a group of researchers led by Garcia-Canaveras conducted a study on the Lactobacillus brevis NADH Oxidase (LbNOX) enzyme for augmenting the antitumor potency and metabolic processes of human CAR T cells. The introduction of LbNOX into CAR T cells enhanced oxygen consumption, promoting the conversion of lactate to support anaplerotic processes in the TCA cycle and conferring resistance to inhibition of the electron transport chain. Moreover, LbNOX also led to increased intracellular NAD+ regeneration in CAR T cells (115). The expression of intracellular enzyme IDO in tumor cells and by inflammatory mediators, particularly IFN-γ, has been considered a negative regulator of CD19-CAR-T activation (116). It is noteworthy that a future approach to cancer immunotherapy could involve combining IDO inhibitors with CAR-T cells (116). Moreover, administering agents such as fludarabine and mafosfamide could potentially boost the therapeutic effectiveness of CAR-T cells beyond their standalone performance (117).

On the other hand, hypoxia amplifies PD-L1 up-regulation in neoplastic cells, weakening the tumor-killing capacity of CAR T cells (118). It is crucial to note that monoclonal antibodies that obstruct the PD-1/PD-L1 axis have been authorized to enhance the potency of engineered CAR T cells and restore exhausted CAR-T cells residing in the TME (119). Recent investigations have revealed the potential to genetically modify CAR T cells to produce a scFv that blocks PD-1 and directly targets tumor cells (119, 120). Hence, this approach potentially mitigates the adverse effects associated with immune checkpoint blockade (120). Additionally, there is promising progress towards creating an advanced generation of CAR-T cells that can release scFv fragments capable of detecting other molecules such as TIM-3 and CTLA-4, which was previously beyond expectations (121).

The hypoxic region has a striking effect on Carbonic anhydrase IX (CA IX) gene expression in cancerous cells. CA IX is crucial in various cancer processes, including migratory pathways and an aggressive/invasive phenotype (122). Because this gene is expressed in many tumor types, it could be an appropriate general marker of tumor hypoxia (122). CA IX antigen is a promising target for developing CAR T cells. According to a study by Cui *et al.*, a hypoxic environment in GBM leads to increased CAIX levels (123). The study found that administering anti-CAIX CAR T cells through direct intratumoral injection can effectively inhibit tumor growth. Therefore, targeting hypoxia-induced CAIX represents a hopeful avenue for the development of CAR T cell therapies (123). Because of these challenges, HypoxiCAR is designed to firmly resist a hypoxic environment and overcome the risk of on-target/off-tumor toxicity in murine studies. In addition, in murine liver, CAR T cells cannot expand, infiltrate, and accumulate against hypoxic tumor cells (124). In tumors, PGK1, SLC2A1, CA9, ALDOA, and VEGFA genes have been suitable targets for HypoxiCAR (125) (Figure 4). Overall, HypoxiaCAR T-cells represent a promising approach to enhance the safety and therapeutic impact of CAR T-cell therapies targeting solid tumors by leveraging their unique low-oxygen microenvironment.

***Metabolic crosstalk among immune cells in the hypoxic TME***

Hypoxia drives a complex metabolic interplay among tumor-infiltrating immune cells. The hypoxic TME is "a unique system for intercellular metabolic interactions," in which tumor and stromal metabolites reshape immune function. Glycolytic cancer cells export lactate via MCT4, which is then imported by nearby M2-like macrophages via MCT1 to fuel oxidative metabolism (126). This metabolic "symbiosis" contrasts with nutrient antagonism: intensive tumor glycolysis and glutaminolysis deplete oxygen and key fuels, while generating inhibitory byproducts. For example,

