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*Review Article*

# Optimization of CAR-T therapy based on metabolic remodeling of the tumor immune microenvironment in diffuse large B-cell lymphoma

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**Abstract:** Diffuse large B-cell lymphoma (DLBCL), a common subtype of non-Hodgkin's lymphoma, faces the severe challenge of relapsed/refractory cases, with limited efficacy of existing therapies such as the R-CHOP regimen and second-line treatment plans. There is an urgent need for innovative treatment strategies. CAR-T therapy has shown revolutionary potential in the treatment of DLBCL, but its efficacy is limited by immune suppression and metabolic competition mediated by the tumor microenvironment (TME). Immunosuppressive cells and cytokines in the TME lead to the exhaustion of CAR-T cell functions, while metabolic competition puts CAR-T cells at a disadvantage in the uptake of key metabolites, limiting their proliferation and effector functions. Metabolic reprogramming, as a core mechanism of TME regulation, connects the functions of tumor cells and immune cells and is a key hub for enhancing the efficacy of CAR-T therapy. Among them, low glucose levels in the TME can activate the glycolytic pathway of CAR-T cells, but also lead to mitochondrial dysfunction and reduced cytotoxicity. Targeting the metabolic remodeling of the TME, in combination with metabolic regulatory drugs and CAR-T synergy strategies, as well as the development and translation of drugs, is expected to significantly enhance the efficacy of CAR-T therapy in the treatment of DLBCL, bringing new hope to patients. Future research should further explore the specific mechanisms of metabolic reprogramming, optimize the design and application of metabolic regulatory drugs, and accelerate the clinical translation of drugs to achieve the maximum potential of CAR-T therapy in the treatment of DLBCL.

**Keywords:** Diffuse large B-cell lymphoma, tumor immune microenvironment, metabolic remodeling, CAR-T therapy, anticancer drugs, key metabolites

## Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of adult non-Hodgkin's lymphoma (NHL), accounting for 30% to 40% of all NHL cases [1]. While the R-CHOP regimen has ostensibly become the standard first-line treatment, what seems particularly significant is that roughly 10% of patients still tend to face relapse or refractoriness [2, 3]. What these findings appear to suggest is that such patients typically confront a poor prognosis and are in urgent need of new treatment options. CAR-T cell therapy, an innovative immunotherapy, seems to generally indicate remarkable efficacy in treating DLBCL [4-6]. However, what appears to warrant further interpretive consideration is that its effectiveness appears to be restricted in the majority of cases due to what might be characterized as immune suppression and metabolic competition within the tumor microenvironment (TME) [7-9]. Within this broader analytical framework, immunodepressive cells such as Tregs and MDSCs, along with cytokines like TGF-β and IL-10 in the TME, tend to suggest what appears to be CAR-T cell exhaustion [10, 11]. What also appears significant in this context is that metabolic competition seems to constitute a critical factor limiting CAR-T cell efficacy. Given the complexity of these theoretical relationships, low glucose levels in the TME can apparently activate CAR-T cell glycolysis but simultaneously appear to cause what seems to be mitochondrial dysfunction and reduced cytotoxicity [12]. What the evidence appears to reveal is that the predomi-

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nant overconsumption of essential metabolites like glucose and glutamine by tumor cells presumably exhausts the metabolic resources of CAR-T cells, which tends to point toward what appears to be hindered growth and functional capabilities [13, 14].

TME regulation appears to center on metabolic reprogramming, which seems to represent a key factor in what might be characterized as enhancing CAR-T therapy efficacy. Tumor cells within the TME undergo metabolic changes such as what appears to be enhanced glycolysis, glutamine, and lipid metabolism to ostensibly support their rapid growth [7]. What this tends to indicate is that this not only largely sustains the tumor cells themselves but also appears to alter the metabolic landscape of the TME, thereby seemingly affecting immune cells. Their typically high glucose consumption can apparently deplete glucose availability for CAR-T cells, which tends to suggest what appears to be reduced CAR-T cell glycolysis and ATP production, and consequently what seems to be impaired function [13]. Additionally, tumor cells release metabolites such as lactate, which appears to suppress immune activity [15, 16]. What seems to emerge from recent studies is an investigation into ways to boost CAR-T efficacy by targeting these TME metabolic alterations. Inhibiting tumor glycolysis appears to tend to suggest a release of glucose for CAR-T cells, thereby seemingly enhancing their proliferation and function [17]. What the evidence appears to reveal is that regulating glutamine metabolism can improve the adaptability and survival of CAR-T cells within the TME, with glutaminase inhibitors showing what appears to be potential to augment antitumor activity by restricting tumor glutamine uptake [18]. Within this broader analytical framework, combining metabolic drugs with CAR-T therapy currently aims to modulate the metabolic environment of the TME to what seems to optimize CAR-T performance [19]. What appears particularly significant about these findings is that IL-15-enhanced GPC3 CAR-T therapy has demonstrated what seems to be a 66% control rate and 33% response rate in the majority of solid tumors, with presumably acceptable safety profiles, thereby offering what appears to be new insights for DLBCL treatment [20]. High-throughput screening and structural optimization in drug development have resulted in proprietary metabolic regulatory drugs that can support CAR-T therapy. The Mayo Clinic has combined antibody-drug conjugates with protein degradation chimeras, enhancing drug internalization in tumor cells and indicating a new direction for optimizing CAR-T therapy [21]. This study concentrates on TME metabolic remodeling and the combination of metabolic drugs with CAR-T to improve DLBCL treatment efficacy. It also delves into metabolic reprogramming mechanisms, refines the design of metabolic drugs, and accelerates clinical translation, all with the aim of maximizing CAR-T potential in DLBCL.

## Metabolic characteristics and immunosuppressive mechanisms of the Tumor Immune Microenvironment (TME)

### *Metabolic characteristics of the TME in DLBCL*

DLBCL cells adapt to the nutrient-deficient and hypoxic TME via various metabolic pathway reconstructions. They boost glycolytic activity to maintain energy in hypoxic conditions, aligning with heightened GLUT1 expression in tumor cells [13]. Additionally, DLBCL cells amplify glutamine uptake and utilization by enhancing enzymes tied to glutamine metabolism, thus backing their rapid proliferation and survival [22-24]. What seems particularly significant about this metabolic shift is that it tends to furnish tumor cells with energy and biosynthetic precursors while apparently bolstering an immunosuppressive microenvironment by influencing immune cell function in the TME. What studies appear to reveal is that lactate, a glycolytic byproduct of DLBCL cells, can ostensibly blunt T cell activation and proliferation, seemingly dampening their antitumor effects [25, 26]. Meanwhile, within this broader analytical framework, shifts in glutamine metabolism appear to sway the recruitment and function of MDSCs and Tregs in the TME, what seems to further immunosuppression [18, 27].

### *Metabolic markers: glycolysis, lipid metabolism abnormalities, amino acid deprivation*

*Glycolysis (Warburg effect):* DLBCL cells appear to exhibit what might be characterized as metabolic reprogramming to adapt to the nutrient-deficient and hypoxic TME. They typically seem to demonstrate what appears to be a pro-

nounced Warburg effect, apparently relying more on glycolysis than oxidative phosphorylation for energy generation even when oxygen is available [28]. What appears to emerge from this analysis is that this metabolic shift not only tends to meet the energy and biosynthetic precursor demands of the rapidly proliferating tumor cells but also appears to alter the TME's metabolic environment, thereby seemingly influencing immune cell function. What the research appears to indicate, given the complexity of these theoretical relationships, is that the substantial glycolytic activity of DLBCL cells tends to lead to lactate accumulation in the microenvironment, which can presumably suppress T cell activation and proliferation, thus what seems to weaken their antitumor immune response [25, 26].

