Hypoxia in lymphoma: Mechanistic remodeling of the tumor microenvironment, disease progression and therapeutic resistance (Review)

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Abstract. Hypoxia is increasingly recognized as a determinant of tumor behavior across multiple malignancies; yet, its role in lymphoma remains incompletely defined and is frequently generalized across biologically distinct disease entities. In lymphoma, hypoxia is not merely a consequence of rapid tumor expansion and abnormal vascularization, but an active driver of tumor microenvironment remodeling, metabolic adaptation, immune escape, angiogenesis and therapeutic resistance. Emerging evidence suggests that hypoxia-inducible signaling, lactate accumulation, adenosine metabolism, macrophage polarization and altered mitochondrial fitness collectively shape lymphoma progression and treatment response. However, the strength of evidence varies markedly by lymphoma subtype and a notable proportion of mechanistic assumptions is still derived from solid tumors or non-lymphoma systems. The present review provides a structured summary of current knowledge regarding hypoxia in lymphoma, with emphasis on microenvironmental regulation, disease progression and resistance to chemotherapy, radiotherapy, antibody-based therapy and cellular immunotherapy. Particular attention is given to the distinction between direct lymphoma-derived evidence and indirect extrapolation. The present review also highlights major unresolved questions, including subtype-specific heterogeneity, differences between acute and chronic hypoxia, and the need for clinically actionable biomarkers and combination strategies. A more rigorous understanding of hypoxia in lymphoma may improve biological stratification and identify context-specific therapeutic vulnerabilities.

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Abbreviations: ABC, activated B cell-like; ADCP, antibody-dependent cellular phagocytosis; CAIX, carbonic anhydrase IX; CAR-T, chimeric antigen receptor T cell; HL, Hodgkin lymphoma; cHL, classical HL; CTCL, cutaneous T cell lymphoma; DLBCL, diffuse large B cell lymphoma; ECM, extracellular matrix; FL, follicular lymphoma; HIF, hypoxia-inducible factor; HK2, hexokinase 2; MCL, mantle cell lymphoma; NHL, non-HL; PCNSL, primary central nervous system lymphoma; ROS, reactive oxygen species; TME, tumor microenvironment; VEGF, vascular endothelial growth factor; BACH2, BTB and CNC homology 2

Key words: lymphoma, hypoxia, TME, HIF-1α, metabolic reprogramming, immune evasion, angiogenesis, therapeutic resistance

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1. Introduction

Hypoxia is a common feature of the tumor microenvironment (TME) and has been extensively studied in solid malignancies. However, lymphoma represents a biologically distinct disease system in which hypoxic signaling is shaped by the architecture of lymphoid tissues, extranodal dissemination, immune-cell-rich niches and treatment-induced microenvironmental remodeling (1). Therefore, findings derived from solid tumors cannot be directly extrapolated to lymphoma without considering subtype- and site-specific differences.

Lymphoma represents a heterogeneous group of malignant tumors arising from the lymphohematopoietic system. It is characterized by the clonal expansion of lymphoid cells in lymph nodes, lymphoid tissues, bone marrow, peripheral blood or extranodal organs (2). According to clinicopathological and molecular features, lymphoma is broadly classified into Hodgkin lymphoma (HL) and non-HL (NHL), with NHL comprising multiple biologically distinct subtypes, including diffuse large B cell lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL), marginal zone lymphoma, T cell lymphoma and natural killer (NK)/T cell lymphoma (3). These entities differ markedly in cellular origin, mutational landscape, microenvironmental dependence, therapeutic sensitivity and prognosis. Although modern immunochemotherapy, targeted therapy, immune checkpoint blockade and cellular therapy have improved outcomes for numerous patients, relapse, refractory disease and therapy-related resistance remain major clinical challenges (4-6).

Although numerous reviews have summarized the features of hypoxia, hypoxia-inducible factor (HIF) signaling, immune suppression and therapeutic resistance across cancer types, numerous lymphoma-specific questions remain insufficiently addressed: Where hypoxia emerges in lymphoma, which lymphoma subtypes and cellular compartments are most affected, how robust the supporting evidence is for the hypoxia-driven molecular and pathological mechanisms in lymphoma and which mechanisms are closest to clinical translation. These unresolved questions form the central focus of the present review. A growing body of evidence indicates that lymphoma progression cannot be explained solely by tumor cell-intrinsic genetic events (7-9). Lymphoma cells develop within immune-rich tissues and are continuously shaped by surrounding non-malignant cells, soluble mediators, extracellular-matrix (ECM) components, vascular structures, metabolites and physical constraints (10). Therefore, the TME acts as an active ecological system that influences tumor-cell survival, immune escape, dissemination, metabolic adaptation and treatment response (11). In some lymphoma subtypes, microenvironmental dependencies are so strong that malignant cells cannot be fully understood outside their anatomical and immunological niche. For instance, classical Hodgkin lymphoma (cHL) Hodgkin-Reed-Sternberg (HRS) cells rely heavily on signals from surrounding reactive immune-stromal compartments (12).

Hypoxia is one of the most biologically influential features of the TME. In solid tumors, hypoxia is commonly generated by rapid tumor growth, abnormal vascular architecture and insufficient oxygen delivery. In lymphoma, hypoxia may also occur in bulky nodal masses, bone marrow niches, lymphoid follicles, extranodal lesions and metabolically active tissue compartments (13). Unlike a simple physical shortage of oxygen, hypoxia acts as a selective pressure that induces adaptive transcriptional, metabolic, epigenetic and immunological programs. Central to this response are HIFs, particularly HIF-1α and HIF-2α, which regulate genes involved in glucose metabolism, angiogenesis, cell survival, immune regulation, ECM remodeling and therapeutic resistance (14).

The clinical relevance of hypoxia in lymphoma is increasingly apparent. Hypoxia-related gene signatures can identify biologically distinct lymphoma subgroups, correlate with immune infiltration and checkpoint expression, and predict prognosis or drug sensitivity in certain settings (15). Hypoxic signaling can also weaken the efficacy of chemotherapy, radiotherapy, antibody-based therapy, immune checkpoint blockade, photodynamic therapy and chimeric antigen receptor T-cell (CAR-T) therapy; some of these functional readouts have been well established in solid tumors but remain to be systematically validated in lymphoma (16). The consequences of hypoxia are not uniform. Depending on lymphoma subtype, anatomical site, stromal composition, vascular structure and immune contexture, hypoxia can support tumor survival, suppress immune surveillance or even enhance selected immune-effector functions (17).

The present review summarizes the current understanding of hypoxia in lymphoma, with emphasis on the formation of hypoxic niches, HIF-mediated and HIF-independent signaling, metabolic and immune reprogramming, invasion and dissemination, treatment resistance and emerging therapeutic strategies. By integrating mechanistic and translational perspectives, it can be proposed that hypoxia may represent a context-dependent regulator of lymphoma biology and a potential therapeutic vulnerability that requires further lymphoma-specific validation. Improved understanding of hypoxia-driven lymphoma ecology may support refined risk stratification frameworks and inform the rational design of combination therapies integrating HIF-pathway modulation, metabolic intervention, vascular normalization, immunotherapy, cellular therapy and nanomedicine-based approaches.

Although hypoxia has been extensively reviewed in the context of solid tumors and generalized cancer biology, lymphoma presents a distinct biological setting in which hypoxic signaling is shaped by unique anatomical niches, subtype-specific cell states and therapy-dependent microenvironmental remodeling. Existing reviews on tumor hypoxia have mainly emphasized canonical HIF biology, angiogenesis, immune suppression and treatment resistance across cancer types.but they do not resolve.

This distinction between solid tumor and lymphoma-specific hypoxia biology is relevant as lymphoma develops in lymphoid organs and extranodal tissues with specialized stromal, vascular and immune contexts, and hypoxia may exert different effects in nodal disease, bone marrow infiltration, central nervous system lymphoma, cutaneous lymphoma and other site-specific disease settings (1,18). Furthermore, the biological consequences of hypoxia are not uniform across DLBCL, MCL, FL, HL, peripheral T cell lymphoma and related entities.

Therefore, the present review does not merely summarize general hypoxia pathways; instead, it proposes a lymphoma-specific framework that integrates lymphoma subtype, anatomical niche, relevant cell type, evidence strength and therapeutic maturity. By organizing the field around these dimensions, the present review aims to clarify what is known, what remains uncertain and which hypoxia-driven programs represent actionable vulnerabilities in lymphoma.

The present narrative review retrieved literature from PubMed (https://pubmed.ncbi.nlm.nih.gov) and Web of Science (https://www.webofscience.com), with searches conducted from inception up to August 2026. Search key words included ‘lymphoma’, ‘hypoxia’, ‘HIF-1α’, ‘tumor

microenvironment', 'metabolic reprogramming', 'immune evasion', 'angiogenesis', 'therapeutic resistance', 'CAR-T' and 'targeted therapy'. Reference lists of key papers were manually screened for additional records. Only English-language peer-reviewed original articles and reviews were included; abstracts, case reports and preprints were excluded. Primary data from lymphoma-related cell models, patient specimens and clinical cohorts were prioritized. Mechanisms solely from solid tumor studies were explicitly marked as indirect extrapolations in-text. Formal full Preferred Reporting Items for Systematic reviews and Meta-Analyses systematic screening was not performed for the present narrative review (19).

2. Formation and regulation of the hypoxic lymphoma microenvironment across subtypes and anatomical niches

Formation of hypoxic niches in lymphoma. The formation of hypoxic niches in lymphoma is not uniform across disease entities or anatomical sites. In contrast to solid tumors, lymphoma develops within lymphoid organs and extranodal tissues that are already structured and immune rich, including lymph nodes, bone marrow, spleen, skin and central nervous system compartments. These tissue contexts influence oxygen availability, vascular organization and stromal interactions, thereby creating heterogeneous hypoxic environments (1).

The hypoxic lymphoma microenvironment arises from an imbalance between oxygen supply and oxygen consumption. Rapidly proliferating lymphoma cells exhibit high metabolic activity and may consume oxygen faster than it can be delivered by the local vasculature (20). At the same time, tumor-associated vessels are often immature, tortuous, leaky and poorly organized, leading to heterogeneous perfusion and impaired oxygen diffusion. In bulky lymphoma masses, oxygen gradients may develop between well-perfused peripheral regions and poorly oxygenated tumor cores. In bone marrow and lymphoid tissues, local oxygen tension is also influenced by stromal density, vascular architecture, cellular crowding, inflammatory mediators and metabolic competition (21).