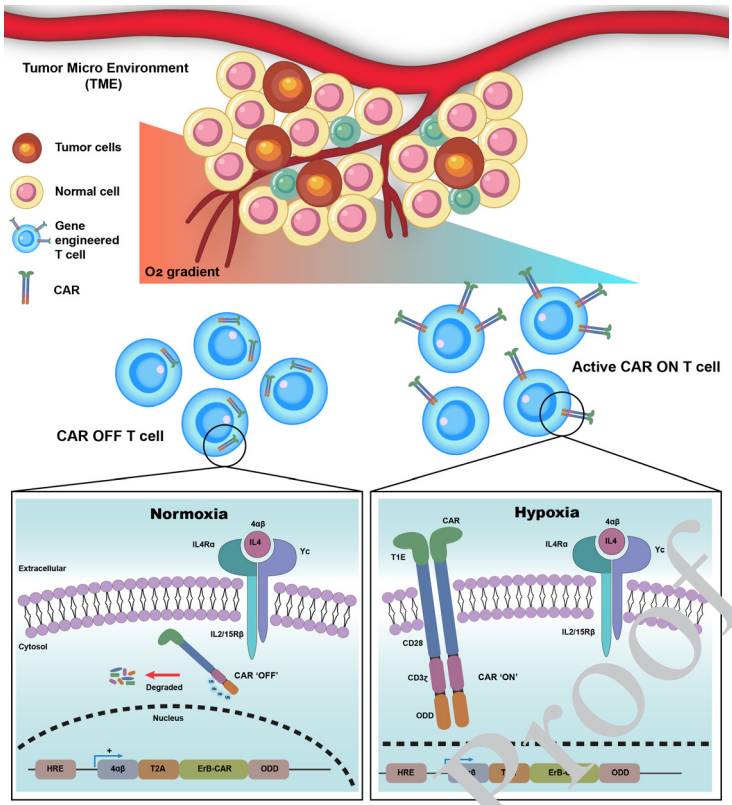


**Figure 4.** Schematic illustration of hypoxia-inducible CAR T cell activation in the tumor setting
The figure depicts the oxygen ($O_2$) gradient within the TME, with gene-engineered CAR T cells remaining inactive (CAR OFF) under normoxic conditions due to proteasomal degradation of the CAR construct. Under hypoxic conditions, hypoxia response elements (HRE) and oxygen-dependent degradation domains (ODD) stabilize CAR expression, resulting in CAR T cell activation (CAR ON). Insets detail the molecular mechanisms regulating CAR expression in normoxia versus hypoxia, highlighting the role of HRE, ODD, and associated signaling domains in controlling T cell activity for targeted tumor immunotherapy.

PET and imaging studies show that TAMs and tumor cells, together, outcompete effector T cells for glucose and glutamine (127). In practice, TAMs (high GLUT1) and tumor cells (high glutamine transporters) acquire most of these nutrients, creating a metabolic barrier to $CD8^+$ T cells (127). Thus, hypoxia fosters tight metabolic coupling: suppressive macrophages and Tregs thrive on shared metabolites, while effector CTLs and NK cells are starved and inhibited (Figure 5).

*Lactate shuttling and immune polarization*

Lactate is a central metabolite mediating immune cross-talk. In hypoxic tumors, elevated glycolysis drives extracellular lactate accumulation, acidifying the TME (128). High lactate/low pH directly impairs $CD8^+$ T cells and NK cell cytotoxicity, for example, by inhibiting their glycolysis

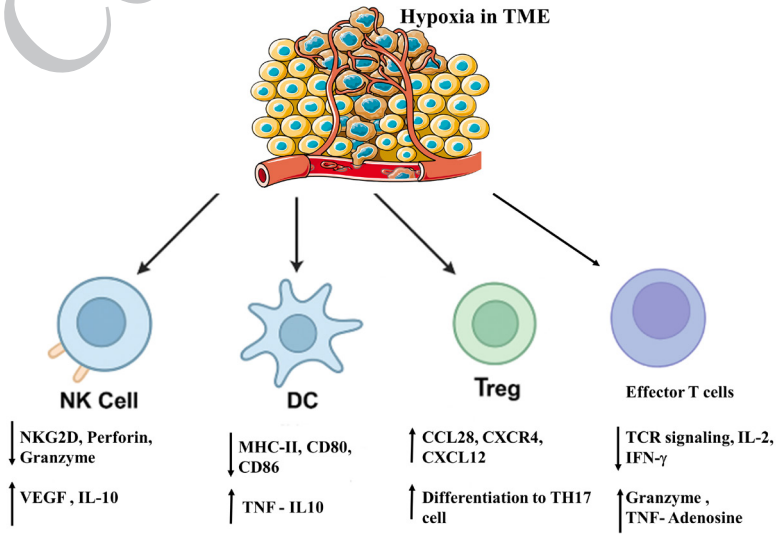


**Figure 5.** Impact of hypoxia on key immune populations within the tumor microenvironment (TME)
Central hypoxia (cloud) drives distinct phenotypic and functional changes in innate and adaptive immune cells. Arrows indicate direction of change (↑, increase; ↓, decrease). These hypoxia-driven alterations are commonly mediated by HIF-1α–dependent metabolic and signaling reprogramming (adenosine and lactate accumulation), thereby contributing to immune suppression within hypoxic tumor niches.

and perforin–CD107a expression (128). In contrast, immunosuppressive cells are favored: lactate stabilizes HIF-1α/NF-κB and enhances regulatory phenotypes (129). Notably, tumor-derived lactate "drives macrophage polarization toward the pro-tumor M2 phenotype" (129). Lactate-educated M2 TAMs up-regulate ARG1 and IL-10, remodel chromatin (like histone acetylation at Arg1), and shift to oxidative metabolism, further skewing immunity (129). Tregs are also "avid" lactate users: they express high levels of MCT1 and can catabolize lactate to sustain FoxP3 expression and suppressive capacity (129). Indeed, Tregs incubated with lactate up-regulate PD-1 and secrete more IL-10/TGF-β, whereas effector $CD8^+$ T cells in the same milieu become exhausted. Thus, lactate shuttling creates a feedback loop: glycolytic neighbors feed Tregs and TAMs while starving CTLs. Even dendritic cells (DCs) are impaired: lactate blocks DC maturation and antigen-presentation (down-regulating MHC-II and co-stimulatory molecules), crippling their ability to activate CTLs (130). In melanoma models, blocking lactate production rescued DC function and T cell priming (131). Collectively, lactate accumulation in hypoxic niches enforces an immunosuppressive network – M2-like macrophages, Tregs, and myeloid suppressors – at the expense of effector T and NK activity (132).

