Mechanisms of T-cell metabolic reprogramming in the microenvironment of acute myeloid leukemia and its therapeutic potential (Review)

YANHONG LUO[1], JIE LUO[2], MIN YANG[1] and XUEYA ZHAO[3]

[1]Department of Hematology, Affiliated Hospital of Zunyi Medical University, Zunyi, Guizhou 563000, P.R. China; [2]Bishan Hospital of Chongqing Medical University, Chongqing 402760, P.R. China; [3]Department of Hematology, The First Affiliated Hospital of Chongqing Medical University, School of Basic Medical Sciences, Chongqing Medical University, Chongqing 400016, P.R. China

Received March 14, 2025; Accepted June 17, 2025

DOI: 10.3892/ol.2025.15201

Abstract. Acute myeloid leukemia (AML) is an aggressive hematological malignancy that is often resistant to conventional therapies. The present narrative review discusses on the role of T cell metabolic reprogramming in the AML tumor microenvironment (TME), which markedly impacts the effectiveness of immunotherapy. The TME of AML, influenced by factors such as high lactic acid (LA) levels, hypoxia and nutrient competition, hampers T cell functions such as glycolysis, lipid metabolism and amino acid metabolism, leading to impaired T cell proliferation and antitumor response. Metabolic waste products, including LA and adenosine, further contribute to the immunosuppressive environment. T cell exhaustion, induced by nutrient deprivation and metabolic dysregulation, serves a key role in the failure of immune responses. Moreover, strategies to modulate T cell metabolism, such as targeting glycolysis and fatty acid oxidation, show promise in enhancing immunotherapy outcomes. The current review also highlights emerging technologies, such as single-cell metabolomics and CRISPR screening, which are critical for identifying metabolic targets and advancing personalized therapies. Despite challenges in translating these findings to clinical settings, understanding T cell metabolism in the AML TME offers new therapeutic avenues for improving patient outcomes.

Correspondence to: Professor Min Yang, Department of Hematology, Affiliated Hospital of Zunyi Medical University, 149 Dalian Road, Huichuan, Zunyi, Guizhou 563000, P.R. China
E-mail: 1194738784@qq.com

Professor Xueya Zhao, Department of Hematology, The First Affiliated Hospital of Chongqing Medical University, School of Basic Medical Sciences, Chongqing Medical University, 1 Youyi Road, Yuanjiagang, Yuzhong, Chongqing 400016, P.R. China
E-mail: 103137@cqmu.edu.cn

Key words: immunization, T cells, tumor immunology

Contents

1. Introduction

Acute myeloid leukemia (AML) is an aggressive cancer marked by the rapid growth of immature myeloid cells, which disrupts normal blood cell production (1). Despite advancements in treatments such as chemotherapy and stem cell transplantation (2), the lack of understanding of the tumor microenvironment (TME) has hindered the effectiveness of immunotherapies. The TME includes tumor cells, immune cells, fibroblasts, blood vessels and cytokines, all interacting to influence tumor progression. Immunotherapy aims to boost antitumor responses whilst reducing immunosuppressive effects (3). In leukemia, the bone marrow is the primary site for leukemia stem cells, with secondary lymphoid organs also part of the TME. Current therapies such as checkpoint inhibitors combined with chemotherapy and hypomethylating agents, show promise. Further research into the immune microenvironment of AML is essential to develop more effective immunotherapies (4).

Unlike in solid tumors, the AML TME is primarily in the bone marrow, with unique anatomical, cellular and metabolic features. It includes hematopoietic stem/progenitor, stromal, endothelial and immune regulatory cells, but lacks tumor-associated fibroblasts and persistent antigenic stimulation typical of solid tumors (5). The AML TME is highly

immunosuppressive, marked by increased regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs) and exhausted T cells, which limit immune responses (6). Leukemia cells remodel the TME by altering C-X-C motif chemokine ligand 12 (CXCL12) expression in stromal cells, suppressing normal hematopoiesis and promoting their survival (7). The metabolic profile, hypoxia and immune composition of AML differ from solid tumors, further reducing immunotherapy efficacy (8). Recent studies have highlighted that AML TME characteristics are associated with disease progression and serve as a key factor for patient risk stratification (9,10). Therefore, understanding AML-specific TME structure and function is crucial for optimizing immunotherapy strategies.