Hypoxia in lymphoma is not merely a consequence of tumor mass. Physiological lymphoid microenvironments can exhibit fluctuating oxygen tension, and normal lymphocyte activation, germinal center reactions and plasma-cell differentiation are associated with notable metabolic remodeling (22). Therefore, malignant lymphoid cells may inherit or exploit oxygen-adaptive programs that already operate during normal immune responses. In B cell lymphomas, mitochondrial transcription, mitochondrial translation and oxidative-metabolic adaptation can influence germinal center entry, lymphomagenesis and sensitivity to mitochondrial-targeted therapies (23). This link between physiological lymphoid biology and tumor hypoxia helps explain why lymphoma can display hypoxia-related features despite not being a classical solid tumor.

Vascular and coagulation-related processes can further amplify oxygen deprivation. Abnormal endothelial activation, tissue factor expression, microthrombus formation and local inflammation may impair oxygen delivery and create regions of perfusion-limited hypoxia. Such perfusion-limited hypoxia is well described in solid tumors and could occur within lymphoma lesions; however, direct evidence in lymphoma tissues remains limited (24,25). Therapy itself may intensify this process. For example, vascular-targeted photodynamic therapy depends on oxygen-mediated reactive oxygen species (ROS) generation; however, oxygen consumption and vascular injury during treatment can worsen local hypoxia and reduce therapeutic efficacy (26). Thus, hypoxia should be regarded as a dynamic and treatment-modifiable state rather than a static feature.

Collectively, these observations support the view that hypoxic niche formation in lymphoma is determined by both tumor burden and anatomical context, with distinct implications for different subtypes and disease sites.

HIF-dependent signaling. Hypoxia in lymphoma is regulated by both oxygen-dependent and -independent pathways. The canonical stabilization of HIF-1α and HIF-2α under low oxygen conditions remains central, but lymphoma cells also activate hypoxia-associated programs (including glycolytic reprogramming, redox homeostasis adaptation, angiogenesis signaling, extracellular matrix remodeling and immune-modulatory transcriptional programs) through oncogenic signaling, metabolic stress and microenvironmental crosstalk (27). The relative contribution of these pathways appears to vary across lymphoma subtypes. Unlike in numerous solid tumors, hypoxia-related signaling in lymphoma is embedded in a dynamic immune and stromal ecosystem. As a result, the same hypoxic stimulus may elicit different transcriptional and metabolic responses depending on the cellular compartment involved, including malignant B cells, T cells, macrophages, fibroblasts and endothelial cells (1).

HIFs are master regulators of cellular adaptation to oxygen deprivation (28). Under normoxic conditions, HIF-α subunits are hydroxylated by oxygen-dependent prolyl hydroxylase domain enzymes, recognized by the von Hippel-Lindau complex, ubiquitinated and degraded by the proteasome. Under hypoxia, hydroxylation is suppressed, allowing HIF-α stabilization, nuclear translocation, dimerization with HIF-β and activation of hypoxia-responsive genes [including glucose transporter 1 (GLUT1), hexokinase 2 (HK2), 3-phosphoinositide-dependent protein kinase 1, vascular endothelial growth factor (VEGF), carbonic anhydrase IX (CAIX) and monocarboxylate transporter-4 (MCT4)] (29). In lymphoma, HIF-1α is the most extensively studied isoform, although HIF-2α and other oxygen-sensing regulators may exert distinct and occasionally opposing functions (30).

HIF-1α promotes metabolic adaptation by increasing glucose uptake and glycolytic flux through the induction of glucose transporters, HKs, lactate dehydrogenase, pyruvate dehydrogenase kinase and carbonic anhydrases (31,32). These changes allow lymphoma cells to maintain ATP production and biosynthesis under low-oxygen conditions while reducing mitochondrial oxygen consumption. HIF-1α also induces expression of VEGF and other angiogenic mediators (33). However, hypoxia-induced angiogenesis often generates abnormal vessels that fail to restore effective oxygenation, resulting in a self-reinforcing cycle of hypoxia, aberrant angiogenesis and microenvironmental dysfunction (34,35). This feedback loop is well characterized in multiple solid tumor models and may similarly operate within lymphoma tissues.

Beyond metabolism and angiogenesis, HIF-1α regulates survival, migration, immune escape and therapeutic resistance.

It can influence BCL-2 family proteins, autophagy-related pathways, DNA damage responses, immune checkpoint expression, cytokine networks and stromal-cell communication (36-39). In MCL, HIF-related suppression of BTB and CNC homology 2 (BACH2) may facilitate adhesion, dissemination and resistance to proteasome inhibition (40). In cutaneous T cell lymphoma (CTCL), the IL-9-HIF-1α-Cofilin-1 axis may promote malignant T-cell migration (41). In T cell lymphomas and selected experimental models, HIF signaling can interact with Notch, Myc, PI3K-AKT-mTOR and other oncogenic pathways (17,42,43). Numerous downstream consequences of these crosstalk events have been demonstrated in solid tumors but remain to be validated in the majority of lymphoma subtypes.

Thus, hypoxia regulation in lymphoma should be viewed as a context-dependent network rather than a linear HIF-centered pathway.

HIF-independent and context-dependent adaptation. Although HIF signaling is central to hypoxic adaptation in lymphoma, hypoxic adaptation is not exclusively HIF-dependent. ROS-mediated signaling, mitochondrial dysfunction, sirtuin 3 loss, unfolded protein response activation, autophagy, epigenetic remodeling and non-coding RNA regulation can also shape the lymphoma response to oxygen stress, as inferred from solid tumor studies, albeit direct lymphoma-specific validation remains limited. A subset of these observations derives from non-lymphoma cancer models; however, their quantitative contribution to hypoxic adaptation in primary lymphoma cells remains incompletely defined (44-47). These pathways may operate independently of HIFs or cooperate with HIF-mediated transcription to create a broader stress-adaptive phenotype.

Global HIF inhibition may not uniformly benefit patients. HIF-1α and HIF-2α exert divergent functions dictated by cell identity. In malignant lymphoma cells, HIF-1α principally drives glycolytic reprogramming, anti-apoptotic survival signaling, VEGF-driven pro-angiogenic gene expression, stromal adhesion and therapeutic resistance. By contrast, in $CD8^+$ cytotoxic T cells, HIF-1α supports glycolytic metabolism, tissue migration and effector cytokine production required for antitumor cytotoxicity; therefore, HIF-1α does not universally mediate immunosuppression. HIF-2α also displays cell-type-specific activity: In certain preclinical settings (overexpression of FIH-insensitive mutant HIF-2α in mouse $CD8^+$ T cells and human anti-CD19 CAR-T cells co-expressing this variant in lymphoma xenograft adoptive transfer models), HIF-2α enhances $CD8^+$ T-cell cytotoxic capacity, while, within tumor-associated macrophages, both HIF-1α and HIF-2α can promote an immunosuppressive M2-like phenotype and upregulate inhibitory fragment crystallizable γ (Fcγ) receptors to impair antibody-dependent cellular phagocytosis (ADCP). Within endothelial cells, HIF-1α triggers the formation of immature, leaky tumor vessels that perpetuate intratumoral hypoxia. In mesenchymal stromal cells of lymphoma-infiltrated niches, HIF-1α upregulates C-X-C motif chemokine ligand 12 (CXCL12) and IL-6 to reinforce prosurvival crosstalk with malignant lymphocytes and sustain minimal residual disease, particularly within the bone marrow microenvironment. Therefore, HIF pathways can promote tumor growth in lymphoma cells; however, they may also support selected immune-effector functions in cytotoxic T cells under nutrient- and oxygen-limited conditions (42,48,49). Furthermore, HIF-1α and HIF-2α can have different roles depending on cell type and microenvironmental context. HIF-1α often supports glycolysis and immunosuppression, whereas HIF-2α may enhance cytotoxic T-cell activity in non-lymphoma experimental systems and remains to be verified in lymphoma-infiltrating T-cell populations (50). Therefore, hypoxia-targeted therapy requires cell-type-specific and subtype-specific understanding rather than non-selective suppression of all oxygen-sensing pathways (Fig. 1).

Subtype- and niche-specific features of hypoxia in lymphoma. Hypoxia exerts divergent biological effects across lymphoma subtypes, shaped by cell of origin, intrinsic oncogenic drivers, tissue-specific anatomical niches, vascular architecture and local immune microenvironment. Key subtype- and niche-dependent features are summarized below.

DLBCL. DLBCL frequently presents as bulky nodal masses with heterogeneous intratumor oxygen gradients between well-perfused peripheral zones and hypoxic tumor cores. Activated B cell-like (ABC)- and germinal-center B cell-like (GCB)-DLBCL demonstrate distinct metabolic and immune responses to hypoxia. Hypoxia-driven glycolysis, high HIF-1α activity and programmed death-ligand 1 (PD-L1) upregulation are more commonly reported in ABC-DLBCL, contributing to immunosuppression and chemoresistance (1). Hypoxic gene signatures correlate with inferior prognosis, reflecting both metabolic reprogramming and macrophage-dominated suppressive stroma. Bone-marrow-infiltrating DLBCL cells additionally encounter physiologically hypoxic bone marrow niches that promote minimal residual disease (20).

MCL. MCL exhibits marked tropism for bone marrow and lymph nodes. In hypoxic niches, the HIF-1α-mediated repression of BACH2 enhances lymphoma-cell adhesion, dissemination and resistance to proteasome inhibitors (40). The C-X-C chemokine receptor type 4 (CXCR4)-CXCL12 axis, amplified under low-oxygen conditions, supports retention within bone-marrow stromal compartments, conferring niche-mediated drug protection (1,51).

FL. FL arises within germinal-center structures that already possess physiological fluctuating oxygen tension. Hypoxia interacts with follicular dendritic cell and mesenchymal stromal cell signaling to sustain tumor B cell survival (10). In indolent FL, angiogenic changes are relatively modest; however, hypoxia becomes more prominent during histological transformation to high-grade lymphoma, selecting for aggressive subclones and promoting immune escape (1).

cHL. The cHL microenvironment is dominated by abundant reactive immune-infiltrates and stromal components with relatively sparse malignant HRS cells. HRS cells upregulate HIF-1α and VEGF even in less hypoxic conditions, driving vascular remodeling and PD-L1 expression (28). Hypoxia amplifies cHL-associated immunosuppression; however, the immune-rich microenvironment partly explains the relatively high responsiveness of cHL to immune-checkpoint blockade compared with numerous B cell NHLs (52,53).