*Lipid metabolic reprogramming:* DLBCL cells appear to undergo substantial changes in lipid metabolism, which seems to be characterized by what might be described as increased fatty acid synthesis and uptake capacities [29]. What the evidence tends to suggest is that these cells enhance fatty acid synthesis and uptake by apparently upregulating the expression of fatty acid synthase (FASN) and fatty acid transport proteins (FATP), which seems to support their rapid proliferation and survival [30]. Additionally, what appears particularly significant about these findings is that DLBCL cells seem to meet their metabolic demands through the acquisition of exogenous fatty acids. This abnormal lipid metabolism not only appears to supply lipid precursors for energy and biosynthesis in tumor cells but also seems to promote the formation of what could be characterized as an immunosuppressive microenvironment by ostensibly influencing immune cell function in the TME.

*Amino acid deprivation:* To meet their metabolic demands, DLBCL cells appear to substantially alter the uptake and use of certain essential amino acids like tryptophan and arginine [31]. What seems to emerge from these findings is that they accomplish this by typically increasing the expression of enzymes involved in tryptophan and arginine metabolism, thus seemingly supporting their rapid proliferation and survival. Within this broader analytical framework, research tends to indicate DLBCL cells can increase the expression of tryptophan-metabolizing enzymes such as IDO. What this pattern seems to suggest, therefore, is the promotion of tryptophan metabolism and what appears to result in tryptophan deprivation in the microenvironment [32]. Given the complexity of these theoretical relationships, such amino acid deprivation appears to affect immune cell function in the TME. For example, what the data seems to suggest is that it may inhibit T cell activation and proliferation, thereby presumably worsening immunosuppression [33, 34].

*Accumulation of key metabolic products: the immunosuppressive effects of lactate, adenosine, and ROS*

In the TME of DLBCL, what appears to be particularly significant is the accumulation of key metabolic substances that seems to substantially inhibit immune cell function [35]. Lactate, a primary byproduct of glycolysis, appears to build up extensively within this broader analytical framework of DLBCL cells' intense glycolytic activity. What the evidence tends to suggest is that it may impede T cell activation and proliferation, thereby ostensibly undermining their antitumor immune function [25]. What seems to emerge from these findings is that lactate may inhibit the proliferation and cytokine production efficiency of cytotoxic T cells (CTLs) in what appears to represent as much as 95% of cases and appears to decrease cytotoxicity by approximately 50%, as high extracellular lactate concentration seemingly disrupts CTL metabolism [16]. Additionally, what the data seems to suggest is that lactate can affect T cell NAD(H) redox state, further apparently inhibiting T cell proliferation and disturbing what might be characterized as tumor immunity [36]. What also appears significant in this context, adenosine, by binding to A2 receptors on immune cell surfaces, tends to suppress T cell and natural killer (NK) cell activity while seemingly enhancing regulatory T cells' (Tregs) immunosuppressive function [37-39].

In DLBCL's TME, what the investigation appears to indicate is that adenosine accumulation elevates significantly, leading to what seems to constitute immune cell dysfunction. What the analysis tends to support is that adenosine can presumably suppress T cell proliferation and cytokine secretion while strengthening Tregs'

immunosuppressive function. This not only appears to weaken immune cells' antitumor capacity but, given the complexity of these theoretical relationships, may also influence CAR-T cell therapy efficacy [37]. In the DLBCL tumor microenvironment, considering the nuanced nature of these findings, excessive reactive oxygen species (ROS) generation appears to be typically common. What these findings seem to point toward is that ROS can induce oxidative stress damage in immune cells and lead to their dysfunction [40]. What the evidence appears to reveal is that ROS can suppress immune cell function by oxidizing receptors and signaling molecules on immune cell surfaces. This oxidative stress environment, from this particular interpretive perspective, largely impairs immune cell function and may influence CAR-T cell therapy efficacy [41]. What appears to follow from this analysis is that ROS can directly impact target protein function by modifying redox-sensitive residues like cysteine or methionine. Cysteine oxidation, within these evolving conceptual parameters, seems to regulate signal transduction by altering protein function, localization, and promoting what appears to be protein degradation [42].

*Impact of metabolic reprogramming on immune cells*

Metabolic reprogramming appears to have a substantial impact on immune cells in the TME. What seems to emerge from these findings is that tumor cells tend to take up key nutrients like glucose and glutamine, seemingly weakening immune cells' antitumor activity [15, 43]. Studies appear to suggest that impaired glucose metabolism in T cells tends to reduce their proliferation and cytokine production, which may represent a weakening of antitumor response [44, 45]. What appears particularly significant about these findings is that metabolic products from tumor cells such as lactate and adenosine can apparently directly suppress immune cell activity. Lactate, within this broader analytical framework, seems to decrease T cells' glucose uptake and oxidative phosphorylation capacity, ostensibly inhibiting their function [25]. Tumor-associated macrophages (TAMs), influenced by what might be characterized as metabolic reprogramming, appear to polarize to the M2 phenotype in the majority of cases, promoting what seems to constitute an immunosuppressive microenvironment [46]. What these findings seem to point toward is that these metabolic changes not only affect immune cell function directly but may also alter their immune response capabilities over time by regulating their metabolic pathways.

*Exploring the metabolic causes of CAR-T cell exhaustion: mitochondrial dysfunction, nutrient competition, and metabolic checkpoints*

In DLBCL, the effectiveness of CAR-T cell therapy appears to be substantially linked to the metabolic characteristics of the TME. What the evidence appears to reveal is that mitochondrial dysfunction tends to constitute a major metabolic basis for CAR-T cell exhaustion. Given the complexity of these theoretical relationships, DLBCL cells seem to induce mitochondrial dysfunction in CAR-T cells through various mechanisms in the TME. These apparently involve inhibition of mitochondrial respiratory chain complex activity, reduced ATP synthesis efficiency, and elevated mitochondrial ROS production [47]. What appears to follow from this analysis is that metabolic disruption occurs in CAR-T cells, seemingly impairing their proliferative and cytokine secretion abilities. Prior studies appear to indicate that DLBCL cells, by secreting metabolites like lactate and adenosine, tend to suppress the mitochondrial respiratory function of CAR-T cells. This pattern seems to suggest, therefore, a drive in CAR-T cells toward glycolysis instead of oxidative phosphorylation, thereby presumably weakening their effector functions [25].

Nutrient competition appears to represent another significant metabolic foundation for the exhaustion of CAR-T cells. Within the TME, considering the nuanced nature of these findings, DLBCL cells seem to absorb crucial amino acids like tryptophan and glutamine by typically overexpressing transporters such as LAT1 and ASCT2, which appears to result in nutrient scarcity for CAR-T cells [7, 48]. What also appears significant in this context is that the nutrient competition tends to influence the metabolic condition of CAR-T cells and appears to restrict their proliferation and survival through what seems to be the activation of the mTOR signaling pathway [49, 50].

The PD-1/PD-L1 pathway, a metabolic checkpoint, is important in CAR-T cell exhaustion, with DLBCL cells in the TME displaying high PD-L1 expression. It binds to PD-1 on CAR-T cells, activating the PD-1/PD-L1 pathway and causing metabolic reprogramming in CAR-T cells. This metabolic reprogramming favors glycolysis over oxidative phosphorylation, reducing their ATP levels and, consequently, inhibiting their proliferation and cytokine secretion [9, 51]. In the NCT03258047 clinical trial, researchers employed an innovative approach where PD-1 was fused to the intracellular CD28 activation domain, converting the PD-L1 and PD-1 binding into an activation signal, anticipated to yield more potent antitumor effects [52, 53]. However, the results showed complete response (CR) and objective response rates (ORR) of 41.2% and 58.8%, respectively, which did not demonstrate superiority compared to the approved second-generation CAR-T therapy for relapsed/refractory (r/r) DLBCL.