*Nutrient competition: amino acid depletion in hypoxia*

Hypoxia also amplifies competition for scarce nutrients among immune subsets. Cancer cells and stromal elements aggressively seize amino acids required for immunity. For example, tumors and cancer-associated fibroblasts (CAFs) markedly up-regulate glutamine transporters (e.g., SLC1A5) and take up glutamine (and serine) far more efficiently than lymphocytes (133). In situ imaging shows that intratumoral myeloid cells and cancer cells dominate glucose and glutamine uptake, leaving CTLs deprived of these fuels (134, 135). Such deprivation "profoundly impact[s] antitumor immunity," as effector T cells require glycolysis and glutaminolysis for proliferation and cytokine secretion. Similarly, arginine is entrapped by the tumor stroma and suppressive myeloid cells (135). TGF-β–driven fibrosis drives fibroblasts to convert arginine into proline (for collagen), effectively sequestering extracellular arginine. M2 TAMs and MDSCs express high ARG1 to continuously hydrolyze arginine to ornithine, depleting it from the milieu (136). This arginine sink undermines T cell receptor expression and proliferative capacity (136). Lastly, tryptophan is catabolized by indoleamine-2,3-dioxygenase (IDO1/TDO2) in cancer and immune cells. Up-regulated IDO/TDO exhausts tryptophan from the TME, causing CTL dysfunction and even apoptosis (137). The accumulating catabolite kynurenine is immunosuppressive – it engages the aryl-hydrocarbon receptor (AhR) in Tregs and macrophages, promoting Treg expansion and an M2-like macrophage program (137). In sum, hypoxic tumors deplete glutamine, arginine, and tryptophan via both tumor metabolism and myeloid enzymatic activity, starving effector lymphocytes and feeding regulatory and myeloid suppressor cells.

*Metabolic enzymes and sensors in hypoxia*

Key metabolic enzymes and sensors integrate these cross-talk signals. IDO1/TDO2 in tumor or dendritic cells triggers tryptophan catabolism, while ARG1 in TAMs/MDSCs degrades arginine (136). HIF-1α is up-regulated under low oxygen and by lactate, and drives transcription of glycolytic genes, VEGF, and Arg1 (138). In lactate-rich microenvironments, HIF-1α sustains ARG1/VEGF expression in TAMs, reinforcing suppressive M2 polarization (139). Nutrient-sensing mTORC1 also modulates immune crosstalk: TAMs employ mTOR-driven programs to boost nutrient uptake (e.g., GLUT1, GLS1) in hypoxic zones (139). By contrast, chronic stress signals can inhibit mTOR in T cells: for instance, elevated extracellular $K^+$ from necrotic tumor cells suppresses T cell Akt–mTOR signaling via PP2A, further weakening effector function (140). Aryl hydrocarbon receptor (AhR) serves as a metabolic receptor: its activation by kynurenine skews myeloid cells toward a tolerogenic phenotype (141). Indeed, high AhR activity in TAMs correlates with rapid progression and resistance to therapy, whereas AhR deletion reinvigorates $CD8^+$ responses (141). Thus, hypoxia and its metabolites harness enzymes (IDO1, ARG1) and sensors (HIF-1α, mTOR, AhR) in immune cells to coordinate a metabolically suppressive state.

*Synergistic immune suppression by metabolic stress*

In combination, nutrient scarcity and metabolite accumulation synergistically disable anti-tumor immunity. As one review summarizes, "metabolic antagonism in the TME suppresses CD8+ T cell function by depleting essential nutrients and generating toxic byproducts" (142). Glucose and amino acid depletion starve CTLs and force them into energetically unfit states, while accumulated lactate, protons, kynurenine, and even potassium ions activate inhibitory pathways (NF-κB, STAT3, AhR, PP2A) that induce exhaustion and tolerance (142). Together, these effects tilt the balance in hypoxia: effector T and NK cells are metabolically crippled and enter an exhausted phenotype, whereas Tregs, MDSCs, and M2 macrophages are fueled and stabilized by the altered metabolite milieu (143). Understanding this multifaceted immune–immune metabolic interplay is critical, as it reveals how hypoxic nutrient depletion and the buildup of suppressive metabolites jointly skew the TME toward immune evasion and may guide therapies to restore immune function.