Primary central nervous system lymphoma (PCNSL). PCNSL resides within the unique central-nervous-system

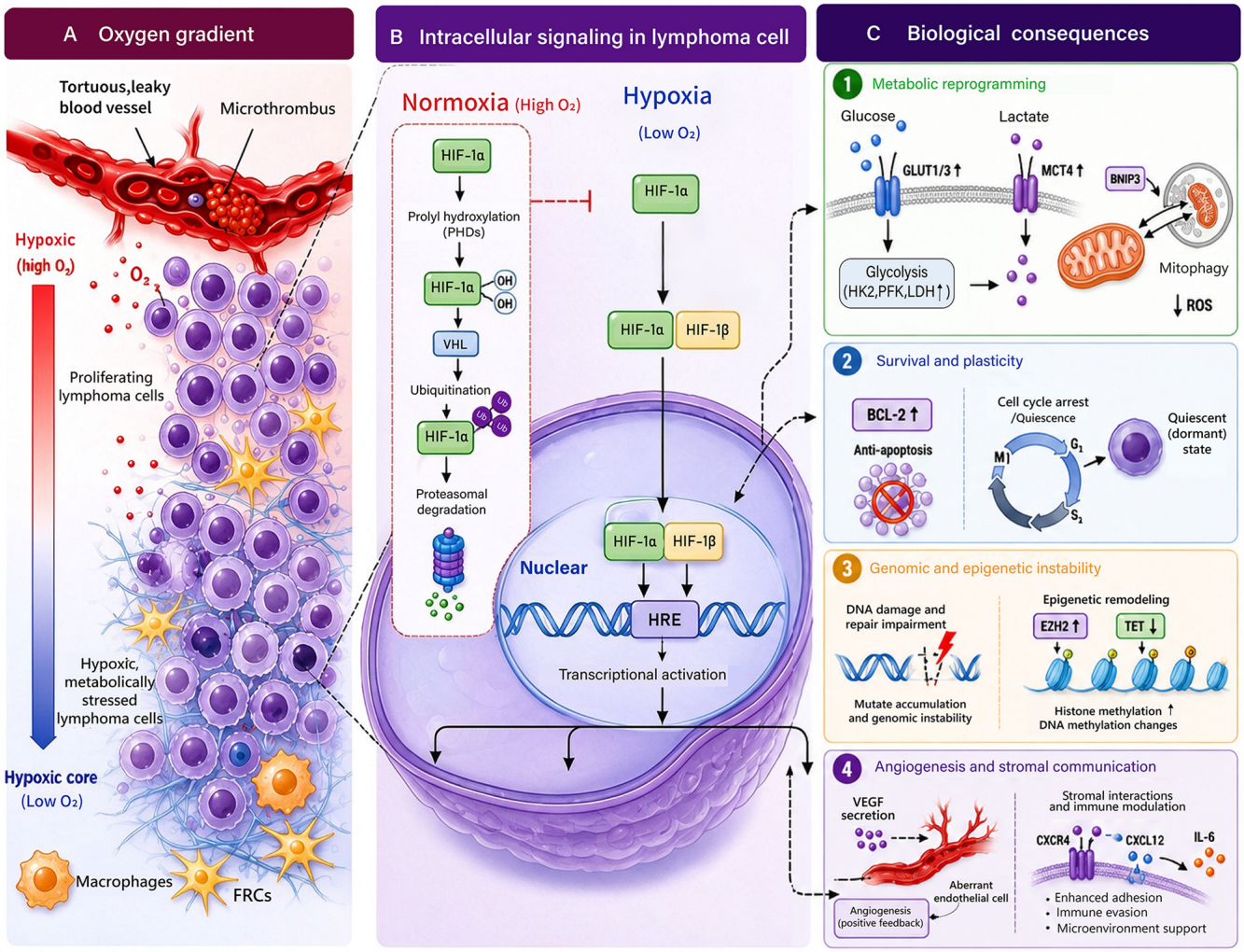


Figure 1. Oxygen gradient and HIF-1α signaling pathways conferring malignant hallmarks to hypoxic lymphoma cells. (A) Lymphoma tissues establish an oxygen gradient from oxygen-rich lesion edges to severely hypoxic tumor cores, with tortuous leaky vessels, microthrombi, proliferating lymphoma cells, macrophages and FRCs distributed across this niche. (B) Under normoxia, HIF-1α is hydroxylated by PHDs, recognized by VHL, ubiquitinated and degraded by proteasomes; hypoxia stabilizes HIF-1α, which heterodimerizes with HIF-1β, translocates into the nucleus, binds HREs and initiates downstream gene transcription. (C) HIF-1α signaling promotes metabolic reprogramming marked by enhanced glycolysis, lactate export and mitophagy to reduce ROS, supports cell survival and quiescence via BCL-2 upregulation and cell cycle arrest, induces genomic and epigenetic instability through impaired DNA repair and aberrant histone and DNA methylation, and triggers pro-angiogenic VEGF secretion alongside stromal crosstalk mediated by CXCR4-CXCL12 and IL-6 signaling. TME, tumor microenvironment; HIF-1α, hypoxia-inducible factor-1α; ROS, reactive oxygen species; GLUT1, glucose transporter type 1; HK2, hexokinase 2; PFK, phosphofructokinase; LDH, lactate dehydrogenase; BNIP3, BCL2/adenovirus E1B 19 kDa-interacting protein 3; VEGF, vascular endothelial growth factor; EZH2, enhancer of zeste homolog 2; TET, ten-eleven translocation; CXCL12, C-X-C motif chemokine ligand 12; CXCR4, C-X-C chemokine receptor type 4; HRE, hypoxia response element; FRCs, fibroblastic reticular cells; VHL, von Hippel-Lindau protein; MCT4, monocarboxylate transporter 4; PHD, prolyl hydroxylase domain protein.

perivascular niche, which is characterized by limited vascular perfusion, blood-brain barrier constraints and distinct nutrient availability. Hypoxia-HIF-1α signaling cooperates with endoplasmic reticulum stress to support malignant B-cell survival. Hypoxia-associated metabolic adaptations contribute to treatment resistance and limited drug penetration within the brain parenchyma (54).

CTCL, including Sézary syndrome. The skin is an anatomically heterogeneous niche with inherent oxygen gradients across epidermal and dermal layers. In CTCL, the IL-9-HIF-1α-Cofilin-1 signaling axis drives malignant T-cell migration and skin infiltration. Hypoxia remodels dermal macrophages and cytokine networks to establish a locally immunosuppressive skin microenvironment, supporting disease persistence (41).

Epstein-Barr virus (EBV)-associated lymphomas. EBV-driven lymphomas (including EBV-positive DLBCL and extranodal NK/T cell lymphoma) combine viral oncogenic signaling with hypoxia-triggered stress responses. Hypoxia stabilizes HIF-1α and cooperates with NF-κB, JAK-STAT and viral gene programs to increase genomic instability, promote survival under metabolic stress and augment immune evasion. Numerous mechanistic observations are derived largely from preclinical models, while direct human *in vivo* data on EBV-associated lymphoma remain limited (55).

It should be emphasized that multiple downstream hypoxia-regulated pathways (including glycolysis, angiogenesis, immune-checkpoint upregulation and stromal crosstalk) are shared across lymphoma subtypes. However, their phenotypic output and clinical consequences are heavily modulated

by the cellular origin of malignant clones and the properties of their resident anatomical niches. Distinct hypoxia-associated molecular pathways, experimental models, biological consequences, clinical associations and evidence levels across major lymphoma subtypes are summarized in Table I.

3. Biological consequences of hypoxia in lymphoma cells

Metabolic reprogramming and mitochondrial adaptation. Metabolic reprogramming is one of the most consistent consequences of hypoxia. Lymphoma cells under hypoxic stress shift toward glycolysis, increase glucose uptake, enhance lactate production and alter intracellular pH regulation (56). This glycolytic adaptation supports survival when mitochondrial oxidative phosphorylation is constrained. At the same time, acute hypoxia can reduce mitochondrial mass and oxygen consumption, lowering basal mitochondrial ROS generation and limiting immediate oxidative damage and apoptosis. However, this effect is context-dependent: Sustained chronic hypoxia or reoxygenation episodes can trigger excess ROS production, driving DNA injury and genomic stress (24). Some of these mitochondrial-stress phenotypes have been well studied in solid tumors; however, their exact magnitude in primary lymphoma cells may vary by disease subtype.

Mitochondrial adaptation is not simply a reduction in respiration. Hypoxic lymphoma cells may activate mitophagy, mitochondrial quality control and stress-response pathways to preserve metabolic homeostasis (57). BCL2/adenovirus E1B 19 kDa-interacting protein 3 (BNIP3) and BNIP3-like (BNIP3L)-mediated mitophagy, together with overlapping with the m-AAA protease 1 homolog-dependent mitochondrial stress responses and protein kinase RNA-like endoplasmic reticulum kinase-eukaryotic initiation factor 2α-activating transcription factor 4 signaling can support survival under metabolic pressure (58). Evidence for these mitophagy-related survival circuits is robust in numerous solid tumor models (59-61); however, the mechanism by which they function across diverse lymphoma subtypes remains to be fully validated. These processes allow malignant cells to remove damaged organelles, limit excessive ROS accumulation and preserve viability in adverse microenvironmental conditions.

Hypoxia also alters lipid and amino acid metabolism. HIF signaling can promote fatty-acid synthesis, lipid storage and reductive glutamine metabolism, thereby providing substrates for membrane biosynthesis, redox balance and anabolic proliferation. These metabolic rewiring events are well documented in solid tumor systems and could contribute to lymphoma pathophysiology (62). In certain lymphoma preclinical models, hypoxia selectively enhances the translation of metabolic enzymes such as HK2, linking oxygen stress to subtype-specific metabolic vulnerability (63). This finding is supported by DLBCL experimental data but remains unvalidated in other lymphoma subtypes (63). These findings suggest that hypoxia-induced metabolism is not a uniform 'glycolytic switch', but a coordinated remodeling of glucose, mitochondrial, lipid, amino acid and redox pathways.

Regulation of proliferation, apoptosis and cellular plasticity. Cellular plasticity describes the ability of lymphoma cells to dynamically reshape transcriptional profiles, cytoskeletal architecture and adhesion-related molecules to adapt to diverse microenvironmental niches (64). Epithelial-mesenchymal transition (EMT)-like features refer to cytoskeletal and adhesion receptor remodeling that phenotypically resembles EMT; given the non-epithelial ontogeny of lymphoma cells, this is not true EMT (65). Dissemination indicates the migration of malignant lymphoid cells from primary sites and the colonization of distant anatomical sites such as bone marrow and extranodal tissues (66). Tissue infiltration represents local accumulation and invasion of lymphoma cells within tissue parenchyma. Consistent with lymphoma pathobiology, the present study uses the terms dissemination and tissue infiltration instead of the solid tumor-specific term metastasis throughout the manuscript (65,66).

Hypoxia exerts complex effects on lymphoma cell proliferation and survival. Acute or severe hypoxia can slow down proliferation, induce cell-cycle arrest and trigger apoptosis. By contrast, chronic or adaptive hypoxia may select for clones that tolerate metabolic stress, evade apoptosis and acquire therapy-resistant phenotypes (67). This dual effect explains why hypoxia can both suppress immediate cell proliferation and ultimately promote aggressive disease.