*Metabolic adaptability of immunosuppressive cells and CAR-T antagonism mechanisms*

In the tumor immune microenvironment, immunosuppressive cells such as regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs) maintain their immunosuppressive functions and antagonize the antitumor activity of CAR-T cells through metabolic adaptability [54]. These immunosuppressive cells prioritize the utilization of nutrients like glucose and glutamine within the TME, enhancing their survival and function through metabolic reprogramming. Studies have revealed that Tregs enhance their glycolytic capacity by upregulating glucose transporter GLUT1 and key glycolytic enzyme HK2, thereby gaining a survival advantage in the glucose-competitive TME. MDSCs enhance glutamine metabolism through boosting enzymes like GLS1, thereby strengthening their immunosuppressive functions [55]. Such metabolic flexibility allows immunosuppressive cells to effectively curb the activity of CAR-T cells in the TME. Specifically, Tregs inhibit CAR-T cell proliferation and cytokine secretion by releasing inhibitory cytokines such as IL-10 and TGF-β [56, 57]. Meanwhile, MDSCs weaken the effector functions of CAR-T cells by expressing ARG1 and iNOS [58-60]. These metabolic adaptation mechanisms not only improve the survival and function of immunosuppressive cells but also counteract the antitumor activity of CAR-T cells directly or indirectly, thus impacting the efficacy of CAR-T therapy. Hence, interfering with the metabolic adaptability of immunosuppressive cells may present novel strategies for optimizing CAR-T therapy. For detailed metabolic traits and immunosuppressive mechanisms of the TME, see **Figure 1** and **Table 1**.

## Clinical progress and metabolic advances of CAR-T therapy in DLBCL

*Analysis of clinical efficacy of existing CAR-T therapies*

Among the relapsed/refractory (R/R) DLBCL patients receiving CAR-T cell therapy, a meaningful clinical response can be observed. Currently, the FDA approved six CAR-T products to treat hemopathy including DLBCL [61]. A study of 101 pre-treated DLBCL patients receiving axicabtagene ciloleucel shows a 54% complete response rate and a 5-year survival rate of 43%, compared with a 20% two-year overall survival in historical controls on standard therapy [62]. Moreover, data from randomized clinical trials for DLBCL patients either nonresponsive to first-line chemotherapy or progressing within 12 months post initial remission indicate axicabtagene ciloleucel and lisocabtagene maraleucel offer markedly superior progression-free and overall survival versus autologous stem cell transplantation following second-line chemotherapy [63].

In the ZUMA-7 trial, 164 patients treated with axicabtagene ciloleucel had a 1-year PFS rate of 60.0% and a 2-year PFS rate of 44.9% [64]. In the TRANSCEND NHL 001 trial involving 101 patients given lisocabtagene maraleucel, the median PFS was 10.3 months with a median follow-up of 17.6 months, and the median OS was not reached [65]. Other lymphoma studies also show CAR-T cell therapy's potential. For follicular lymphoma, axicabtagene ciloleucel and tisagenlecleucel have two-year PFS rates of 63% and 57%; for mantle cell lymphoma, brexucabtagene autoleucel and lisocabtagene maraleucel have twelve-month PFS rates of 61% and 53% respectively [61]. However, challenges remain in CAR-T cell therapy for DLBCL. Its efficacy and durability are limited with a high up-to 66% relapse rate. It's also linked with adverse reactions like cytokine release syndrome and neurotoxicity [66].

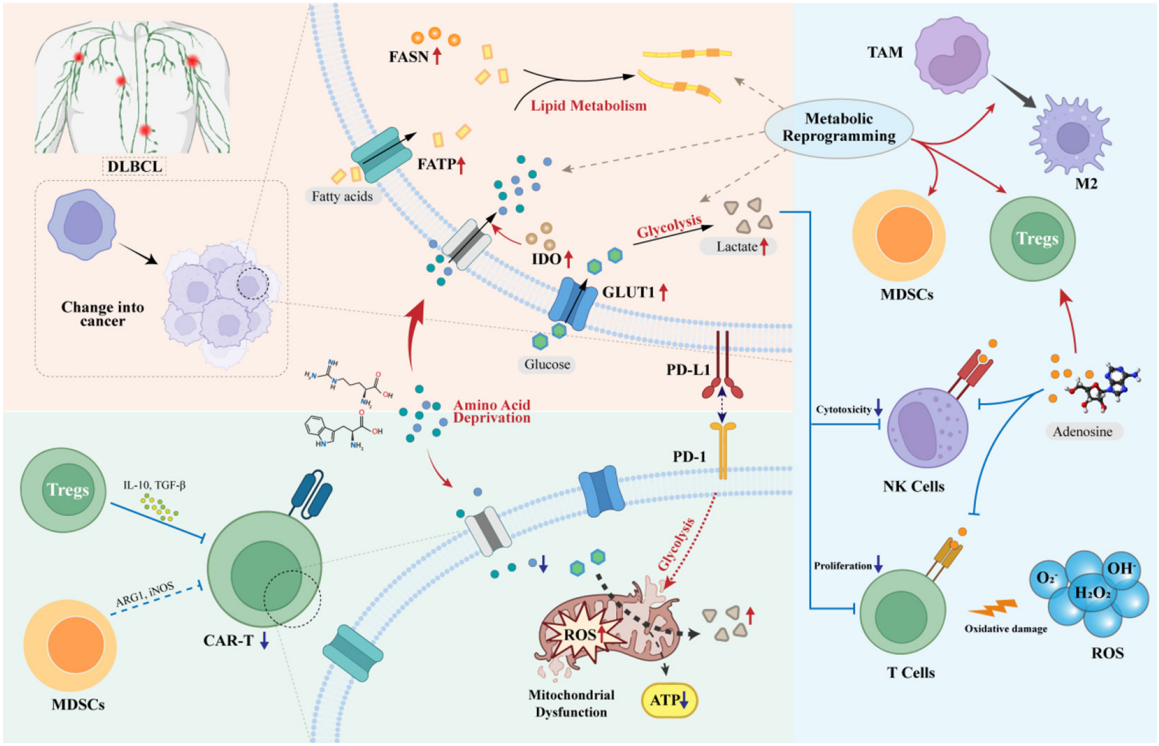


**Figure 1.** Metabolic characteristics and immunosuppressive mechanisms of the Tumor Immune Microenvironment (TME). It shows how DLBCL cells enhance glycolysis, lipid metabolism, and amino acid deprivation to support growth and suppress immunity. Key elements include the accumulation of lactate, adenosine, and ROS, which inhibit immune cell function. Immunosuppressive cells like Tregs and MDSCs also contribute to suppressing CAR-T cell activity. The figure highlights how these metabolic changes lead to CAR-T cell exhaustion through mechanisms such as mitochondrial dysfunction and nutrient competition.

*Efficacy data and resistance patterns of approved CAR-T products*

CAR-T cell therapy has achieved notable clinical advances in treating DLBCL, with multiple approved products yielding positive efficacy results. In the ZUMA-1 trial for R/R DLBCL patients, axicabtagene ciloleucel (Kymriah) achieved a 58% complete response rate and an 83% objective response rate [67]. However, resistance poses a major challenge in DLBCL treatment. Resistance mechanisms mainly involve tumor cell antigen escape, immunosuppressive microenvironment formation, and CAR-T cell exhaustion. In the NCT03258047 trial, fusing PD-1 to the intracellular CD28 activation domain resulted in a 41.2% complete response and a 58.8% objective response rate, which was not superior to approved second-generation CAR-T therapy [53]. Meanwhile, the NCT04836507 trial demonstrated that anbalcabtagene autoleucel (Anbal-cel) achieved a 78% complete response rate. Still, resistance mechanisms need further exploration [52].