Furthermore, T cells are crucial in antitumor immunity, especially $CD8^+$ cytotoxic T lymphocytes (CTLs), which kill tumor cells via granzyme B, perforin and interferon-γ (IFN-γ), improving prognosis (6). Helper T cells (Th) 1, 2 and 17 also serve roles: Th1 enhances CTL activity through IFN-γ and IL-2; Th2 recruits eosinophils and macrophages; and Th17 can have pro or antitumor effects (11). Conversely, Tregs suppress effector T cells (Teffs), often associated with poor prognosis (12). In numerous cancers, Tregs are more abundant in tumor tissues than in adjacent healthy tissues. Their presence in the TME inhibits effector T cell function, promoting disease progression and poor outcomes, as observed in colorectal cancer (11).

Cells require nutrients for normal function, and immune cells rely on nutrient uptake to regulate their activities (13). T cell activation drives metabolic shifts, boosting glycolysis to meet energy needs for proliferation. Unlike cancer cells, which experience dysregulated metabolism, T cells respond normally to these changes (14). Lipid and amino acid metabolism are also crucial; lipid biosynthesis affects mTOR, a key regulator of metabolic reprogramming (15), whilst amino acid availability, particularly L-arginine, influences T cell survival and adaptability (16). In the TME, tumor cells compete with T cells for essential nutrients such as glucose, glutamine and arginine, impairing T cell function and promoting tumor progression. Through the Warburg effect, tumor cells outcompete T cells for glucose, whilst programmed death-1 (PD-1) expression further inhibits glycolysis. Fatty acid accumulation disrupts mitochondrial function, driving T cell exhaustion. Tumor cells also deplete arginine and glutamine, reducing their availability for T cells. Other immune cells, such as dendritic cells, MDSCs and tumor-associated macrophages, overexpress enzymes such as arginase and indoleamine 2,3-dioxygenase (IDO), depleting essential amino acids and altering T cell activation and differentiation. The accumulation of immunosuppressive Tregs further exacerbates T cell exhaustion (17).

The AML TME is marked by high glucose metabolism and lactic acid (LA) accumulation, creating an acidic environment that suppresses T cell function (18). Neutralizing acidity with sodium bicarbonate (NaBi) has been reported to enhance $CD8^+$ T cell immunotherapy efficacy (19). The fms-related tyrosine kinase 3-internal tandem duplication mutation increases glycolytic activity, contributing to chemotherapy resistance and impaired T cell function (20). Elevated glucose metabolism in AML cells further drives chemoresistance. Excessive glucose consumption and high LA levels in AML cells inhibit T cell function, weakening antitumor immunity (21,22). Lipid metabolism also serves a key role in tumor progression (23), immune evasion and drug resistance (24). Dysregulated lipid metabolism alters the balance between Tregs and Teffs in the TME (13).

Additionally, recent studies have highlighted the critical role of T-cell metabolic reprogramming in the AML TME. The abnormal metabolic features of the AML microenvironment, such as high LA levels, hypoxia and nutrient competition, directly suppress T cell effector functions and drive exhaustion by altering metabolic pathways such as glycolysis and fatty acid oxidation (FAO) (25-27). These factors notably contribute to immunotherapy failure. The present review assesses the molecular mechanisms of T cell metabolic reprogramming in the AML TME, focusing on the way metabolic imbalances impair T cell functionality. It also explores potential strategies for combining metabolic interventions with immunotherapy. By synthesizing current research, the current review aims to provide a theoretical foundation for developing novel AML therapies based on metabolic regulation.

2. Factors in the TME that influence T cell metabolism in AML

High levels of LA. A defining feature of the AML TME is the production of excessive LA, creating a highly acidic environment (18). A study reported that LA inhibits T cell growth and proliferation, and its accumulation in the TME disrupts LA efflux from T cells, impairing their metabolism, function and antitumor immunity (28). Additionally, LA downregulates perforin and granzyme B, which are essential for T cell-mediated tumor cell killing and proliferation (29,30). Dichloroacetic acid (DCA) targets pyruvate dehydrogenase kinase (PDK), an enzyme that drives glucose metabolism toward glycolysis instead of oxidative phosphorylation (OXPHOS) in tumor cells. By inhibiting PDK, DCA offers a potential strategy to modulate glucose metabolism in the AML TME (31). DCA can inhibit the shift toward glycolysis, reducing LA levels and notably enhancing T cell proliferation, and cytokine production and function whilst decreasing apoptosis (32). Tregs use monocarboxylate transporter 1 to uptake LA, which activates signaling pathways that promote nuclear factor of activated T cells 1 translocation to the nucleus, upregulating PD-1 expression (Fig. 1) (33). Therefore, high LA levels increase PD-1 expression in Tregs, amplifying their immunosuppressive effects. Additionally, LA accumulation and the resulting acidic pH in the TME inhibit $CD4^+$ T cell activity, particularly the secretion of key cytokines such as IL-2 and IFN-γ. These cytokines are crucial for immune responses, and their reduction weakens $CD4^+$ T cell proliferation and helper function, further promoting immunosuppression (34). In summary, high LA levels in the AML TME are a major contributor to T cell dysfunction, impairing antitumor immunity through metabolic disruption, cytotoxic inhibition and induction of exhaustion.