Cell-cycle regulation is a key component of this adaptation. Hypoxia can induce quiescence or checkpoint activation, reducing sensitivity to drugs that primarily target rapidly dividing cells (68). At the same time, hypoxia can increase anti-apoptotic signaling through BCL-2 family proteins, PI3K-AKT activation, autophagy and stress-response pathways (28). In EBV-associated lymphomas, hypoxia may cooperate with viral oncogenes, NF-κB, JAK-STAT signaling and DNA damage responses to support survival and genomic instability (69).

Hypoxia may also promote phenotypic plasticity. In lymphoid malignancies, the term EMT should be used cautiously since lymphoma cells are not epithelial in origin. However, hypoxia can induce EMT-like or plasticity-associated programs involving cytoskeletal remodeling, adhesion changes, chemokine receptor expression and invasive transcriptional networks (70). Hypoxia-driven EMT-like transcriptional programs are well described in epithelial tumors, while their functional roles in lymphoma invasion are hypothetical and require experimental validation in lymphoma models.

A number of these hypoxia-driven plasticity signatures were originally described in epithelial-derived tumors, and their functional impact on lymphoma invasion and dissemination remains to be comprehensively evaluated in lymphoma-specific models (71). These invasive programs are particularly relevant for MCL and CTCL, which display high tissue dissemination propensity. These programs may enhance motility, tissue infiltration and relapse potential.

Genomic instability and epigenetic remodeling. Hypoxia can promote genomic instability through multiple mechanisms. While acute hypoxia may suppress basal mitochondrial ROS, chronic hypoxic adaptation and cycles of hypoxia-reoxygenation alter ROS levels and induce oxidative stress, alongside increased replication stress and impaired DNA repair, collectively selecting for cells capable of surviving genomic damage (72). Hypoxia can also suppress homologous recombination and mismatch repair pathways in certain tumor contexts

Table I. Hypoxia-associated molecular evidence across major lymphoma subtypes.

Lymphoma subtype	Hypoxia/HIF marker or pathway	Cell type	Experimental model or patient cohort	Biological consequence	Clinical association	Evidence level[a]	(Refs.)
ABC-DLBCL	HIF-1α, glycolytic program, PD-L1	Malignant B cell, TAM	Patient biopsies, DLBCL cell lines, PDX	Glycolytic reprogramming, immunosuppression, chemoresistance	Hypoxia gene signature correlates with inferior R-CHOP response, poor PFS rate	A+B	(20,63)
GCB-DLBCL	HIF-1α, EZH2 crosstalk	Malignant B cell	Cell lines, preclinical models	Epigenetic silencing, therapy tolerance	Less robust hypoxia signature compared with ABC-DLBCL	B	(118)
MCL	HIF-1α-BACH2 axis, CXCR4-CXCL12	Malignant B cell, bone marrow stroma	Cell-stroma co-culture, PDX	Enhanced stromal adhesion, dissemination, proteasome-/BTK-inhibitor resistance	Bone-marrow niche-mediated minimal residual disease risk	B	(40)
FL	HIF-1α, follicular dendritic cell-stromal crosstalk	Malignant B cell, FDC, mesenchymal stromal cells	Germinal-center preclinical models	Sustain tumor-B cell survival; promotes high-grade transformation during histological progression	Hypoxia linked to histological transformation risk	B	(10)
cHL	HIF-1α, VEGF, PD-L1	HRS cell, myeloid cells	Patient biopsy cohorts, *in vitro* HRS models	Vascular remodeling, T-cell suppression	Supports response heterogeneity to PD-1 blockade	A+B	(11)
PCNSL	HIF-1α, ER-stress axis	Malignant B cell	Preclinical CNS lymphoma models	Promotes malignant cell survival, impairs drug penetration across blood-brain barrier	Contributes to treatment failure in central nervous system compartment	B	(97)
CTCL (Sézary syndrome)	IL-9-HIF-1α-Cofilin-1 axis	Malignant T cell, dermal macrophage	CTCL cell lines, patient skin specimens	Malignant T-cell skin infiltration, local immunosuppressive skin niche	Associated with skin disease persistence	B	(41,98)
EBV-associated lymphoma	HIF-1α + NF-κB/JAK-STAT, viral oncogenic signaling	EBV + malignant B/NK/T cell	Preclinical EBV-lymphoma models	Genomic instability, metabolic stress survival, immune evasion	Limited *in vivo* human cohort validation	B-C	(69)

[a]Level A for human patient-derived data; level B for lymphoma-specific preclinical models; level C for indirect extrapolation from solid tumor studies. ABC, activated B cell-like; cHL, classical Hodgkin lymphoma; CTCL, cutaneous T cell lymphoma; DLBCL, diffuse large B cell lymphoma; FL, follicular lymphoma; HIF, hypoxia-inducible factor; MCL, mantle cell lymphoma; PCNSL, primary central nervous system lymphoma; VEGF, vascular endothelial growth factor; NK, natural killer; PFS, progression-free survival; JAK, Janus kinase; ER, endoplasmic reticulum; CNS, central nervous system; GCB, germinal-center B cell-like; PD-L1, programmed death-ligand 1; PD-1, programmed cell death protein 1; CXCL12, C-X-C motif chemokine ligand 12; CXCR4, C-X-C chemokine receptor type 4; HRS, Hodgkin-Reed-Sternberg; EBV, Epstein-Barr virus; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; EZH2, enhancer of zeste homolog 2; BTK, Bruton tyrosine kinase; TAM, tumor-associated macrophage; PDX, patient-derived xenograft; BACH2, B-cell and B-lymphoma-associated transcription factor 2; FDC, follicular dendritic cell.

(as inferred from solid tumor studies), thereby increasing mutation accumulation and chromosomal instability (73-75); hypoxia-mediated repression of DNA repair pathways are best characterized in solid tumors and may similarly drive mutational accumulation in lymphoma (76). In lymphoma, these processes may cooperate with intrinsic oncogenic lesions such as Myc activation, BCL-2 dysregulation, tumor protein p53 disruption or PI3K pathway activation (7).

Epigenetic remodeling is another mechanism whereby hypoxia drives genomic instability and malignant progression in lymphoma cells. Hypoxia can alter histone methylation, histone acetylation, DNA methylation, chromatin accessibility and non-coding RNA expression (77). Enzymes such as enhancer of zeste homolog 2 (EZH2), G9a (also known as euchromatic histone-lysine N-methyltransferase 2), ten-eleven translocation proteins and DNA methyltransferases (DNMTs) are sensitive to metabolic and oxygen-dependent regulation. Numerous lymphoma subtypes are strongly driven by epigenetic lesions, including EZH2 mutations in germinal center-derived lymphomas; therefore, hypoxia may amplify pre-existing epigenetic vulnerabilities or create new ones (78). This provides a rationale for combining hypoxia-targeted strategies with epigenetic therapy in selected patients. However, causal links between hypoxia-driven epigenetic shifts and lymphoma progression still require more direct evidence from patient-derived material.

Angiogenesis and stromal niche remodeling. Hypoxia-induced angiogenesis is a major feature of lymphoma progression. HIF-1α-mediated VEGF expression promotes endothelial-cell activation, vascular remodeling and microvessel formation (79). However, the newly formed vasculature is often abnormal and inefficient, perpetuating hypoxia rather than resolving it. In aggressive lymphomas such as DLBCL, angiogenic activity may correlate with tumor growth, metabolic demand and poor prognosis (80). In indolent lymphomas, angiogenesis may become more prominent during transformation, relapse or microenvironmental evolution (81).

The stromal niche also participates in hypoxia-driven remodeling. Macrophages and mesenchymal stromal, fibroblastic reticular, follicular dendritic and endothelial cells can provide survival signals to lymphoma cells through chemokines, cytokines, adhesion molecules and ECM components (82). Hypoxia strengthens these interactions by inducing CXCR4-CXCL12 signaling, IL-6 production, CD40-NF-κB activation, hyaluronic acid-CD44 interactions and matrix remodeling (as directly demonstrated in lymphoma models) (83). Numerous hypoxia-regulated stromal-lymphoma crosstalk axes have been characterized in non-hematological tumor systems. Their exact quantitative contributions within lymphoma niches could differ across anatomical sites and disease subtypes. These pathways support tissue retention, dissemination, immune escape and drug resistance (Fig. 2).

4. Hypoxia-mediated immune evasion

Hypoxia is a potent regulator of antitumor immunity. It limits immune surveillance by affecting T-cell infiltration, T-cell exhaustion, macrophage polarization, regulatory T-cell function, myeloid-derived suppressor cells, dendritic-cell maturation and metabolic competition (16,84). In the lymphoma TME, where malignant cells are embedded in immune organs, these effects are particularly consequential. Numerous mechanistic details of hypoxia-driven immune suppression originate from solid tumor studies and remain to be fully recapitulated within primary lymphoma immune microenvironments.

One major mechanism of hypoxia-driven immune suppression is immune checkpoint regulation. Hypoxia can increase PD-L1 expression on tumor or microenvironmental cells, while also promoting inhibitory receptor expression on exhausted T cells. HIF-driven PD-L1 upregulation is well documented in ABC-DLBCL and cHL (85). These changes reduce cytotoxic activity and may influence the clinical response to programmed cell death protein 1 (PD-1)/PD-L1 blockade (86). In addition, hypoxia increases adenosine generation through purinergic metabolism, creating a metabolically immunosuppressive niche (87). Adenosine signaling suppresses T- and NK-cell function and may cooperate with checkpoint pathways to maintain immune escape (88).

Macrophages are another key target of hypoxia. Hypoxic conditions can promote an M2-like, tissue-remodeling or immunosuppressive macrophage phenotype (89). HIF activation in mononuclear phagocytes can upregulate inhibitory Fcγ receptors and impair ADCP, thus reducing the efficacy of anti-CD20 antibodies and other antibody-based therapies (90). This mechanism is relevant as monoclonal antibodies form a central component of lymphoma treatment.

Hypoxia also has context-dependent effects on cytotoxic T cells. On the one hand, low oxygen, lactate accumulation, nutrient depletion and checkpoint signaling can impair T-cell infiltration and cytotoxicity. On the other hand, certain HIF-dependent programs, including induction of glycolytic enzymes (GLUT1 and HK2), CXCR3 chemokine receptor and effector cytokines, may support T-cell glycolysis, migration and effector function under stress (91). This duality implies that therapeutic strategies should avoid indiscriminate suppression of HIF signaling in all cellular compartments. Instead, future approaches should aim to inhibit tumor-promoting hypoxia pathways while preserving or engineering immune-effector adaptation. Hypoxia-driven functional alterations, core molecular mechanisms and corresponding evidence sources for immune cells and lymphoma tumor cells are summarized in Table II. Some of the opposing HIF-dependent T cell phenotypes (including the HIF-mediated immunosuppressive phenotype and the hypoxia-adaptive effector phenotype of $CD8^+$ T cells) are defined in non-lymphoma experimental systems; however, the mechanism by which they operate within lymphoma-infiltrating T-cell populations requires further investigation.