*NK–DC cross-talk under hypoxia*

Although direct reports specifically characterizing NK–DC cross-talk in hypoxic tumor niches are still emerging, convergent evidence indicates that hypoxia markedly alters both NK cell effector function and dendritic cell stimulatory capacity, which would be expected to impair their bidirectional communication. Hypoxia and HIF-1α signaling reduce NK cytotoxicity, the expression of activating receptors, and NK recruitment into tumor nests (144). Concurrently, HIF-1α can promote a more anti-inflammatory/tolerogenic DC phenotype and limit DC-mediated T-cell stimulation. Together, these hypoxia-driven changes — including increased adenosine production via CD73 and metabolic stressors such as lactate — create an environment that is likely to disrupt NK–DC reciprocal activation and weaken downstream adaptive responses (145). We therefore highlight the need for focused studies that directly probe NK–DC interactions in hypoxic TMEs and for therapeutic strategies that restore NK and DC function in low-oxygen niches

***Targeting of hypoxia via HIF-1 for therapeutic implications***

While cancer immunotherapy utilizing immune

checkpoint blockade has shown impressive long-term results across various cancer types, recent studies suggest that a significant obstacle to its effectiveness is the hypoxic TME. This milieu leads to immune system suppression and hinders therapeutic success by driving numerous tumor biological changes and imposing considerable cellular stress (146). Among the various strategies developed to address hypoxia in cancer (Table 1), the most prominent include inhibiting HIF signaling, targeting hypoxia-driven pathways, including the UPR, through hypoxia-activated prodrugs (HAPs), and implementing metabolic interventions. A growing number of drugs designed to target HIF are currently in development, categorized by their diverse molecular mechanisms that block HIF dimerization, hinder DNA binding, modulate mRNA or protein synthesis and degradation, and affect transcriptional activity based on their distinct modes of action (147).

Research has shown that antisense targeting of HIF1-α to reduce HIF-1 expression boosts T-cell performance and promotes effective CD8+ T-cell antitumor immunity, leading to tumor destruction (148). Furthermore, inhibiting HIF1-α in combination with DC-based immunotherapy may lead to tumor shrinkage and improved survival. In a breast cancer model, this method enhances cytotoxic T cell proliferation and function, as well as IFN-γ release (149). According to Xu *et al.*, a benzofuran compound inhibited tumor progression by targeting the HIF-1α/VEGF signaling pathway in low-oxygen environments (150). The novel benzofuran-based analog MO-460, derived from (R)-(-)-moracin-O, inhibits HIF-1α protein synthesis by targeting the start of its translation. MO-460 binds to the glycine-rich C-terminal domain of hnRNPA2B1, thereby preventing this protein from attaching to the 3'-untranslated region of HIF-1α mRNA (151). The PEGylated SN-38 compound EZN-2208, derived from irinotecan metabolism, effectively disrupts HIF-1 pathway activity via suppression of HIF-1α mRNA expression (152). This leads to a decrease in crucial molecules involved in tumor angiogenesis, including TGFβ1, MMP2, GLUT1, GLUT3, and VEGF1 (152). Some pharmacological agents exert direct effects on HIF mRNA, including aminoflavone, thioredoxin pathway blockers such as AJM290 and AW464, and antisense oligonucleotides targeting HIF-1α, such as EZN-2698 (153).

Despite their intended actions, these compounds have also been reported to stabilize HIF-1α and HIF-2α. EZN-2968, a locked nucleic acid (LNA) oligonucleotide, suppresses the translation of HIF-1α mRNA, thereby reducing HIF-1α protein synthesis (154). The use of EZN-2968 to inhibit HIF-1α has been identified to significantly decline tumor growth by impeding cell proliferation, which may be attributed to a delay in S-phase progression and a shift toward mitochondrial oxidative metabolism (154). Moreover, daunorubicin and doxorubicin are part of the anthracycline group of antibiotics, which interfere with HIF-1's access to HRE sequences, thereby suppressing hypoxia-driven gene transcription (155). A range of drugs that can