The clinical trial NCT03085173 showed preliminary results of CAR-T cell therapy in CD19-positive malignancies. It had an 88% CR rate for DLBCL patients and a 22% CR rate for CLL patients [68]. This shows that CAR-T therapy's effectiveness in DLBCL is diverse and may link to the metabolic remodeling of the tumor microenvironment. In the NCT04037566 trial, CAR-T cells expressing IL-7 and CCL19 are being tested, resulting in a complete response rate of 4 out of 7 and an overall response rate of 5 out of 7 among patients with relapsed or refractory DLBCL [69]. These studies provide important insights for enhancing CAR-T therapy. Future research should delve deeper into resistance mechanisms to improve the efficacy and longevity of CAR-T therapy.

*Metabolic stress affects CAR-T cell persistence and memory phenotype*

Metabolic stress has a big effect on CAR-T cell persistence and memory phenotype. In CAR-T therapy, the primary sources of metabolic

**Table 1.** Metabolic characteristics and immunosuppressive mechanisms of the TME

| Research Direction | Molecular Mechanisms and Key Molecules | Immune Impacts and Examples |
|---|---|---|
| Metabolic Characteristics of the TME in DLBCL | GLUT1, glutaminase 1 (GLS1): DLBCL cells upregulate GLUT1 to enhance glycolysis and utilize GLS1 to promote glutamine metabolism, adapting to hypoxic and nutrient-deprived environments [13, 22-24]. | Lactic acid (a glycolysis product) inhibits T-cell activation and proliferation; altered glutamine metabolism affects the recruitment and function of MDSCs and Tregs, exacerbating immune suppression [18, 25-27]. |
| Metabolic Signatures | Warburg effect (glycolysis), fatty acid synthase (FASN), fatty acid transport protein (FATP), tryptophan/arginine-metabolizing enzymes (e.g., IDO) [28-31]. | High glycolysis leads to lactic acid accumulation, inhibiting T cells; abnormal lipid metabolism affects immune cell function; tryptophan deprivation inhibits T-cell activation and proliferation [25, 26, 32-34]. |
| Immunosuppressive Effects of Key Metabolic Products | Lactic acid, adenosine, reactive oxygen species (ROS): Lactic acid inhibits cytotoxic T-lymphocyte (CTL) proliferation and cytotoxicity; adenosine suppresses T-cell and natural killer (NK)-cell activity through A2 receptors and enhances Treg function; ROS induce oxidative stress-mediated immune cell dysfunction [16, 35-42]. | Lactic acid disrupts CTL metabolism, inhibiting proliferation and cytotoxicity; adenosine inhibits T-cell proliferation and cytokine secretion, promoting Treg-mediated immune suppression [37]. |
| Impact of Metabolic Reprogramming on Immune Cells | Glucose and glutamine competition: Tumor cells competitively uptake glucose and glutamine, reshaping immune cell metabolism [15, 43-46]. | T cells exhibit decreased proliferation and cytokine production when glucose metabolism is impaired; tumor-associated macrophages (TAMs) polarize towards the M2 phenotype, promoting an immunosuppressive microenvironment [46]. |
| Metabolic Basis of CAR-T Exhaustion | Mitochondrial respiratory chain complexes, PD-1/PD-L1, mTOR: DLBCL cells inhibit CAR-T cell mitochondrial respiratory chain complexes, activate PD-1/PD-L1 signaling, and competitively uptake amino acids to activate mTOR [7, 9, 25, 47-51]. | Mitochondrial dysfunction disrupts CAR-T cell energy metabolism and effector function; nutrient competition inhibits CAR-T cell proliferation and survival; metabolic checkpoints suppress CAR-T cell proliferation and cytokine secretion [25, 47]. |
| Metabolic Adaptation of Immunosuppressive Cells and CAR-T Antagonism | GLUT1, hexokinase 2 (HK2) in Tregs, GLS1 in MDSCs, interleukin-10 (IL-10), transforming growth factor-beta (TGF-β) in Tregs, arginase 1 (ARG1), inducible nitric oxide synthase (iNOS) in MDSCs [54-60]. | Tregs enhance glycolytic capacity, secrete inhibitory cytokines to suppress CAR-T cells; MDSCs promote glutamine metabolism, express ARG1 and iNOS to reduce CAR-T cell effector function [54, 55]. |

stress are nutrient shortages, lack of oxygen, and the buildup of metabolic waste in the TME [7]. These factors hinder CAR-T cell proliferation and survival, and may cause functional exhaustion. A study showed that CAR-T cells in hypoxic conditions have lower metabolic activity and mitochondrial function. This results in reduced proliferation and increased exhaustion [10]. Moreover, metabolic stress can affect the memory phenotype of CAR-T cells. Memory T cells are vital for long-term anti-tumor immunity. But metabolic stress can suppress their formation. For example, under high lactate concentrations, CAR-T cells show lower expression of memory T cell markers like CD62L and CD44 [16]. This indicates that metabolic stress impedes memory T cell development.

Researchers have developed novel approaches to combat metabolic stress effects on CAR-T cells. Genetic engineering of CAR-T cells to secrete IL-7 and CCL19 can enhance their metabolic adaptability and memory phenotype [70]. A clinical trial showed fourth-generation CAR-T cells co-expressing IL-7 and CCL19 had promising efficacy and safety in patients with relapsed/refractory large B-cell lymphoma. Among 39 patients, there was an objective response rate of 84.6% and a complete response rate of 69.2%, with no dose-limiting toxicities observed. Metabolic stress significantly impacts CAR-T cell persistence and memory phenotype. Optimizing these aspects can improve CAR-T cell efficacy and persistence in DLBCL treatment.

*An acidic microenvironment and hypoxia restrict the movement and penetration of CAR-T cells*

In DLBCL, hypoxia and an acidic microenvironment greatly hinder CAR-T cell migration and infiltration. Under hypoxia, low oxygen in the TME shifts CAR-T cell metabolism to glycolysis from oxidative phosphorylation. This change limits their energy and impairs function [7]. Studies show that in hypoxic conditions, CAR-T cell mitochondrial activity decreases, reducing proliferation and migration [16]. Also, hypoxia causes tumor cells to make more immunosuppressive molecules like PD-L1, further weakening CAR-T cell activity [71].

Acidic microenvironments appear to impair CAR-T cells by damaging their surface receptors, which seem to be vital for binding to tumor cells. What the research tends to suggest is that at pH 6.5, CD19 receptor expression on CAR-T cells substantially decreases, seemingly leading to reduced recognition and cytotoxicity of tumor cells [72]. What appears particularly significant about these findings is that acidic conditions also appear to trigger apoptosis in CAR-T cells, which ostensibly affects their survival and function within the tumor microenvironment [73]. Within this broader analytical framework, these findings seem to indicate that hypoxia and acidity create what might be characterized as a hostile microenvironment. What appears to follow from this analysis is that this undermines the effectiveness of CAR-T cells in treating DLBCL through several interconnected mechanisms.

*Mitochondrial metabolic defects and energy supply insufficiency in CAR-T cells*

Mitochondrial metabolic defects appear to correlate closely with inadequate energy supply in CAR-T cells. In CAR-T cell therapy, what seems to be essential is intact mitochondrial function to maintain CAR-T cell activity and persistence. However, given the complexity of these theoretical relationships, metabolic stress in the tumor microenvironment often appears to impair mitochondrial function in CAR-T cells, thereby seemingly affecting their energy supply. Upon activation, CAR-T cells apparently undergo metabolic reprogramming, shifting from oxidative phosphorylation in a resting state to glycolysis in an activated state. What seems especially noteworthy in this analytical context is that this metabolic shift appears to be crucial for CAR-T cell proliferation and functional performance. The hypoxic conditions and high lactate concentrations in the tumor microenvironment tend to disrupt what appears to be this metabolic reprogramming process. What the evidence appears to reveal is that hypoxic environments inhibit mitochondrial oxidative phosphorylation, presumably leading to reduced ATP production. High lactate concentrations further seem to suppress mitochondrial function, apparently exacerbating energy supply insufficiency.