5. Hypoxia, invasion, dissemination and relapse

Hypoxia promotes lymphoma dissemination by reshaping adhesion, migration and tissue-homing programs. HIF-dependent induction of chemokine receptors such as CXCR4 can enhance migration toward CXCL12-rich niches, including bone marrow and extranodal tissues (92). Activation of the CXCR4-AKT-mTOR axis may increase survival and migratory capacity in aggressive B cell lymphomas (93). This axis is functionally critical for bone marrow homing in

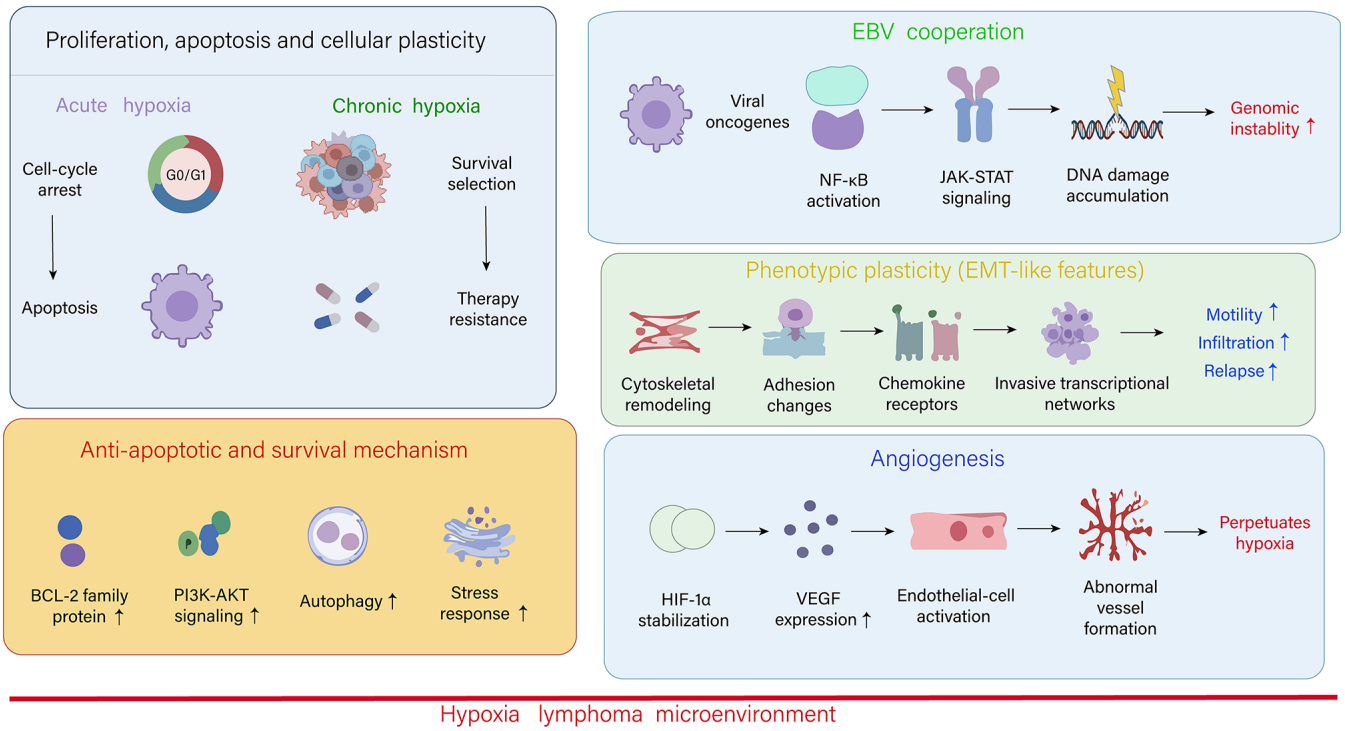


Figure 2. Multifarious oncogenic outcomes of hypoxia within the lymphoma microenvironment across five subpanels. The top-left subpanel shows that acute hypoxia induces G_0/G_1 cell-cycle arrest and apoptosis, while chronic hypoxia selects therapy-resistant clones. The bottom-left subpanel presents underlying pro-survival mechanisms: Upregulated BCL-2 family proteins, activated PI3K-AKT signaling, enhanced autophagy and stress responses. The top-right subpanel illustrates that hypoxia cooperates with EBV oncogenes to trigger NF-κB/JAK-STAT cascades, driving DNA damage and genomic instability. The middle-right subpanel shows hypoxia promotes EMT-like plasticity via cytoskeletal remodeling, adhesion shifts, chemokine receptors and invasive transcription programs, increasing motility, infiltration and relapse risk. The bottom-right subpanel demonstrates HIF-1α/VEGF-mediated abnormal angiogenesis, which perpetuates intratumoral hypoxia. JAK, Janus kinase; HIF, hypoxia-inducible factor; VEGF, vascular endothelial growth factor; EMT, epithelial-mesenchymal transition; EBV, Epstein-Barr virus.

MCL (51). Hypoxia can also enhance CD44, matrix metalloproteinases, cytoskeletal regulators and ECM remodeling programs, facilitating invasion through tissue barriers (1). A number of these hypoxia-driven invasion mediators are well studied in solid epithelial tumors and may drive lymphoma dissemination (1,94); however, direct functional validation across lymphoma subtypes remains limited. CD44-mediated hypoxic invasion phenotypes have been demonstrated in glioma (95); however, whether analogous mechanisms operate in lymphoma remains to be determined.

The bone marrow niche represents a site of hypoxia-associated lymphoma persistence. Bone-marrow oxygen tension is spatially heterogeneous and varies with measurement approaches; specific sub-regions within the marrow are physiologically low in oxygen (hypoxic). This niche is metabolically specialized and enriched in stromal cells that provide survival signals, including chemokine CXCL12, cytokine IL-6, cell-adhesion cues and metabolic substrates. Lymphoma cells that colonize this niche may gain protection from chemotherapy through adhesion-mediated drug resistance, stromal cytokine support, metabolic exchange and immune suppression (96). This niche protection can contribute to minimal residual disease and relapse.

In extranodal lymphomas, tissue-specific oxygen environments may shape disease behavior. PCNSL develops in a unique neurovascular and immune microenvironment, where hypoxia-related metabolic programs may interact with perivascular growth patterns and endoplasmic reticulum stress (97). CTCL and Sézary syndrome develop in the skin, a tissue characterized by oxygen gradients, inflammatory signals and barrier-related stress (98). Hypoxia-related pathways in these diseases may influence malignant T-cell migration, immune dysfunction and phenotypic plasticity. Hypoxia may also contribute to histological transformation and clonal evolution (97-99). By promoting genomic instability, epigenetic plasticity, immune escape and survival under stress, hypoxia can create selection pressure favoring aggressive subclones. Hypoxia-fueled clonal selection driving disease progression is established in solid tumors; causal links between hypoxia and histological transformation in human lymphoma cohorts await longitudinal investigation (100). In indolent lymphomas, this hypoxia-mediated clonal selection may contribute to relapse, progression or transformation into more aggressive disease. Therefore, hypoxia should be considered not only a marker of advanced tumor burden, but also a driver of evolutionary adaptation.

6. Hypoxia-induced therapeutic resistance

Hypoxia confers broad, multi-modal treatment resistance across lymphoma subtypes. Previous mechanistic summaries are largely generic (11,101); the following section contextualizes resistance against established clinical regimens for major lymphoma subtypes and explicitly distinguishes direct

Table II. Core mechanisms of hypoxia-mediated immune escape in lymphoma.

A, Immune cells

Cell type	Hypoxia-mediated functional changes	Core molecular mechanisms	Evidence source	(Refs.)
Cytotoxic T cells	Reduced infiltration, decreased cytotoxic function, enhanced exhausted phenotype	PD-1/PD-L1 axis, adenosine signaling, lactate metabolism, nutrient deprivation	*In vitro* hypoxia co-culture and *in vivo* hypoxic-niche studies demonstrate $CD8^+$ T-cell dysfunction; checkpoint and adenosine-pathway studies	(16,86,87,91)
	HIF pathway modulation (for example, HIF-2α, in certain settings) can enhance effector function in a cell-type-specific manner	HIF-2α, T cell metabolism-related transcription factors	Genetic perturbation of the HIF pathway (FIH inhibition, PHD2/3 deficiency, HIF stabilization) in $CD8^+$ T cells demonstrates context- dependent enhancement of effector function	(17,42,43,49)
Macrophages	Polarization toward an immunosuppressive, tissue-remodeling phenotype[a]	HIF-1α, IL-6/IL-10, TGF-β, NF-κB	Single-cell/spatial transcriptomics of lymphoma TAMs; HIF-1α-dependent TAM reprogramming and immunosuppressive macrophage studies	(20,39,89,91, 96,152)
	Imbalanced Fcγ receptor expression, decreased antibody-dependent phagocytosis	HIF-1α, FcγRIIb; CD47-SIRPα axis	Direct evidence of HIF-dependent upregulation of inhibitory FcγRIIb impairing antibody-based immunotherapy; hypoxia-induced CD47 upregulation strengthening the CD47-SIRPα axis; Fcγ receptor biology	(91,122,149)
Regulatory T cells	Enhanced immunosuppressive function and increased tumor infiltration	HIF-1α, CCL28-CCR10 axis, adenosine signaling	Direct evidence of hypoxia-induced CCL28-mediated Treg recruitment via HIF-1α; adenosine-mediated amplification of suppressive function; hypoxic TME immune reprogramming	(87,128)
Myeloid-derived suppressor cells	Enhanced immunosuppressive function and accumulation in the TME	HIF-1α, arginase I/iNOS, ENTPD2/CD39L1	Direct evidence of HIF-1α regulating MDSC differentiation and function; HIF-1-dependent ENTPD2 maintaining MDSC accumulation; hypoxic TME immune reprogramming	(128)
Dendritic cells	Impaired maturation, decreased antigen-presenting function, weakened immune activation	HIF-1α, NF-κB, cytokine-related pathways	Direct evidence that hypoxia suppresses dendritic-cell maturation and antigen-presentation capacity; hypoxia-mediated immune suppression in the TME	(16,128)

Table II. Continued.