**Table 1.** Application of various agents for targeting hypoxia via HIF-1α for therapeutic implications.

| Study | Phase | Drug | Dose | Mechanism | Diseases | Results | Ref. |
|---|---|---|---|---|---|---|---|
| Choueiri *et al.*, 2024 | III | Belzutifan | 120 mg/daily | HIF-2α inhibitor | Renal-cell carcinoma (RCC) | PFS<br>ORR | (192) |
| Wiley *et al.*, 2024 | II | Belzutifan | 120 mg/daily | HIF-2α inhibitor | Retinal hemangioblastoma (RCH) | Eye improvement | (193) |
| Brugarolas *et al.*, 2024 | I | ARO-HIF2 | 22[illegible] weekly | siRNA for HIF-2α | RCC | ORR= 7.7%<br>DCR= 38.5% | (194) |
| Tsang *et al.*, 2024 | I | Abexinostat | [illegible] mg/m² | HDAC inhibition down-regulates HIF-1α | Solid tumor malignancies | long-term disease control | (195) |
| Borad *et al.*, 2015 | II | TH-302 + Gemcita[illegible] | 240-340 mg/m² | Hypoxia-activated prodrugs | Pancreatic cancer | Increased OS, PFS<br>Decreased MDSC | (196) |
| Chawla *et al.*, 2014 | II | TH-302 + Doxorubicin | 240- 575 mg/m² | Hypoxia-activated prodrugs | Soft tissue sarcoma | Increase: OS<br>Decrease: MDSC density | (197) |
| Kummar *et al.*, 2011 | I | Topotecan | 1.6 mg/m² | Direct HIF-1α inhibition | Refractory advanced solid neoplasms | Decrease: HIF-1α expression, tumor blood flow | (198) |
| Jayaprakash *et al.*, 2018 | Preclinical mouse model | TH-302 | 200 mg/m² | Hypoxia-activated prodrugs | prostate cancer | Complete cure in tumors increase: CD8+ T cells, Cytotoxicity, IFN-γ<br>Decrease: MDSC density | (199) |
| Jeong *et al.*, 2013 | A pilot trial | EZN-2968 | 18 mg/kg | Direct HIF-1α targeting by antisense oligodeoxynucleotide | Refractory solid tumors | Decrease: HIF-1α mRNA and protein expression | (200) |
| Tang *et al.*, 2016 | *In vitro* study | EZN-2698 | 0.01 mg/ml | Direct HIF-1α inhibition | U251 human glioma cells | Inhibition of HIF-1α mRNA expression | (201) |
| Terzuoli *et al.*, 2010 | Xenograft model | Aminoflavone | 60 mg/kg | Direct HIF-1α inhibition | Adenocarcinoma | Inhibition of HIF-1α mRNA expression | (202) |
| Chen *et al.*, 2018 | II | CRLX101 + Olaparib | 15 mg/m² | Direct HIF-1α inhibition | mCRPC | Improved ORR and PFS | (203) |
| Hendricksen., 2012 | II | Apaziquone | 0.1 mg/ml | Hypoxia-activated prodrug | Bladder cancer. | Decrease: Recurrence Score and Progression score | (177) |
| Hutson *et al.*, 2014 | III | Temsirolimus | 25 mg/weekly | Indirect targeting HIF-1α via mTOR | Renal Cell Carcinoma | longer OS | (204) |
| Sun *et al.*, 2001 | Xenograft model | Antisense -HIF-1α | - | targeting HIF signaling | EL4 tumor | Decrease: Tumor Size, VEGF expression,<br>Increase: NK cell cytotoxicity | (205) |
| Kheshtchin *et al.*, 2016 | Mouse model | PX-478 | 40 mg/kg | targeting HIF signaling | Breast cancer | Increase: T cell proliferation, cytotoxicity, IFN-γ production<br>Decrease: Tregs, tumor growth | (149) |
| Mabjeesh *et al.*, 2003 | Mouse model | 2-Methoxyoestradiol (2ME2) | 30 mg/kg | Dysregulation of HIF-1α | Breast cancer | Reduction of HIF-1α protein level and VEGF mRNA expression | (206) |
| Bulle *et al.*,2020 | Xenograft model | Acriflavine | - | Inhibition of HIF-1 dimerization | Pancreas Cancer | Decrease: Tumor growth, angiogenic cytokines | (207) |
| Kong *et al.*, 2005 | *In vitro* assay | Echinomycin | 320 nmol/l | Targeting HIF1- DNA binding activity | U251 human glioma cells | Prevention of HIF-1 DNA binding | (208) |
| Cook *et al.*, 2009 | *In vitro* assay | ETP | 25 μM | Dysregulation of HIF-1α | HCT 116 colorectal cells | Inhibition of HIF-1 transcriptional activity | (209) |
| Chun *et al.*, 2001 | *In vitro* assay | YC-1 | 100 -200 μM | post-translational inhibition of HIF-1α | Hematoma cell line | Inhibition of HIF-1 protein synthesis and accumulation | (210) |
| Li *et al.*, 2012 | Xenograft model | b-elemene | 25-100 mg/kg | Direct HIF-1α inhibition | Lung adenocarcinoma | Increase: tumor radioresponse<br>Decrease: HIF-1 expression | (211) |
| Chiu *et al.*, 2017 | Mice Model | POM-1(ENTPD2 inhibitor) | 10 mg /kg | HIF-1 promotes MDSCs accumulation through ENTPD2 | Hepatocellular carcinoma | Increased: T cell infiltration, improved survival with immunotherapy | (169) |

disrupt the translational control of HIF-1α mRNA has been identified. These include agents that inhibit topoisomerase I, such as irinotecan and topotecan, PI3K/AKT/mTOR pathway inhibitors, and the antiangiogenic compound 2-methoxyestradiol (2ME2)(156). Furthermore, the destabilization of HIF-1α through enhanced degradation has been associated with agents such as histone deacetylase inhibitors—examples include belinostat, 6-gingerol, panobinostat (LBH589), vorinostat, and romidepsin (FK228) (157).