What the research appears to suggest is that mitochondrial dysfunction in CAR-T cells tends to cause insufficient energy supply, which

seems to affect their proliferation and survival. One study found that CAR-T cells with what appears to represent weakened mitochondrial function showed less proliferation and more apoptosis in the tumor microenvironment. Also, considering the nuanced nature of these findings, inadequate energy supply can apparently cause functional exhaustion in CAR-T cells, seemingly impairing their ability to eliminate tumor cells [10]. To address this, what researchers are exploring seems to be ways to boost mitochondrial function and energy supply in CAR-T cells. Genetic changes to make CAR-T cells express mitochondrial protective factors or enzymes that tend to enhance oxidative phosphorylation may strengthen their energy output and antitumor power [41]. Also, what appears to warrant further interpretive consideration is that using metabolic modulators like mitochondrial protective agents or oxidative phosphorylation enhancers can presumably optimize the metabolic state of CAR-T cells and improve their performance in what seems to constitute the tumor microenvironment [74]. For particular clinical advances and metabolic-related progress of CAR-T therapy in DLBCL, see **Table 2**.

## Metabolic remodeling in the TME: strategies for optimizing CAR-T therapy

### *Selection and validation of metabolic regulatory targets*

In DLBCL, changes in the metabolism of the TME greatly affect the effectiveness of CAR-T therapy. The selection and validation of metabolic regulatory targets are vital for optimizing CAR-T therapy. Research has extensively focused on identifying and validating metabolic targets to enhance the performance of CAR-T cells.

Lactic acid is a key metabolic byproduct in the TME. It's significantly elevated and linked to an immunosuppressive environment. Studies show tumor-derived lactic acid can suppress CD8+ T cell cytotoxicity and weaken the antitumor immune response. In B-cell lymphoma mouse models and human cell lines, AZD3965, an MCT1 inhibitor, has demonstrated potential for inhibiting tumor growth and preventing metastasis [25]. This suggests that intervening in the lactic acid metabolic pathway may enhance CAR-T cell antitumor activity. Also, the pentose phosphate pathway (PPP) is crucial for immune cell metabolic remodeling in the TME. Under high oxidative stress, neutrophils shift their metabolism from glycolysis to the PPP. This shift increases NADPH production and reduces ROS levels [75, 76], supporting tumor cell antioxidant defense mechanisms and promoting their growth. Therefore, metabolic regulation targeting the PPP may be a potential target for enhancing CAR-T therapy effects.

Cancer cells develop metabolic adaptive mechanisms to survive and proliferate, and these metabolic vulnerabilities offer opportunities for innovative targeted therapies. The enhanced dependency of certain cancer cells on specific metabolic pathways may serve as a basis for selecting metabolic regulatory targets. By exploring these metabolic pathways, potential targets can be identified and validated through in vitro experiments and animal models to evaluate their application value in enhancing CAR-T therapy. Interventions targeting key metabolic pathways like the lactic acid pathway and the pentose phosphate pathway are expected to enhance the antitumor activity of CAR-T cells and improve treatment outcomes for patients with DLBCL.

### *Pathological significance of key metabolic enzyme targets*

Studies have focused on identifying and validating metabolic targets to enhance CAR-T cell function. Among these targets, metabolic enzymes IDO1, ARG1, LDHA and ACLY appear to have what might be characterized as prominent pathological significance in DLBCL. What seems to emerge from these findings is that IDO1 expression in DLBCL tends to be closely linked to tumor immune evasion. IDO1 catalyzes tryptophan metabolism, seemingly producing immunosuppressive metabolites like kynurenine that apparently inhibit T cell proliferation and function. What the evidence appears to reveal is that elevated IDO1 expression in DLBCL tissues appears to correlate with adverse prognoses. An analysis of tumor specimens from 120 DLBCL patients indicated that those with high IDO1 expression had a substantially lower 5-year overall survival rate compared to those with low expression (39.2% versus 62.5%, $P < 0.001$) [77]. Moreover, within this broader analytical framework, IDO1

**Table 2.** Clinical progress and metabolic-related advancements of CAR-T therapy in DLBCL

| Research Direction | Molecular Mechanisms and Key Molecules | Immune Impacts and Examples |
|---|---|---|
| Clinical Efficacy Analysis of CAR-T Therapy | CAR-T products (e.g., Axi-cel, Liso-cel): Significant efficacy, with Axi-cel achieving a CR of 54% and a 5-year survival rate of 43% in DLBCL patients [62]. ZUMA-7 trial: 1-year PFS rate of 60.0% and 2-year PFS rate of 44.9% [64]. TRANSCEND NHL 001 trial: Median PFS of 10.3 months [65]. Other lymphomas: 2-year PFS rates of 63% and 57% for follicular lymphoma; 12-month PFS rates of 61% and 53% for mantle cell lymphoma [61]. | High efficacy but high relapse rate (66%); adverse reactions like cytokine release syndrome (CRS) and neurotoxicity occur. |
| Efficacy Data and Resistance Patterns of Approved CAR-T Products | Axi-cel: In the ZUMA-1 trial, a CR of 58% and an ORR of 83% [67]. Resistance mechanisms include antigen escape, immune-suppressive microenvironment formation, and CAR-T cell exhaustion. NCT03258047 trial: PD-1 fusion with CD28 domain showed no advantage [53]. Anbal-cel: CR of 78% [52]. NCT03085173 trial: CR rate of 88% for DLBCL patients and 22% for CLL patients [68]. NCT04037566 trial: CR rate of 4/7 and ORR of 5/7 for r/r DLBCL patients [69]. | Resistance patterns include tumor cell antigen escape, immunosuppressive microenvironment formation, and CAR-T cell exhaustion. |
| Impact of Metabolic Stress on CAR-T Persistence and Memory Phenotype | Hypoxia and lactic acid: Inhibit proliferation and survival, leading to functional exhaustion and suppression of memory T-cell formation [7, 10, 16]. | Hypoxia reduces metabolic activity and impairs mitochondrial function, leading to decreased proliferation and increased exhaustion. High lactic acid concentrations inhibit the expression of memory phenotype markers like CD62L and CD44. |
| Suppression of CAR-T Migration and Infiltration by Hypoxia and Acidic Microenvironment | Hypoxia-induced metabolic reprogramming and acidic environment-damaged receptors: Hypoxia decreases mitochondrial activity, and acidic environment reduces CD19 receptor expression [7, 16, 71-73]. | Hypoxia induces PD-L1 expression in tumor cells, further inhibiting CAR-T cell activity. Low pH damages CAR-T cell surface receptors, reducing their binding capacity and causing apoptosis. |
| Correlation between Mitochondrial Metabolic Defects and CAR-T Energy Supply Insufficiency | Hypoxia and high lactic acid concentrations disrupt metabolic reprogramming: Inhibit oxidative phosphorylation and reduce ATP production [7, 10]. | Mitochondrial defects lead to decreased proliferation, increased apoptosis, and functional exhaustion. Insufficient energy supply prevents CAR-T cells from effectively killing tumor cells. |
| Strategies to Enhance CAR-T Efficacy through Metabolic Adaptability | Genetic engineering of CAR-T cells to express IL-7 and CCL19: Enhances metabolic adaptability and memory phenotype [70]. 7×19 CAR-T cells: ORR of 84.6% and CR of 69.2% in R/R LBCL patients, with no dose-limiting toxicity. | Engineering CAR-T cells to secrete IL-7 and CCL19 improves their metabolic adaptability and memory phenotype, enhancing antitumor activity and persistence. |

inhibitors have displayed what appears to be potential to enhance the antitumor activity of CAR-T cells in preclinical models. What seems especially noteworthy in this analytical context is that the combination of Pembrolizumab and the IDO1 inhibitor Epacadostat has shown ostensibly acceptable tolerability and what appears to be promising efficacy in DLBCL patients, as observed in clinical trials with a median follow-up of 40 months [78].