Hypoxia. Hypoxia is a defining feature of the bone marrow TME, markedly impacting AML cell growth, metabolic reprogramming and immune interactions. Studies have reported that patients with higher hypoxia risk scores tend to have shorter overall survival rates, linking hypoxia to poor prognosis in AML. Elevated hypoxia risk scores are

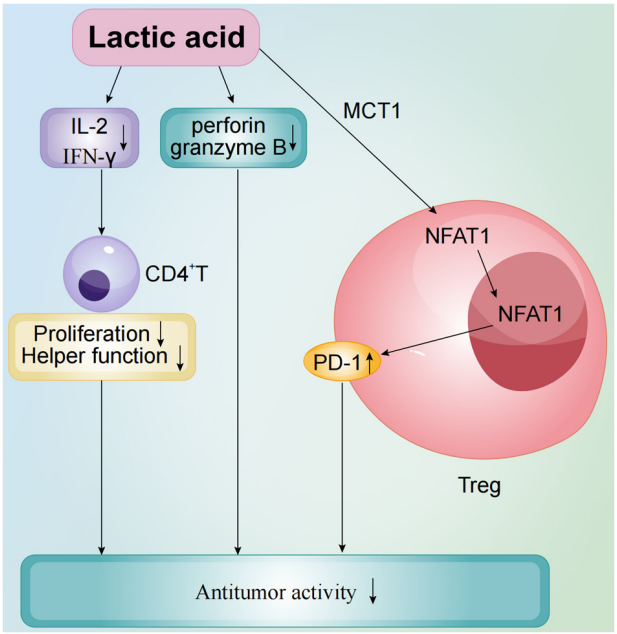

Figure 1. Acute myeloid leukemia tumor microenvironment is characterized by high lactic acid levels, which create an acidic milieu that impairs T cell function. Lactic acid inhibits perforin and granzyme B, essential for T cell-mediated tumor cell killing, and reduces the secretion of cytokines such as IL-2 and IFN-γ, critical for $CD4^+$ T cell proliferation. Lactic acid accumulation in Tregs is facilitated by MCT1, activating NFAT1 signaling and upregulating PD-1, enhancing Treg-mediated immunosuppression. IFN-γ, interferon-γ; Treg, regulatory T cell; MCT1, monocarboxylate transporter 1; NFAT1, nuclear factor of activated T cells 1; PD-1, programmed death-1.

also strongly associated with disease progression and the immunosuppressive TME (35,36). Under hypoxic conditions, hypoxia-inducible factor 1α (HIF-1α) is activated and directly upregulates programmed death-ligand 1 (PD-L1) expression. High PD-L1 levels bind to PD-1 on T cells, inhibiting their activation and signaling, further suppressing antitumor immunity (37).

Nutrition competition. AML tumor cells and immune cells compete for essential nutrients such as glucose and amino acids, which are vital for both rapid tumor growth and normal immune function. Tumor cells, with their high metabolic demands, prioritize the uptake of glucose, glutamine and other substrates for energy and biosynthesis, depriving immune cells of these resources. For instance, AML cells depend on glutamine for OXPHOS, and the inhibition of glutaminase-1 has been reported to suppress AML development in mouse models (38). Glutamine is also critical for T cell activation, proliferation and cytokine production (39). Glutamine deficiency in the TME promotes the generation of Tregs, further exacerbating immunosuppression (40). Glutamine deficiency not only restricts effector T cell proliferation and function, but also supports the metabolic adaptation of Tregs, enhancing their immunosuppressive activity. Studies have highlighted the antisense non-coding RNA at the INK4 locus (ANRIL) as a key regulator of glucose metabolism in AML, where it is notably upregulated. ANRIL modulates glucose metabolism via the AMP-activated protein kinase (AMPK)/ sirtuin 1 pathway, promoting AML cell survival. Its knockdown reduces glucose uptake and inhibits AML cell maintenance (41,42). Under oxygen-sufficient conditions, AML cells rely heavily on glucose as their primary metabolic substrate, rapidly converting it to LA through glycolysis to meet energy demands (43). A study by Cunningham and Kohno (44) using 18FDG labeling in 124 patients reported consistently high glucose uptake in AML bone marrow, highlighting the glucose dependence of AML cells. This excessive glucose consumption by AML cells suppresses T cell activation, induces exhaustion and drives leukemia progression.