Other drugs have been identified that can suppress the transcriptional activity of HIFs, including PT2385, FM19G11, and acriflavine, which specifically target HIF-2α (158). Additionally, chetomin has been shown to disrupt the interaction between HIF and p300, thereby inhibiting HIF-DNA binding (159).

Panobinostat, a histone deacetylase inhibitor (HDACi), and carfilzomib, a proteasome inhibitor, have been studied in combination for relapsed/refractory multiple myeloma (RRMM), with emerging evidence linking their mechanisms to HIF-1α modulation (160). Panobinostat destabilizes HIF-1α, a transcription factor critical for cancer adaptation to low oxygen conditions and chemotherapy resistance (160).

In addition, Vorinostat was the first histone deacetylase inhibitor (HDACi) to receive FDA approval for the management of cutaneous T-cell lymphoma, and it effectively prevents the stabilization of HIF-1α. It does this by acetylating its associated chaperone, Hsp90, which subsequently suppresses downstream elements such as VEGF, EPO, and GLUT1 (161). It has been shown that SCH66336 exerts antiangiogenic effects by dissociating HIF-1α from its chaperone Hsp90, destabilizing HIF-1α, and reducing its expression (162). While some clinical studies reported no objective responses to SCH66336 when used alone in taxane-refractory or resistant metastatic NSCLC patients, SCH66336 combined with paclitaxel showed minimal toxicity and was generally well tolerated (163).

Under hypoxic conditions, the enzyme UCHL1 stabilizes HIF-1α by blocking its degradation. Inhibiting UCHL1 accelerates HIF-1α breakdown, reducing the activity of its cancer-promoting downstream genes. This suppression decreases tumor-associated factors, effectively curbing UCHL1-driven cancer cell growth and spread (164). Furthermore, acriflavine binds specifically to the PAS-B domain of HIF-1α, thereby blocking its dimerization with HIF-1β. This disruption impairs HIF-1 transcriptional activity, ultimately leading to suppression of tumor progression and a reduction in tumor-associated angiogenesis (165). Additionally, 2-Methoxyestradiol (2ME2, Panzem), a natural metabolite of estradiol that inhibits HIF-1α transcriptional activity, demonstrated significant antiangiogenic and antiapoptotic effects in cancer cells (166).

A potential strategy to suppress HIF-1α activity involves the combined use of PX-478, a known HIF-1α inhibitor, with immune checkpoint blockade. This combination has been shown to potentiate T cell-mediated tumor cell killing, possibly by interfering with the HIF-1α-driven LOXL2 and VEGF signaling cascade (167). Additionally, CRLX101 (inhibits both topoisomerase I and HIF-1α) has shown synergistic effects with immunotherapy in preclinical models (168).

Interestingly, Chiu *et al.* showed that combining ENTPD2 inhibitors (targeting HIF-1α) with anti-CTLA-4/PD-1 therapy significantly outperformed anti-CTLA-4/PD-1 monotherapy in tumor-bearing mice. This dual approach boosted T cell entry into tumors and prolonged survival, highlighting its promise for improved cancer therapy (169). Another interesting agent, WELIREG (MK-6482), a groundbreaking HIF-2α inhibitor, received FDA approval in 2021 for treating adults with Von Hippel-Lindau (VHL) disease. It suppresses the transcription and expression of HIF-2α target genes involved in cell growth, blood vessel formation, and tumor development (170). A Phase III trial (NCT04195750) is assessing the effectiveness and safety of MK-6482 versus everolimus in previously treated patients with advanced clear cell renal cell carcinoma (ccRCC) (171).

Hypoxia-activated prodrugs (HAPs) are initially non-toxic molecules that become pharmacologically active only under low-oxygen conditions via specific enzymes, allowing them to selectively target and eliminate tumor cells (172). This transformation is facilitated by cellular reductases, which utilize a single electron to create a prodrug radical. This radical can subsequently be reoxidized to its original form in non-hypoxic cells. Alternatively, the prodrug may be directly converted into a cytotoxic agent via a two-electron reduction pathway (172).

Initial research indicated that mitomycin C and tirapazamine (TPZ) are preferentially activated in hypoxic environments, allowing them to selectively target and kill hypoxic cells (173). Ajnai *et al.* developed a nanomedicine by conjugating TPZ, a hypoxia-activated prodrug, with gold nanoparticles (GNPs) using BSA as a binding mediator. The resulting GNPs–TPZ nanoparticles demonstrated enhanced tumor targeting and therapeutic efficacy in MKN45 xenograft models, specifically targeting hypoxic tumors while maintaining safety by not altering blood biochemical parameters in animals (174). Similarly, SN30000, an analog of tirapazamine with improved pharmacokinetic and pharmacodynamic profiles, has shown potent antitumor activity in xenograft studies (175).