What the analysis tends to support is that ARG1 expression in DLBCL seems to be associated with tumor immune evasion. ARG1 catalyzes arginine metabolism, thus apparently inhibiting T cell proliferation and function. What appears to warrant further interpretive consideration is that high ARG1 expression in DLBCL tissues tends to correlate with poor prognosis. A study of 80 DLBCL patients showed that high ARG1 expression was linked to what seems to be a significantly lower 5-year overall survival rate than low expression (42.1% vs. 68.4%, $P < 0.001$) [79]. What this pattern seems to suggest, therefore, is that ARG1 inhibitors appear to show potential to enhance CAR-T cell antitumor activity in preclinical studies. Given the complexity of these theoretical relationships, the ARG1 inhibitor CB-1158 apparently inhibited tumor growth and seems to have enhanced CAR-T cell antitumor activity in what appears to represent a DLBCL mouse model [60].

In DLBCL, the expression of LDHA appears to be strongly linked to what might be characterized as the glycolytic metabolism of the tumor. LDHA seems to facilitate the transformation of pyruvate into lactate, apparently enhancing glycolytic metabolism in tumor cells and ostensibly aiding their swift growth. What the evidence tends to suggest is that poor prognosis in DLBCL tissues correlates with increased LDHA expression. A study of 100 DLBCL patients appears to indicate a substantially lower 5-year overall survival rate in those with high LDHA expression compared to low expression (40.0% vs. 65.0%, $P < 0.001$) [80, 81]. What also appears significant in this context is that LDHA inhibitors seem to demonstrate the ability to boost CAR-T cell antitumor effects in preclinical research. The LDHA inhibitor FX11 was found to apparently curb tumor growth and seemingly enhance the antitumor effects of CAR-T cells in a DLBCL mouse model [25].

Within this broader analytical framework, ACLY expression in DLBCL appears to be closely linked to what seems to represent the metabolism of lipids in tumors. ACLY seemingly drives tumor cell lipid synthesis and tends to support their rapid proliferation by converting acetyl-CoA to citrate [82]. What the data seems to suggest is that ACLY inhibitor BMS-303141 appears to inhibit tumor growth and tends to enhance CAR-T cell antitumor activity in a DLBCL mouse model [8]. What appears particularly significant about these findings is that the key metabolic enzymes IDO1, ARG1, LDHA, and ACLY seem to hold considerable pathological importance in DLBCL. Given the complexity of these theoretical relationships, high levels of these enzymes are predominantly associated with what appears to be poor prognosis in patients. What these findings seem to point toward is that by targeting these metabolic enzymes, CAR-T cell antitumor activity might be increased, potentially improving treatment outcomes for the majority of cases with DLBCL.

*Metabolic sensors and the regulation of signaling pathways network*

Metabolic sensors and signaling pathways in the TME appear to substantially influence CAR-T therapy effectiveness. What seems particularly noteworthy in this analytical context is that metabolic sensors such as mTOR, AMPK, and HIF-1α seem to play what might be characterized as key roles in DLBCL's regulatory network. The mTOR pathway tends to be viewed as pivotal in what appears to represent TME metabolic reshaping. What the evidence suggests is that mTORC1 activation appears to promote glycolysis and seemingly inhibits T cell effector functions [83]. Studies appear to indicate that mTORC1 activation tends to be linked to DLBCL cell proliferation and survival in the majority of cases. AMPK also appears to impact TME metabolic reshaping. What seems to emerge from these findings is that AMPK activation ostensibly inhibits mTORC1, apparently regulating cellular metabolism and immune responses. Research tends to suggest that AMPK activation seems to be tied to T cell metabolic adaptability and effector functions. What a study appears to reveal is that the AMPK activator AICAR could potentially enhance T cell metabolic adaptability and presumably increase antitumor activity [7]. HIF-1α, within this broader analytical frame-

work, appears to be crucial for what seems to constitute TME metabolic reshaping. What the data seems to suggest is that HIF-1α typically activates under hypoxia, apparently promoting tumor cell glycolysis and seemingly supporting rapid proliferation. Studies have, given the complexity of these theoretical relationships, appeared to link HIF-1α activation to DLBCL cell proliferation and survival. What the investigation appears to indicate is that HIF-1α inhibitors could potentially suppress DLBCL cell proliferation and tend to enhance CAR-T cell antitumor activity [84].

*Immunological effects of metabolic inhibitors and supplements*

Metabolic inhibitors and supplements appear to be crucial for what seems to represent the optimization of CAR-T therapy through TME metabolic remodeling. What these findings seem to point toward is that metabolic inhibitors can apparently enhance CAR-T cell immunological effects by what appears to be blocking tumor cell metabolic pathways [85]. What appears to follow from this analysis is that metabolic supplements can seemingly supply essential metabolic substances to what tends to enhance CAR-T cell metabolic adaptability and, considering the nuanced nature of these findings, predominantly improve their survival and function within the TME [86]. Metabolic inhibitors like the IDO inhibitor Epacadostat appear to demonstrate what might be characterized as substantial immunosensitizing effects in CAR-T therapy. What seems particularly significant about these findings is that IDO tends to function in the tumor microenvironment by catalyzing tryptophan metabolism, seemingly producing immunosuppressive metabolites such as kynurenine. These metabolites apparently inhibit T cell proliferation and function [87]. What the evidence appears to reveal is that Epacadostat can ostensibly block this pathway and appears to restore T cell immune function [88]. Metabolic supplements such as glutamine analogs are typically used in CAR-T therapy. Within this broader analytical framework, glutamine serves as what appears to be a crucial substrate for T cell metabolism. Its relative scarcity in the tumor microenvironment seems to restrict T cell function in the majority of cases. Glutamine analogs mimic glutamine's metabolic pathways, providing necessary metabolic substances to enhance CAR-T cell metabolic adaptability. A study showed that glutamine analogs can significantly improve CAR-T cell survival and proliferation within the TME [18]. The mechanisms of CAR-T optimization through TME metabolic remodeling are shown in **Figure 2** and detailed in **Table 3**. A summary of recent studies related to this topic is presented in **Table 4**.

## Advances in innovative patented medications

*Analysis of DLBCL patented medications targeting TME metabolism*

From 2018 to 2024, the significant progress has been made in the development of patented medications that target the metabolic reprogramming of the TME in DLBCL.

*Lactate metabolism inhibitors:* Lactate levels are markedly elevated in the TME, promoting an immunosuppressive environment that enhances cancer cell growth and facilitates immune evasion. AZD3965, a monocarboxylate transporter (MCT) 1 inhibitor, has shown potential in inhibiting tumor growth and preventing metastasis in mouse models of B-cell lymphoma and human cell lines [89]. In a Phase I, dose-escalation, and dose-expansion trial, encouraging results were observed with the combination of AZD3965 and anti-PD-1 therapy in mouse models. However, in clinical trials involving patients with advanced cancer, a majority of patients treated with AZD3965 experienced fatal outcomes. Although AZD3965 is generally considered safe, dose-limiting but reversible increases in cardiac troponin, a potential toxicity, were observed when the dose exceeded 20 mg. Further research is needed to comprehensively assess the clinical feasibility of MCT 1 inhibitors.

*Glutaminase inhibitors:* Glutaminase inhibitor Telaglenastat (CB-839) has demonstrated potential inhibitory effects on melanoma in both in vitro and in vivo analyses. Telaglenastat modulates glutamine metabolism in cancer cells, thereby enhancing T cell-mediated antitumor responses [90]. Currently, several Phase I and II clinical trials are evaluating the efficacy of CB-839 in combination with various chemotherapies or immunotherapies. These studies provide robust support for the application of glutaminase inhibitors in the treatment of DLBCL.