B, Lymphoma cells (tumor compartment)				
Cell type	Hypoxia-mediated functional changes	Core molecular mechanisms	Evidence source	(Refs.)
Lymphoma cells (tumor compartment)	Upregulated immune checkpoint molecules (PD-L1, CD47) and decreased antigen-presenting capacity	HIF-1α/PD-L1 axis; hypoxia-mediated downregulation of surface MHC class I (β2-microglobulin-dependent) and of antigen-processing machinery	Direct evidence of HIF-dependent downregulation of surface MHC class I and antigen-processing components limiting T-cell recognition; HIF1A-AS2-mediated autophagic degradation of MHC class I protein; hypoxia-induced CD47 upregulation; PD-1/PD-L1 axis	(86)
	Increased production of immunosuppressive metabolites (adenosine, lactate)	CD39/CD73, LDHA, MCT1/4	Adenosine-mediated suppression of antitumor immunity; lactate metabolism and lactylation in tumors; hypoxia-driven glycolytic reprogramming	

[a]Macrophage polarization occurs along a phenotypic spectrum; the terms 'M1' and 'M2' describe extreme *in vitro* phenotypes and are used here only as functional descriptors. Therefore, hypoxia-associated macrophages are described as immunosuppressive/tissue-remodeling rather than strictly 'M2'. PD-L1, programmed death-ligand 1; PD-1, programmed cell death protein 1; HIF, hypoxia-inducible factor; Treg, regulatory T cell; TME, tumor microenvironment; FcγRIIb, fragment crystallizable γ receptor IIB; MHC, major histocompatibility complex; LDHA, lactate dehydrogenase A; MCT1/4, monocarboxylate transporter 1/4; AS2 (HIF1A-AS2), HIF1A antisense RNA 2 (long non-coding RNA); MDSC, myeloid-derived suppressor cell; iNOS, inducible nitric oxide synthase; ENTPD2, ectonucleoside triphosphate diphosphohydrolase 2; CCL28, C-C motif chemokine ligand 28; CCR10, C-C motif chemokine receptor 10; SIRPα, signal regulatory proteinα; TAM, tumor-associated macrophage; PHD2/3, prolyl hydroxylase domain protein 2/3.

lymphoma-derived evidence vs. extrapolation from general hypoxia biology or solid tumor data.

Chemotherapy and radiotherapy resistance. In DLBCL, R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone) remains the standard frontline immunochemotherapy, whereas multiple salvage regimens are utilized in relapsed or refractory (R/R) disease (102,103). Direct evidence from lymphoma studies demonstrates that hypoxia-driven cell-cycle quiescence reduces the killing efficacy of cell cycle-dependent chemotherapeutic agents, including cyclophosphamide and doxorubicin (104,105). Consistent with this mechanism, hypoxic gene signatures identified in biopsies of patients with DLBCL correlate with inferior response to R-CHOP and shorter progression-free survival time (106). Furthermore, preclinical investigations in DLBCL cell lines and xenograft models have demonstrated that HIF-1α stabilization attenuates anthracycline-mediated DNA damage and cytotoxicity (107,108). Beyond these direct tumor-cell-intrinsic effects, extracellular lactate accumulation and resultant microenvironmental acidification are hypothesized to impair drug uptake and intracellular drug activation; although this phenomenon has been well characterized in solid malignancies, it remains presumed rather than formally validated in primary human lymphoma tissues (101,109).

Radiotherapy, another key modality in lymphoma management, relies on oxygen to stabilize radiation-induced DNA double-strand breaks and to generate cytotoxic ROS. Consequently, hypoxia markedly diminishes ROS-dependent cytotoxicity and thereby fosters radioresistance (110). Clinically, radiotherapy is applied in localized DLBCL, bulky disease, extranodal presentations and selected salvage settings. Preclinical lymphoma models provide direct evidence that hypoxic bone marrow and nodal microenvironments reduce radiosensitivity through HIF-1α-dependent mechanisms (1,111). Notably, oxygen-modifying interventions developed to reverse hypoxia-induced radioresistance have been extensively investigated in solid tumors (112,113); yet, such strategies remain largely confined to preclinical stages and have not been formally tested in cohorts of patients with lymphoma.

Resistance to targeted therapy. In MCL, Bruton tyrosine kinase (BTK) inhibitors (such as ibrutinib) and BCL-2 inhibitors (such as venetoclax) are standard therapies across multiple treatment lines (114). Preclinical models demonstrate that hypoxia-driven HIF-1α activation suppresses BACH2, thereby enhancing stromal adhesion and conferring resistance to proteasome inhibitors (40,115). Under hypoxic conditions,

compensatory upregulation of MCL-1 and BCL-extra-large attenuates venetoclax sensitivity, particularly in stromal co-culture systems. Additionally, hypoxia-triggered autophagy and unfolded protein response signaling alleviate proteotoxic stress and diminish BTK inhibitor efficacy. Although metabolic rewiring that bypasses PI3K-AKT-mTOR blockade has been well characterized in other malignancies, patient-level evidence directly linking intratumoral hypoxia to BTK or BCL-2 inhibitor failure in MCL remains scarce and requires prospective validation (116,117).

In relapsed or refractory DLBCL and indolent B cell lymphomas, EZH2 and PI3K inhibitors constitute key targeted therapeutic options (118). Preclinical DLBCL systems indicate that hypoxia-HIF crosstalk directly antagonizes EZH2 inhibitor activity (119). While hypoxia-driven metabolic plasticity enabling escape from PI3K pathway suppression is broadly implicated in cancer biology, robust patient-derived lymphoma data confirming this mechanism are currently lacking (27).

Resistance to antibody therapy and immunotherapy. Anti-CD20 monoclonal antibodies (principally rituximab and obinutuzumab) administered alone or combined with chemotherapy, constitute the standard of care for frontline and maintenance therapy in FL. Their efficacy depends critically on antibody-dependent cellular cytotoxicity (ADCC) and ADCP (120). In lymphoma-bearing models, hypoxia polarizes macrophages toward an immunosuppressive M2-like phenotype and upregulates inhibitory Fcγ receptor IIB on myeloid cells, thereby impairing ADCP and attenuating anti-CD20 activity. Analogous Fc-receptor alterations have been documented in patient-derived lymphoma microenvironment samples (121,122). Although hypoxia-induced adenosine accumulation suppresses NK cell-mediated ADCC in solid tumor systems, its quantitative contribution to clinical anti-CD20 failure in FL remains to be determined.

In relapsed or refractory cHL, PD-1 blockade (nivolumab and pembrolizumab) and the CD30-targeted antibody-drug conjugate brentuximab vedotin represent transformative therapies. The cHL microenvironment is intrinsically enriched in hypoxia-responsive signaling, which upregulates PD-L1 on HRS and associated myeloid cells, potentially contributing to heterogeneous checkpoint-blockade responses (123). Preclinical models further demonstrate that hypoxia-driven adenosine signaling suppresses $CD8^+$ T-cell effector function (124). Conversely, mechanisms by which hypoxia may impair brentuximab vedotin efficacy, such as altered ADC internalization, lysosomal drug processing or tumor-cell drug susceptibility, are largely inferred from general tumor biology, as dedicated cHL hypoxia studies remain sparse (125).

The PD-1/PD-L1 blockade yields variable outcomes in relapsed or refractory DLBCL. Patient transcriptomic datasets indicate that hypoxic gene signatures correlate with PD-L1 expression and T-cell exhaustion, providing correlative evidence linking hypoxia to inferior checkpoint-blockade responses (126). While hypoxia-mediated restriction of T-cell tumor infiltration is widely described in oncology, its independent contribution is difficult to isolate from other microenvironmental variables, including accumulation of regulatory T cells and myeloid-derived suppressor cells, in DLBCL clinical samples (127,128).

CAR-T therapy and hypoxic immune niches. CD19-directed CAR-T cell therapies and CD19xCD3 bispecific antibodies are established treatments for R/R large B cell lymphoma and other B-cell malignancies. A preclinical lymphoma model provides evidence that hypoxic microenvironmental conditions, including lactate accumulation, adenosine signaling, nutrient deprivation and elevated checkpoint ligand expression, impair CAR-T cell trafficking, proliferation, persistence and cytotoxicity against lymphoma targets (129). *Ex vivo* studies further indicate that hypoxia during manufacturing (*ex vivo* CAR-T cell culture and expansion prior to patient infusion) can alter CAR-T cell functional phenotypes (129,130). The impact of intratumoral hypoxia on clinical responses to bispecific antibodies remains largely inferential, extrapolated from shared immunosuppressive mechanisms observed with CAR-T cells; formal correlative studies in bispecific-treated lymphoma cohorts are currently lacking. Similarly, hypoxia-responsive CAR-T engineering strategies, although conceptually promising, remain confined to preclinical investigation without patient-level lymphoma data (131).

This concept illustrates a broader therapeutic principle: Hypoxia is not only an obstacle but also a programmable feature of the tumor niche. Engineering immune cells, nanoparticles or prodrugs to act preferentially in hypoxic regions may improve therapeutic selectivity.

7. Therapeutic strategies targeting hypoxia in lymphoma

In the following section, hypoxia-targeted interventions are explicitly stratified by level of clinical maturity into five categories: i) Approved in oncology but not biomarker-selected for lymphoma; ii) evaluated in lymphoma clinical trials; iii) supported by lymphoma-specific preclinical data; iv) supported only in solid tumor models; and v) entirely hypothetical. For each strategy, representative agents, trial phase, target lymphoma subtypes, potential combination partners and key toxicity/feasibility limitations are summarized (Table III).

Direct inhibition of HIF signaling. Therapeutic agents targeting the HIF axis span a broad translational spectrum. In the first tier, mTOR inhibitors such as everolimus and temsirolimus, which modulate downstream HIF-1α stabilization, are approved for numerous solid malignancies and have been used off-label in relapsed or refractory MCL and DLBCL without hypoxia-directed patient stratification (132). Although combination with proteasome inhibitors or anti-CD20 antibodies is rational, clinical application is constrained by myelosuppression, hyperlipidemia, stomatitis and the non-selective impact of mTOR blockade on both tumor and immune compartments. Furthermore, prospective biomarker-driven selection of hypoxic lymphoma subgroups remains absent. Advancing to the third tier, direct small-molecule HIF-1α inhibitors such as PX-478 have demonstrated preclinical activity in lymphoma models, where suppression of HIF-1α-driven glycolysis, angiogenesis and stromal crosstalk reduces the survival of ABC-DLBCL and MCL cells within hypoxic niches (133,134). These agents may be paired with BCL-2 inhibitors or anti-CD20 monoclonal antibodies; yet, poor pharmacokinetics, the risk of off-target suppression of HIF-dependent $CD8^+$ T-cell effector functions and the lack

of completed lymphoma clinical trials pose notable hurdles. In the fourth tier, HIF-2α-selective antagonists and HIF-β dimerization inhibitors exhibit antitumor efficacy in renal cell carcinoma and other solid tumors, but remain untested in primary lymphoma tissues, and their cell type-specific effects on myeloid and cytotoxic T-cell compartments are likewise undefined in this disease context (135,136).