Animal and clinical data indicate that Evofosfamide (TH-302), a next-generation HAP, does not impair T cell-driven antitumor immunity and can be safely combined with immunotherapy due to its non-lymphotoxic profile (176). In patients with superficial bladder cancer, the local use of EO9 (a mitomycin C analog) has yielded promising clinical outcomes (177). Based on the evidence, EO9 was evaluated in two Phase III trials as a postsurgical adjuvant therapy for bladder cancer. In parallel, CP-506—a nitrogen mustard-based prodrug activated under anoxic conditions—also exhibited beneficial effects within tumor tissues (178).

Recognizing the complexity of hypoxia-activated HIF networks is essential, as they involve multiple overlapping molecular and signaling pathways. Therefore, further investigation into combination anti-tumor therapies that target hypoxia, metabolic pathways (particularly glycolysis), and abnormal angiogenesis is essential. In line with previous reports, the HIF-1α and HIF-2α-mediated up-regulation of carbonic anhydrase IX (CAIX) appears to enhance glycolytic activity and support an immunosuppressive TME, particularly in solid malignancies (179). Accordingly, inhibition of CAIX with monoclonal antibodies or the small-molecule inhibitor SLC-0111 has the potential to boost immune responses by enhancing cytotoxicity, modulating the acidic TME, and reducing glycolytic metabolism in cancer cells (180). Inhibiting CAIX has been shown to sensitize tumors to immunotherapy, resulting in

improved Th1 immune responses and reduced tumor growth and metastasis (181). Additionally, hexokinase 2 (HK2), a crucial regulator of aerobic glycolysis in cancer cells, has become an essential target for cancer treatment. The use of 3-bromopyruvic acid (3-BP) to inhibit HK2 has resulted in significant suppression of tumor growth and cellular proliferation in colorectal cancers expressing HK2 (182).

Respiratory hyperoxia at 60% oxygen increases tumor infiltration by immune cells and reduces cytotoxic T lymphocyte suppression, thereby improving lung tumor elimination alongside combined CTLA-4 and PD-1 inhibition (183). Oxygen therapy, when combined with existing immunotherapies, can help diminish tumor hypoxia and suppress the increase of extracellular adenosine regulated by the HIF-1α-CD39/CD73 signaling route (184). This, in turn, attenuates the A2AR/A2BR-mediated immunosuppressive cascade present in the low-oxygen tumor milieu (Table 1) (184). Therapies targeting angiogenic factors, including VEGF or VEGFR, not only can reduce hypoxia through anti-angiogenic effects but also support immune responses (185). However, using angiogenesis inhibitors as standalone treatments can exacerbate tumor hypoxia, leading to resistance to therapy and potentially worsening clinical outcomes (185). Consequently, delivering anti-angiogenic treatments at low doses has been found to improve immunotherapeutic responses with fewer adverse effects (Table 1).

Despite the identification of numerous small molecules and drugs that inhibit HIF-1α, none have yet become successful anticancer therapies. Clinical trials of HIF-1 inhibitors have repeatedly encountered limited efficacy and safety issues. Key obstacles include lack of drug specificity (leading to off-target toxicity), intratumoral heterogeneity and adaptive resistance, poor patient selection, and delivery barriers in hypoxic tumor regions. Table 2 summarizes these translational challenges.

### *Future perspective*

The future of cancer immunotherapy lies in the strategic targeting of hypoxia within the TME. Low-oxygen conditions, a defining feature of solid tumors, play a significant role in helping tumors evade the immune system and resist treatment by fostering an immunosuppressive TME (69). Addressing hypoxia through innovative therapeutic strategies could improve the efficacy of current immunotherapies, such as CAR T-cell therapies and immune checkpoint inhibitors.

Emerging single-cell spatial metabolomics (scSpaMet) technologies promise to revolutionize our view of the hypoxic microenvironment (186). The application of the scSpaMet platform combines high-resolution mass spectrometry imaging with multiplex protein profiling to map >200 metabolites and ~25 protein markers in each cell *in situ*. By linking metabolic signatures to specific immune and tumor cell types, such methods could reveal how hypoxia reshapes metabolic states at cell-level resolution (187). Ultimately, spatial multi-omics may uncover novel metabolic vulnerabilities in hypoxia-adapted immune populations, guiding tailored interventions in the TME. Meanwhile, AI-assisted drug discovery is accelerating the development of novel HIF-targeted compounds. Recent studies illustrate that machine learning combined with virtual screening can efficiently sift large chemical libraries to predict potent HIF-1α inhibitors (188). These algorithms improve candidate selectivity and reduce development time compared to trial-and-error methods. Looking ahead, AI-driven pipelines may rapidly expand libraries of HIF-1/HIF-2 inhibitors or even suggest entirely new scaffolds, addressing heterogeneity in tumor hypoxia pathways (188).