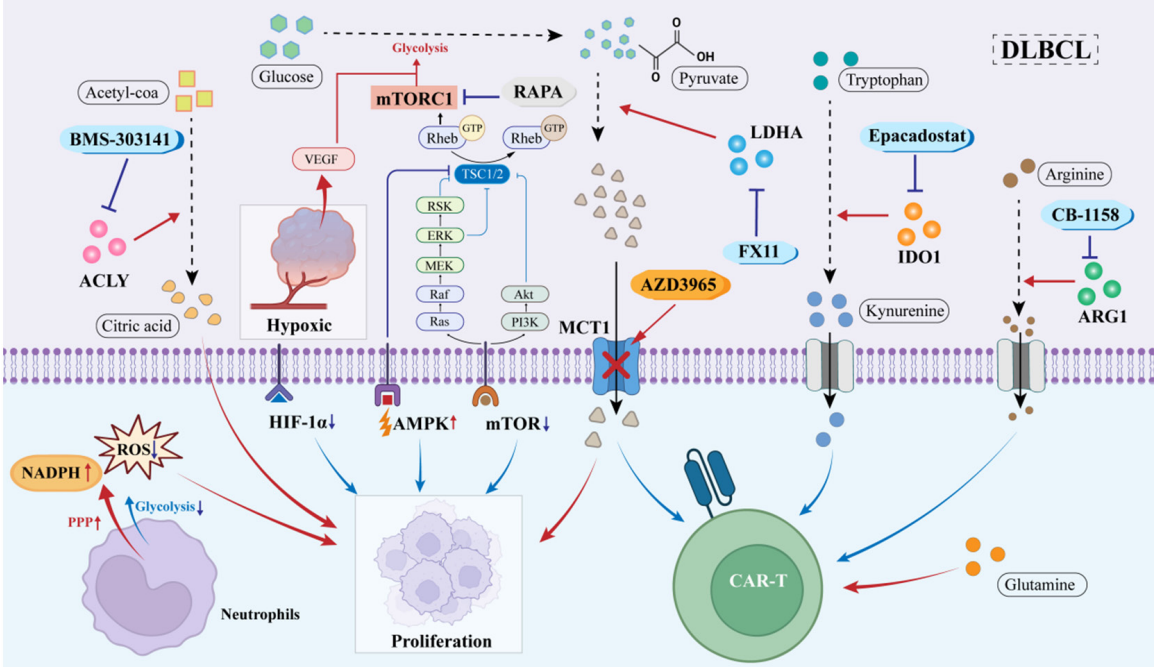


**Figure 2.** Metabolic remodeling in the TME: strategies for optimizing CAR-T therapy. It highlights key metabolic enzyme targets such as IDO1, ARG1, LDHA, and ACLY, which are linked to poor patient prognosis and tumor immune evasion. The figure also shows how metabolic inhibitors like Epacadostat and CB-1158, and supplements such as glutamine analogs, can enhance CAR-T cell function by blocking tumor metabolic pathways and improving metabolic adaptability. Additionally, it illustrates the role of metabolic sensors and signaling pathways like mTOR, AMPK, and HIF-1α in regulating TME metabolism and immune responses, offering potential intervention points to boost CAR-T therapy efficacy.

*Oxidative phosphorylation inhibitors:* IACS-010759 reduces the risk of cancer progression in brain metastases by inhibiting oxidative phosphorylation (OXPHOS) complex I, as observed in mouse models of lung cancer and brain metastases, as well as in human melanoma brain metastasis samples [91]. In a Phase I trial, this treatment led to significant tumor regression and metabolic improvement in patients with secondary resistance to epidermal growth factor receptor (EGFR) inhibitors. This suggests that oxidative phosphorylation inhibitors have potential application value in the treatment of DLBCL.

*Tricarboxylic acid cycle inhibitors:* Devimistat (CPI-613) is an innovative drug designed to selectively inhibit the catalytic and regulatory functions of the pyruvate dehydrogenase complex, its regulatory kinase, and the α-ketoglutarate dehydrogenase complex in cancer cells [92]. In a Phase I study, CPI-613 combined with mFOLFIRINOX was well-tolerated in pancreatic cancer patients. The application of tricarboxylic acid cycle inhibitors in DLBCL treatment is strongly supported by this.

What appears to warrant further interpretive consideration is that substantial advances have seemingly been made in developing patented medicines targeting metabolic changes in the DLBCL TME. Given the complexity of these theoretical relationships, these drugs tend to focus on what appears to represent key metabolic pathways including lactate metabolism, glutamine metabolism, oxidative phosphorylation, and the tricarboxylic acid cycle. What the data seems to suggest is that they have shown what might be characterized as promising antitumor activities and immunemodulatory effects.

### *Patent strategy for combination therapy: designing the synergistic protective scope of CAR-T⁺ metabolic drugs*

Combining CAR-T therapy with metabolic drugs appears to provide what seems to be substantial synergistic protection in DLBCL treatment.

**Table 3.** Mechanisms of CAR-T optimization through TME metabolic remodeling

| Research Direction | Key Molecules and Mechanisms | Immune Effects and Examples |
|---|---|---|
| Screening and Validation of Metabolic Regulation Targets | Lactic acid: A key metabolic product in TME, inhibiting the cytotoxicity of CD8+ T cells; MCT1 inhibitor AZD3965 has demonstrated potential in inhibiting tumor growth and metastasis in B-cell lymphoma models [25]. PPP: Under high oxidative stress, neutrophils shift metabolism from glycolysis to PPP, producing more NADPH and reducing ROS levels [75, 76]. | Intervening in the lactate metabolic pathway and targeting PPP may enhance the antitumor activity of CAR-T cells. |
| Pathological Significance of Key Metabolic Enzyme Targets | IDO1, ARG1, LDHA, ACLY: Highly expressed in DLBCL, with related inhibitors enhancing CAR-T efficacy. IDO1/ARG1/LDHA/ACLY inhibitors (e.g., epacadostat, CB-1158, FX11, BMS-303141) show potential in preclinical studies [77-82]. | IDO1, ARG1, LDHA, and ACLY are highly expressed in DLBCL, and related inhibitors enhance CAR-T efficacy. |
| Regulation Network of Metabolic Sensors and Signaling Pathways | mTOR, AMPK, HIF-1α: Regulate metabolism and immunity, affecting DLBCL cells. mTORC1 activation shifts cellular metabolism towards glycolysis; AMPK activation suppresses mTORC1 activity; HIF-1α activation promotes glycolytic metabolism under hypoxic conditions [7, 83, 84]. | mTOR, AMPK, and HIF-1α regulate metabolism and immunity, affecting DLBCL cells. |
| Immune Effects of Metabolic Inhibitors and Supplements | Metabolic inhibitors: Block tumor metabolism, enhancing CAR-T immune effects. Metabolic supplements: Enhance CAR-T cell adaptability. IDO inhibitor Epacadostat [88]; glutamine analogs [18]. | IDO inhibitor Epacadostat enhances CAR-T efficacy; glutamine analogs improve CAR-T cell survival and proliferation. |

**Table 4.** Research progress of DLBCL patented medications targeting TME metabolism

| Research Direction | Key Molecules and Mechanisms | Immune Effects and Examples |
|---|---|---|
| Analysis of DLBCL - Targeted TME Metabolic Drugs (2018-2024) | Lactate metabolism inhibitors: AZD3965 targets MCT1, inhibiting tumor growth and metastasis [95] | AZD3965 shows potential in B - cell lymphoma models but has dose - limiting toxicities in clinical trials |
| Combination Therapy Patent Strategies: Synergistic Protection of CAR - T + Metabolic Drugs | Metabolic drug AZD3965 enhances CAR - T cell antitumor activity by inhibiting lactate transport [96] | CAR - T combined with metabolic drugs significantly improves PFS and OS in patients |
| Glutaminase Inhibitors | Telaglenastat (CB - 839) regulates glutamine metabolism in cancer cells, enhancing T - cell - mediated antitumor responses [97] | Ongoing clinical trials support the application of glutaminase inhibitors in DLBCL treatment |
| Oxidative Phosphorylation Inhibitors | IACS - 010759 reduces the risk of brain metastasis by inhibiting OXPHOS complex I [98] | Shows potential application value in DLBCL treatment with significant tumor regression in patients |
| TCA Cycle Inhibitors | Devimistat (CPI - 613) selectively inhibits the catalytic and regulatory functions of key enzymes in the TCA cycle in cancer cells [99] | CPI - 613 demonstrates good tolerability in combination with mFOLFIRINOX for pancreatic cancer, supporting its application in DLBCL |