HIF-directed inhibition faces notable translational challenges. HIFs mediate essential physiological oxygen homeostasis responses with strong cell type-specific effects. Inhibiting HIF in malignant lymphoma cells may confer antitumor benefit; however, pan-HIF suppression within $CD8^+$ cytotoxic T cells can impair antitumor effector differentiation, while HIF blockade in tumor-associated macrophages and mesenchymal stromal cells may produce desirable anti-lymphoma effects by dampening myeloid-mediated immunosuppression and disrupting niche-mediated minimal residual disease protection (49,137). Endothelial HIF-1α inhibition can restrain pathological angiogenesis but may disturb physiological vascular stability. Therefore, successful HIF-targeted therapy will likely require lymphoma-subtype selection, hypoxia-associated biomarker guidance, rational combinatorial regimens and careful monitoring of immune-related adverse outcomes.

Metabolic intervention. Metabolic targeting represents another promising strategy, with potential targets encompassing glycolysis, lactate transport, carbonic anhydrases, mitochondrial quality control, glutamine metabolism, fatty-acid synthesis and redox homeostasis (138). These interventions span different stages of clinical maturity.

At the most advanced tier, acetazolamide, a carbonic anhydrase inhibitor approved for non-oncological indications, disrupts pH homeostasis in hypoxic niches via CAIX blockade (139). Although exploratory application in DLBCL and cHL has been proposed, often in combination with chemotherapy or immune-checkpoint inhibitors, it has not been prospectively evaluated in biomarker-defined hypoxic lymphoma cohorts. Its clinical utility is further constrained by metabolic acidosis, paresthesia and poor tumor-targeting selectivity (140).

Agents supported by lymphoma-specific preclinical data include glycolysis inhibitors (such as 2-deoxyglucose), MCT-4 inhibitors and mitophagy-targeting BNIP3/BNIP3L modulators (27). In hypoxic DLBCL and MCL models, suppression of the glycolysis-lactate axis impairs ATP generation and extracellular acidification, whereas mitophagy inhibition abrogates hypoxia-driven mitochondrial stress tolerance (23,63). These agents may be rationally combined with BCL-2 or proteasome inhibitors; however, systemic glycolysis inhibition disrupts normal lymphocyte metabolism and compensatory metabolic rewiring frequently emerges under monotherapeutic pressure.

Conversely, reductive glutamine inhibitors and selective fatty-acid synthase inhibitors, which disrupt hypoxia-driven anabolic metabolism, have been characterized exclusively in epithelial-derived solid tumor models (141,142). Dedicated lymphoma preclinical datasets are absent, and on-target toxicities to normal proliferative tissues remain a concern.

Metabolic plasticity poses a formidable therapeutic barrier, rendering combinatorial regimens essential to counteract compensatory pathway activation. Since a large number of these metabolic vulnerabilities are extrapolated from solid tumor systems, rigorous validation using lymphoma-derived organoids and primary patient-derived xenograft platforms is imperative (10,143).

Vascular normalization and oxygen modulation. Therapeutic modulation of tumor vasculature and oxygenation encompasses strategies at markedly different stages of clinical maturity. At the most advanced tier, bevacizumab, an anti-VEGF-A monoclonal antibody approved for multiple solid malignancies, has been evaluated in unselected DLBCL and MCL cohorts, typically combined with R-CHOP-like chemoimmunotherapy and without hypoxia-directed stratification (144,145). Its broader application in lymphoma is constrained by hypertension, proteinuria, gastrointestinal perforation risk and inconsistent clinical efficacy in unselected patient populations (144).

Supported by lymphoma-specific preclinical data, VEGF-C/VEGFR3 blockade and high-endothelial-venule-stabilizing agents remodel disordered tumor vasculature, enhance T-cell infiltration and partially relieve intratumoral hypoxia, serving as rational concurrent combination agents together with PD-1/PD-L1 checkpoint blockade (146,147). However, these approaches carry the risk of disrupting physiological lymphatic-vessel homeostasis. By contrast, oxygen-generating nanoparticles and vascular-targeted photodynamic therapy combined with nano-oxygen carriers, modalities that locally ameliorate hypoxia and amplify ROS-mediated tumor killing, have been characterized primarily in solid tumor systems (148). Systematic lymphoma-specific testing remains limited, and notable barriers persist, including drug delivery challenges in bone marrow, central nervous system and cutaneous lymphoma niches, as well as manufacturing complexity for nanomedicine formulations.

Anti-angiogenic monotherapy has demonstrated limited, context-dependent benefit in lymphoma, partly reflecting fundamental differences between lymphoma and solid tumor vascular biology (145). A more refined paradigm is vascular normalization, which seeks to improve vessel structure, perfusion and immune-cell trafficking rather than indiscriminately eliminate blood vessels. Strategies targeting VEGF-VEGFR signaling, the VEGF-C/VEGFR3 pathways, high-endothelial-venule integrity, lymphotoxin signaling and endothelial remodeling may reshape the lymphoma vasculature and restore functional oxygen delivery, thus enhancing the efficacy of oxygen-dependent therapies and immune responses (149). Although oxygen-generating nanoparticles and vascular-targeted photodynamic approaches remain largely preclinical in lymphoma, they provide conceptual support for oxygen-modulating therapy (150).

Immunometabolic and cellular-therapy strategies. Immunometabolic interventions targeting hypoxia-induced immunosuppression span from early clinical evaluation to conceptual preclinical stages. At the clinical-trial level, adenosine-pathway blockade using CD73/adenosine inhibitors combined with anti-PD-1 antibodies is under active investigation in relapsed or refractory cHL and DLBCL, albeit without hypoxia-based patient enrichment; this approach is tempered

Table III. Classification of hypoxia-targeted therapeutic strategies in lymphoma according to clinical maturity.

First author/s, year	Clinical maturity	Therapeutic strategy	Representative agents	Trial status	Relevant lymphoma subtypes	Suggested combinations	Major limitations	(Refs.)
Wiech-Walow *et al*, 2026	Approved, not hypoxia-selected	mTOR inhibition (upstream HIF)	Everolimus, Temsirolimus	Off label	MCL, DLBCL	Proteasome inhibitors, anti-CD20	Myelosuppression, metabolic disturbances; no hypoxia-based selection	(131)
McDonald *et al*, 2022		Carbonic anhydrase inhibition	Acetazolamide	No trials	DLBCL, cHL	Chemotherapy, checkpoint inhibitors	Metabolic acidosis, low selectivity	(158)
		Anti-VEGF-A antiangiogenesis	Bevacizumab	Completed phase II	DLBCL, MCL	R-CHOP-style chemoimmunotherapy	Hypertension, proteinuria, perforation; inconsistent efficacy	(158)
Huang *et al*, 2024		Epigenetic modifiers	Chidamide, Azacitidine, Romidepsin	Approved (not hypoxia-stratified)	CTCL, PTCL, DLBCL	Checkpoint blockade	Myelosuppression, immune-related effects	(118)
Wang *et al*, 2024	Evaluated in lymphoma trials	Adenosine pathway blockade	Anti-CD73 antibodies	Early-phase	cHL, R/R DLBCL	Anti-PD-1 agents	Immune-related toxicities, heterogeneous expression	(87)
Wiech-Walow *et al*, 2026	Preclinical evidence	Direct HIF-1α inhibition	PX-478	Preclinical	ABC-DLBCL, MCL	BCL-2 inhibitors, anti-CD20	Risk to $CD8^+$ T cells, pharmacokinetics	(132)
Zhi *et al*, 2026		Glycolysis/lactate inhibition	2-DG, MCT-4 inhibitors	Preclinical	DLBCL, MCL	Proteasome/BCL-2 inhibitors	Compensatory metabolism	(103)
Yazicioglu *et al*, 2023		Mitophagy modulation	BNIP3 pathway modulators	Preclinical	Aggressive B cell	BCL-2 inhibitors	Off-target mitochondrial effects	(23)
McDonald *et al*, 2022		Vascular remodeling (VEGFR3)	VEGFR3 antagonists	Preclinical	DLBCL, cHL	PD-1/PD-L1 blockade	Lymphatic vessel injury	(158)
Hedge *et al*, 2025		Macrophage reprogramming	HDAC-STAT3 agents	Preclinical	DLBCL, FL	Anti-CD20	Heterogeneous myeloid profile	(96)
Huang *et al*, 2024		EZH2 inhibition (under hypoxia)	EZH2 inhibitors	Preclinical	GCB-DLBCL	BCL-2 inhibitors	Acquired epigenetic resistance	(118)
Zhi *et al*, 2026	Solid tumor only	HIF-2α antagonists, hypoxia-responsive CAR-T, oxygen nanoparticles, metabolic inhibitors	-	No lymphoma data	-	-	Limited lymphoma evidence, toxicity	(103)

Table III. Continued.

First author/s, year	Clinical maturity	Therapeutic strategy	Representative agents	Trial status	Relevant lymphoma subtypes	Suggested combinations	Major limitations	(Refs.)
Liu *et al*, 2025	Hypothetical	Hypoxia-sensing CAR-T	HRE-driven constructs	No data	-	-	Engineering complexity, unknown safety	(137)

HIF, hypoxia-inducible factor; VEGF, vascular endothelial growth factor; PD-L1, programmed death-ligand 1; PD-1 programmed cell death protein 1; BNIP3, BCL2/adenovirus E1B 19 kDa-interacting protein 3; ABC, activated B cell-like; CTCL, cutaneous T cell lymphoma; PTCL, primary central nervous system lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; DLBCL, diffuse large B cell lymphoma; cHL, classical Hodgkin lymphoma; CAR-T, chimeric antigen receptor T cell; GCB, germinal-center B cell-like; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; R/R, relapsed or refractory; EZH2, enhancer of zeste homolog 2; HDAC, histone deacetylase; HRE, hypoxia response element; MCT4, monocarboxylate transporter 4.

by immune-related adverse events and heterogeneous target-pathway expression across tumor biopsies. A preclinical lymphoma model provides more direct support for macrophage-reprogramming strategies that reverse hypoxia-driven M2-like polarization and for lactate-transport inhibition that restores T-cell cytotoxicity within hypoxic niches (151). These modalities enhance ADCP and effector T-cell activity when combined with anti-CD20 monoclonal antibodies or CAR-T cell products, although heterogeneous myeloid composition across individual lesions remains a translational challenge. Metabolically engineered CAR-T cells designed to sustain glycolytic effector function under low oxygen, as well as hypoxia-responsive CAR-T constructs that restrict cytokine release exclusively to hypoxic tumor niches to minimize systemic toxicity, remain largely confined to solid tumor proof-of-concept studies, with few or no lymphoma-oriented *in vitro* or *in vivo* studies published in the literature, to the best of our knowledge (152).