Combining hypoxia-targeted agents with other therapies is another promising avenue. Preclinical and early clinical data show that adding HIF inhibitors can sensitize tumors to chemotherapy, radiotherapy, or immunotherapy (189). In fact, co-administering HIF blockade with immune checkpoint inhibitors could be a "game changer", as it may suppress tumor plasticity and overcome resistance (189). This suggests designing trials where HIF inhibitors are given as adjuncts (e.g., combined with anti-PD-1/PD-L1 antibodies) in hypoxic tumors. Such combination regimens could leverage metabolic modulation to enhance

**Table 2.** Translational barriers to HIF-1–targeted therapies in cancer

| Challenge | Description | Examples / Evidence | Ref. |
|---|---|---|---|
| Off-target toxicity | Many HIF-1 inhibitors lack specificity and interfere with non-HIF pathways, leading to systemic side effects | BAY 87-2243 was terminated in Phase I trials due to safety concerns | 212 |
| Tumor heterogeneity | Spatial and temporal variation in hypoxia leads to inconsistent HIF-1 expression and uneven drug responses | HIF-1α expression is often focal; tumors may compensate with HIF-2α or other pathways | 213 |
| Compensatory pathways | Redundant signaling (e.g., HIF-2α, MYC, mTOR) can bypass HIF-1α inhibition, sustaining tumor survival | Upregulation of HIF-2α after HIF-1 inhibition is well documented | 214 |
| Poor patient selection | Lack of biomarker-based stratification results in treatment of non-hypoxic or HIF-1 low tumors, diluting efficacy outcomes | Trials have enrolled unselected patients, masking potential benefit in HIF-1 high subgroups | 215 |
| Drug delivery barriers | Hypoxic tumor cores are poorly vascularized, reducing drug penetration into the regions where HIF-1 is most active | Hypoxia impairs diffusion of therapeutics into deep tumor tissue | 216 |
| Intrinsic and acquired resistance | Hypoxia-induced resistance mechanisms (e.g., glycolysis, drug efflux pumps) persist despite HIF-1 inhibition | Hypoxia induces MDR1 and glycolytic enzymes, sustaining resistance | 217 |
| Lack of pharmacodynamic Biomarkers | Difficult to measure target engagement or hypoxia modulation *in vivo*, limiting ability to assess efficacy mechanistically | Few validated PD biomarkers for HIF-1 inhibition exist | 218 |
| Need for combination strategies | Monotherapies often underperform; combining HIF-1 inhibitors with immunotherapy or angiogenesis inhibitors is more promising | Emerging studies support combining HIF-1 blockade with VEGF inhibitors or immune checkpoint blockade | 219 |

antitumor immune responses. Despite these advances, several translational barriers remain. Early HIF-1–targeted drugs often lacked specificity, causing off-target toxicities that stalled clinical progress (147). To address this, future drug development should focus on improving selectivity and delivery. For example, nanoparticle carriers or hypoxia-activated prodrugs can concentrate drug activity in the tumor, enhancing pharmacokinetics and reducing systemic side effects (190). Concurrently, novel chemistries should aim for dual HIF-1/HIF-2 inhibition or exploit tumor-specific metabolic pathways to maximize impact while minimizing collateral damage.

Equally important is a more brilliant clinical trial design and patient stratification. Past failures of hypoxia-targeted therapies have been attributed to unselected enrollment of patients without assessing tumor oxygenation. As we advance, trials of HIF inhibitors should be hypoxia-enriched: only patients with confirmed hypoxic or high HIF-expressing tumors should be randomized. Biomarkers such as hypoxia PET tracers, gene-expression signatures, or circulating HIF-regulated factors can identify this subgroup (191). Biomarker-guided trials require fewer patients and yield clearer signals of efficacy. By integrating adaptive designs (e.g., early metabolic or immune readouts) and robust patient selection, these trials will more effectively test the true potential of HIF-targeted agents.

## Conclusion

The hypoxic TME plays a pivotal role in shaping the immune landscape of cancer through intricate metabolic, molecular, and cellular reprogramming. Hypoxia not only drives tumor progression and metastasis but also orchestrates immune evasion by impairing effector T cell and NK cell function, promoting the expansion of immunosuppressive cells such as Tregs, MDSCs, and TAMs, and altering cytokine networks toward tolerance and suppression. Hypoxia-targeted oncology is moving into a new era. The convergence of advanced spatial metabolomic mapping, AI-driven drug design, and rational combination therapies offers a robust toolkit. Addressing translational challenges through innovative delivery systems and biomarker-guided trials will be critical. Together, these strategies lay a roadmap for translating the biology of the hypoxic immune niche into effective treatments, ultimately bringing hypoxiamodulating therapies from bench to bedside.

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## Authors' Contributions

D A suggested the main title and revised the final manuscript. R R drafted and critically revised the work. H M, H KH, and A R wrote the manuscript equally. F A designed the figure. All authors reviewed the manuscript.

## Conflicts of Interest

The authors state that they have no conflicts of interest.

## Declaration

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