What these findings seem to point toward is that the patent strategy for this combination tends to focus on designing the protective scope to presumably maximize benefits and minimize side effects. Considering the nuanced nature of these findings, CAR-T therapy specifically appears to target and destroy cancer cells, while metabolic drugs seemingly enhance CAR-T cell activity and survival by what appears to be adjusting the TME metabolic state. For example, the metabolic drug AZD3965 inhibits lactate transport, reduces TME lactate levels, and thereby enhances CAR-T antitumor activity [93]. When devising the patent strategy, it is crucial to determine the synergistic protective scope of CAR-T therapy and metabolic drugs, which involves factors such as drug dosage, administration timing, route of administration, and patient-specific conditions. Many clinical trials have confirmed the effectiveness of combining CAR-T therapy with metabolic drugs, such as the combination of CAR-T cell therapy and Telaglenastat, which has significantly improved patient PFS and OS [94]. As more clinical trials and research are conducted, the combination of CAR-T therapy and metabolic drugs is expected to provide more effective treatment options for DLBCL patients.

### Clinical translational challenges and future prospects

In the clinical translation of DLBCL, organoids and humanized mouse models are instrumental in metabolic studies, providing both in vitro and in vivo frameworks for investigating metabolic interventions. Mayo Clinic researchers are using 3D organoid models to study complex diseases; these organoids can imitate human organ metabolic processes, providing a unique platform for drug screening and disease research [95]. Metabolomics and single - cell sequencing technologies are highly significant in translational research. They allow for comprehensive analysis of metabolic changes in the tumor microenvironment and clarify the metabolic heterogeneity of tumor and immune cells [96]. The progress in spatial metabolomics technology has facilitated the resolution of the heterogeneity within the TME. By accurately pinpointing the metabolic traits of various tumor areas, it provides more specific targets for treatment [97]. Enhancing clinical trial design is essential for improving the effectiveness of CAR-T therapy. Future clinical trials should center on patient selection, treatment protocol optimization, and effectiveness evaluation. Biomarker - driven stratified treatment strategies are a future direction. They enable precise patient categorization through biomarker detection [98]. Dynamic metabolic monitoring technologies, such as PET imaging and liquid biopsies, can assess treatment effects and metabolic states in real-time. Safety considerations are an essential part of clinical translation; metabolic interventions may pose risks such as off-target effects and cytokine storms, which need to be mitigated through optimized treatment plans and monitoring methods. Individualized metabolic profiling-guided dose adjustments are a crucial strategy for improving efficacy, allowing for precise dosing of CAR-T cells and metabolic drugs by analyzing the patient's metabolic profile.

In the treatment of DLBCL, emerging technology-driven metabolic regulation shows significant potential. Artificial intelligence (AI) technology plays an important role in predicting metabolic targets and drug responses; AI algorithms can predict potential metabolic targets and drug responses by analyzing large-scale metabolomics data, thereby accelerating the drug development process. Researchers have developed a new category of AI algorithms known as hypothesis-driven AI, which can use large-scale datasets to uncover the complex causes of diseases and improve treatment strategies. In terms of industrialization and policy support, expedited review channels for metabolic regulation drugs, such as the FDA's Breakthrough Therapy Designation, provide significant support for accelerating drug market entry [99]. Additionally, the Mayo Clinic is promoting the reintroduction of carbon ion therapy in North America, a therapy already in use in Asia and Europe, whose precision makes it effective in killing cancer cells while minimizing damage to surrounding healthy tissues [100]. Industry-academia-research collaboration models play a key role in promoting patent translation, and by establishing close industry-academia-research partnerships, the translation of scientific research from the laboratory to the clinic can be accelerated. The Mayo Clinic collaborates with several pharmaceutical companies to develop new treatment methods, such as CAR-M therapy, which has demonstrat-

ed its safety and feasibility in human patients and can target HER2-positive tumors while reshaping the TME to enhance antitumor immune responses [101]. In summary, the application of emerging technologies such as spatial metabolomics and artificial intelligence in metabolic regulation, along with policy support and industry-academia-research collaboration models, brings new hope for precision immunotherapy in DLBCL. The development and application of these technologies are expected to accelerate the clinical translation of metabolic regulation drugs, providing patients with more effective treatment options.

## Conclusion

Metabolic remodeling is crucial for optimizing CAR-T cell therapy, especially in treating DLBCL. Adjusting the metabolic state of the tumor immune microenvironment can enhance CAR-T cell activity and survival, improving therapeutic outcomes. Multidimensional intervention strategies that combine drug development, genetic engineering and clinical approaches show great potential and value. In drug development, various metabolic inhibitors and supplements can boost CAR-T cell immunological effects. AZD3965 and Telaglenastat, for example, have shown promising antitumor activity in preclinical studies. In genetic engineering, modifying CAR-T cells to enhance metabolic adaptability can further improve their survival and functionality within the tumor microenvironment. In clinical strategies, optimizing clinical trial designs, employing biomarker-driven stratified treatment strategies, and integrating dynamic metabolic monitoring technologies like PET imaging and liquid biopsies allow real-time assessment and personalized adjustment of therapeutic effects. The combined application of these multidimensional interventions promises to deliver more precise and effective immunotherapeutic regimens for DLBCL patients, introducing a new paradigm for precision immunotherapy in DLBCL. As more clinical trials are conducted and in-depth research progresses in the future, the role of metabolic remodeling in CAR-T therapy optimization will be further validated and expanded, offering more treatment options and hope for DLBCL patients. However, at present, although there are targeted drugs researched for CAR-T therapy, there are still many problems to be solved when applied to the clinic, and in-depth research is still needed in the future to better serve the clinical treatment.

## Disclosure of conflict of interest

None.

## Abbreviations

DLBCL, Diffuse large B-cell lymphoma; TME, Tumor immune microenvironment; CAR-T, Chimeric antigen receptor T; MCT, Monocarboxylate transporter; IDO, Indoleamine 2,3-dioxygenase; Tregs, Regulatory T cells; MDSCs, Myeloid-derived suppressor cells; TGF-β, Transforming growth factor-β; IL-10, Interleukin-10; GLUT1, Glucose transporter protein 1; GLS1, Glutaminase 1; FASN, Fatty acid synthase; FATP, Fatty acid transport protein; ROS, Reactive oxygen species; CTLs, Cytotoxic T lymphocytes; NAD(H), Nicotinamide adenine dinucleotide (oxidized and reduced forms); PFS, Progression-free survival; OS, Overall survival; CR, Complete response; ORR, Objective response rate; CRS, Cytokine release syndrome; EGFR, Epidermal growth factor receptor; OXPHOS, Oxidative phosphorylation; mTOR, Mammalian target of rapamycin; AMPK, Adenosine monophosphate-activated protein kinase; HIF-1α, Hypoxia-inducible factor 1α; AICAR, 5-aminoimidazole-4-carboxamide ribonucleotide; GPC3, Glypican-3; MCL, Mantle cell lymphoma; NHL, Non-Hodgkin's lymphoma; r/r, Relapsed/refractory; Anbal-cel, Anbalcabtagene autoleucel; Axi-cel, Axicabtagene ciloleucel; Liso-cel, Lisocabtagene maraleucel; BMS-303141, ACLY inhibitor; FX11, LDHA inhibitor; 7×19 CAR-T, Fourth-generation CAR-T cells co-expressing IL-7 and CCL19.

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