Current cellular-therapy paradigms are increasingly exploiting hypoxia not as an obstacle to be eliminated, but as a spatial molecular switch that confines antitumor immune activation to tumor tissue. Since hypoxia markedly shapes antitumor immunity, combining checkpoint inhibitors with adenosine-pathway blockade, lactate-transport inhibition, macrophage reprogramming or HIF-modulating agents may potentiate existing therapies by reversing myeloid-mediated suppression, and by restoring phagocytic and cytotoxic efficacy in antibody-treated lymphomas (128). However, the majority of engineered-cell concepts are extrapolated from solid tumor preclinical findings and require rigorous validation in lymphoma-relevant experimental platforms before clinical translation (153).

Epigenetic and combination approaches. Epigenetic targeting intersects with hypoxia-driven oncogenic reprogramming and may reverse microenvironment-induced transcriptional silencing. Clinically approved DNMT inhibitors (such as azacitidine decitabine) and histone deacetylase inhibitors (such as chidamide and romidepsin), which are employed in CTCL, DLBCL and peripheral T cell lymphoma, can restore the expression levels of tumor suppressor genes, enhance antigen presentation and increase immunogenicity under hypoxic conditions. Yet these agents are not biomarker-selected for hypoxia in lymphoma, and toxicities, including myelosuppression, fatigue and gastrointestinal intolerance, remain relevant (154). A preclinical lymphoma model further support EZH2 inhibition to counteract hypoxia-amplified epigenetic repression in GCB-DLBCL, providing rationale for combination with BCL-2 inhibitors, although acquired epigenetic resistance may limit efficacy (154). By contrast, dual epigenetic-HIF-targeted regimens have demonstrated synergy exclusively in epithelial tumor models and lack lymphoma-specific validation (155,156).

Durable clinical benefit is unlikely to arise from single-agent hypoxia-directed therapy. Rather, hypoxia-associated features should guide precision combination frameworks: Patients with hypoxia-high, immunosuppressed DLBCL may benefit from concurrent targeting of HIF signaling, adenosine metabolism and immune checkpoints, while those with hypoxia-driven metabolic dependence may warrant glycolytic

Table IV. Therapeutic strategies targeting hypoxia in lymphoma.

Therapeutic strategy	Core targets/mechanisms	Major obstacles	Evidence stage	Lymphoma-specific	(Refs.)
Direct inhibition of HIF signaling	HIF-1α/2α, PI3K-AKT-mTOR	May impair antitumor immunity in certain contexts	Preclinical/review	Partially (not specific)	(132,137)
Metabolic intervention	Glycolysis, lactate transport, carbonic anhydrases, mitochondrial quality control, glutamine metabolism, fatty-acid synthesis, redox homeostasis	Metabolic plasticity and tumor heterogeneity	Preclinical	Partially (not specific)	(23,140)
Vascular normalization and oxygen modulation	VEGF-VEGFR signaling, VEGF-C-VEGFR3 pathways, endothelial remodeling, oxygen-generating nanoparticles	Preclinical stage	Preclinical	Partially (not specific)	(148,149)
Immunometabolic and cellular-therapy strategies	Adenosine/lactate pathways, engineered CAR-T cells	Risk of immunosuppression; insufficient persistence	Preclinical/early clinical	Partially (not specific)	(128,152)
Epigenetic and combination approaches	EZH2, DNMT, HDAC inhibitors	Individualized subtype selection; combination therapy optimization	Clinical/preclinical	Yes (lymphoma-specific)	(153)

HIF, hypoxia-inducible factor; VEGF, vascular endothelial growth factor; CAR-T, chimeric antigen receptor T cell; EZH2, enhancer of zeste homolog 2; DNMT, DNA methyltransferase; HDAC, histone deacetylase.

or mitochondrial-directed interventions, and individuals with bulky, poorly perfused disease may require vascular-normalizing or oxygen-modulating pretreatment before chemotherapy, radiotherapy or cellular therapy (58,154). Although epigenetic agents combined with checkpoint blockade, HIF modulators or metabolic inhibitors hold conceptual promise, a large number of such combinatorial strategies remain hypothetical in lymphoma and await rigorous preclinical investigation. The therapeutic strategies against hypoxia-driven lymphoma, their core targets, major obstacles and evidence stage are summarized in Table IV.

8. Biomarkers, stratification and future perspectives

The clinical translation of hypoxia biology requires reliable biomarkers. Candidate biomarkers include HIF-1α, HIF-2α, CAIX, GLUT1, HK2, lactate dehydrogenase-related markers, VEGF, hypoxia-related gene signatures, metabolic imaging parameters, immune infiltration patterns and circulating cytokines (139,157-160). Multi-omics approaches integrating transcriptomics, proteomics, metabolomics, spatial profiling and imaging may provide more accurate assessment than any single marker. The majority of hypoxia-associated biomarkers are well validated for solid tumors; however, their diagnostic and prognostic performance across diverse lymphoma subtypes still requires large-scale clinical validation.

Notably, these hypoxia-associated biomarkers lack oxygen specificity. They can be triggered independent of low oxygen by Myc, PI3K-AKT-mTOR hyperactivation, inflammation, viral infection and intrinsic metabolic reprogramming, a pseudohypoxia state that must be distinguished from true oxygen deprivation. Hypoxia is measured via direct and indirect approaches: Oxygen probes and electrodes work in preclinical lymphoma models; yet, they are not clinically feasible for human samples (161). Indirect surrogates include immunohistochemistry, functional imaging and hypoxia transcriptomic signatures, while major confounders include intratumoral spatial heterogeneity, biopsy sampling bias and pre-analytical artifacts such as tissue-ischemia-induced artificial HIF stabilization (161). Multi-modal strategies combining spatial multi-omics and functional imaging are necessary to separate true hypoxia from pseudohypoxia (13).

Major confounders complicate measurement in lymphoma. Spatial intratumor heterogeneity and sampling bias mean single biopsies often fail to capture variable oxygen gradients across tumor cores, peripheries and distinct anatomical niches. Baseline physiological oxygen tension also varies across bone marrow, skin and CNS compartments. No single assay can reliably differentiate true hypoxia from pseudohypoxia in archived lymphoma specimens (162). Multi-modal integration of imaging, protein biomarkers and transcriptomic data together with subtype-specific oncogenic context is required for robust interpretation.

Spatial context is particularly relevant. Hypoxia is heterogeneous within and among tumor sites. A biopsy obtained from one region may not represent the full oxygen landscape of the disease. Spatial transcriptomics, multiplex immunofluorescence, single-cell sequencing and functional imaging may help map hypoxia-related niches and identify cell-cell

interactions that drive therapeutic resistance. Intratumor spatial heterogeneity of hypoxia is well documented across multiple solid malignancies, whereas direct spatial profiling data describing hypoxia niches across human samples of patients with lymphoma remain limited (1,163,164). These technologies could clarify whether hypoxia-associated macrophages, stromal cells, endothelial cells or lymphoma-cell subsets are the dominant therapeutic targets in a given patient.

A number of challenges remain for translating hypoxia-related discoveries into clinical practice for lymphoma. First, hypoxia markers are not standardized across lymphoma subtypes. Second, numerous hypoxia-related studies are derived from solid tumors and require validation in lymphoma-specific models. Third, HIF signaling exhibits cell type-dependent opposing functions: Non-selective HIF suppression may dampen protective $CD8^+$ T-cell effector programs alongside desired tumor cell-directed activity. Therapeutic benefit would ideally rely on approaches that selectively abrogate HIF-driven oncogenic outputs in lymphoma, macrophage, endothelial and stromal populations while preserving the HIF-dependent antitumor functions of cytotoxic T cells. Fourth, preclinical hypoxia models often fail to reproduce the chronic, spatially heterogeneous and treatment-modified hypoxia observed in patients. Fifth, integrating hypoxia-targeted therapy into existing lymphoma regimens will require careful attention to toxicity, sequencing and patient selection.

Therefore, future studies should move beyond descriptive measurement of hypoxia and should define which hypoxia-driven programs are actionable, which lymphoma subtypes depend on them and which combinations can overcome adaptive resistance. Prospective clinical trials incorporating hypoxia biomarkers, immune profiling, metabolic imaging and response assessment are essential for translating hypoxia biology into patient benefit.

9. Conclusions

Hypoxia is a central and dynamic component of the lymphoma microenvironment. Through HIF-dependent and -independent mechanisms, hypoxia reprograms lymphoma metabolism, mitochondrial function, immune surveillance, angiogenesis, stromal interactions, genomic stability, invasion and therapeutic response. The effects of hypoxia are context-dependent, varying across lymphoma subtype, anatomical niche, vascular structure, immune composition and treatment pressure.

Rather than viewing hypoxia as a simple by-product of rapid tumor growth, it should be understood as an ecological force that selects for stress-adapted, immune-evasive and therapy-resistant lymphoma cell states. Hypoxia may represent a context-dependent regulator of lymphoma biology and a potential therapeutic vulnerability that requires further lymphoma-specific validation. This perspective carries translational implications: Hypoxia-associated biomarkers could help refine risk stratification and identify high-risk microenvironmental phenotypes, although their clinical utility remains to be determined. Preclinically, therapeutic strategies targeting HIF signaling, metabolic adaptation, vascular dysfunction, immune suppression and hypoxia-activated delivery systems demonstrate promise to complement existing lymphoma therapies. Future hypoxia research in lymphoma should prioritize precision, defining relevant hypoxia-driven targets, identifying susceptible lymphoma subtypes, characterizing permissive microenvironmental contexts and evaluating optimal therapeutic combinations. Further lymphoma-specific preclinical and prospective clinical work is required to determine whether hypoxia-targeted interventions can be translated into clinical benefit for patients.

The central contribution of the present review is to reframe hypoxia in lymphoma as a context-dependent ecological force whose biological and therapeutic relevance varies by subtype, anatomical niche and cell type, rather than as a universally conserved cancer mechanism. Unlike previous reviews on general hypoxia, the present study emphasizes the lymphoma-specific ecology of hypoxia, including the spatial heterogeneity of lymphoid and extranodal niches, the diversity of cellular responders, and the unequal maturity of evidence across lymphoma subtypes and therapeutic contexts. This framework helps distinguish established biology from emerging hypotheses and identifies research and translational domains most likely to benefit from biomarker-guided and combination therapeutic strategies.

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Availability of data and materials

Not applicable.

Authors' contributions

YZ and CZ designed the review framework, performed the literature review, drafted the original manuscript and prepared all figures. MZ, QH, YH and XT screened and organised extracted references from included publications, cross-checked the plausibility of reported molecular mechanisms described in the review and revised the manuscript. NC conceived the present review, supervised the work, obtained the funding and revised the manuscript. All authors have read and approved the final version of the manuscript. Data authentication is not applicable.

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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