Chemokines and cytokines. The AML TME shapes T cell metabolism and function by secreting chemokines and cytokines, influencing tumor progression (45,46). Studies have reported that chemokines such as chemokine CCL3 and CXCL12 in the AML microenvironment promote Treg accumulation, which competitively inhibits Teffs and indirectly affects their metabolic activity (47,48). Whilst research does not directly address whether chemokines regulate T cell metabolic pathways, it highlights the potential of blocking Treg migration to delay disease progression. Inhibiting these chemokines has been reported to slow AML progression in mouse models (45).

Accumulation of other metabolic waste products. Potassium ions (K^+), abundant in intracellular fluid, are essential electrolytes that regulate immune cell function and several cellular processes (49,50). Tumor cell necrosis releases large amounts of K^+ into the extracellular fluid of the TME. Elevated extracellular K^+ concentrations impair T cell receptor (TCR)-mediated Akt-mTOR phosphorylation, hindering effector T cell activation and function (51). Conversely, higher K^+ levels can enhance T cell stemness, maintaining their undifferentiated state (52). This indicates that K^+ dynamics in the TME influence both immediate T cell effector functions and their long-term survival and potential. However, research on the role of K^+ in the AML TME remains limited.

3. Changes in T cell metabolic pathways in the AML microenvironment

Glycolysis and OXPHOS. Before antigen exposure, naive T cells remain in a quiescent state maintained by IL-7. As they do not require clonal expansion or high cytokine production, their reliance on anabolic pathways for DNA, protein and molecule synthesis is minimal. Instead, they generate ATP primarily through mitochondrial OXPHOS (53). By contrast, tumor cells undergo a notable metabolic shift, favoring glycolysis over OXPHOS despite its lower ATP yield. This adaptation supports their rapid proliferation and survival by quickly meeting energy and metabolic intermediate demands (54). Tregs derived from $CD4^+$ T cells serve a dual role: They maintain immune homeostasis and prevent autoimmune diseases; however, during AML progression, they suppress CTL activity, weakening antitumor immunity and promoting immune evasion (55). Studies have reported that AML blasts promote T cell differentiation into a Treg phenotype by expressing inducible T cell co-stimulator ligand, markedly expanding the Treg population (56,57). At the AML disease site, Tregs suppress CTL activity, limiting their proliferation and hindering the expansion of adoptively transferred

CTLs *in vivo*. This suppression weakens CTL-mediated antitumor effects, further compromising immune responses against AML (58). Research indicates that mTOR and glucose transporter-1 (GLUT-1) regulate $CD4^+$ T cell activation by influencing glycolysis. Increased glycolysis in $CD4^+$ T cells enhances their activation, proliferation and survival whilst promoting effector T cell differentiation and inhibiting Treg development, which suppresses immune responses (59). Similarly, the differentiation of $CD8^+$ T cells from naive to effector states requires upregulated glucose metabolism as glycolysis provides the energy needed for their immune effector functions (60). In mouse $CD8^+$ T cells, branched-chain amino acid (BCAA) accumulation boosts glucose transporter 1 (GLUT1) levels via a forkhead box protein O1-dependent mechanism, enhancing glycolysis and OXPHOS to strengthen antitumor immunity. BCAA supplementation also improves the efficacy of PD-1 immunotherapy in tumors (61). Thus, increased glycolysis serves a crucial role in enhancing antitumor immune responses.

In AML, leukemia cells rely heavily on glycolysis (Warburg effect) for energy, resulting in the accumulation of glycolytic byproducts such as methylglyoxal. These reactive compounds react non-enzymatically with proteins, lipids and DNA, forming advanced glycosylation end products (AGEs) (62). AGEs bind to the receptor for AGEs (RAGE), activating signaling pathways such as NF-κB, MAPK and phosphoinositide 3-kinase (PI3K)/Akt, which drive pro-inflammatory and pro-survival responses, influencing cellular functions and disease progression (63,64). AGE-RAGE signaling promotes the proliferation of AML cell lines, such as HL60 and HEL, by inhibiting apoptosis and autophagy, enhancing cancer cell survival and invasiveness. This mechanism contributes to the progression of several tumors, including AML (64). Consequently, the AGE-RAGE axis represents both a hallmark of AML metabolic reprogramming and a potential diagnostic and therapeutic target.

FAO. Fatty acid uptake and metabolism are essential for AML cell proliferation, providing energy and metabolic intermediates whilst inhibiting apoptosis and conferring resistance to cytotoxic drugs. AML cells thus depend on fatty acid metabolism for survival (65). Lipid metabolism also serves a key role in T cell metabolic reprogramming, supporting membrane expansion through the production of phospholipids and cholesterol. Naive $CD8^+$ T cells in the lymphatic system primarily rely on FAO for energy (66). The differentiation of Teffs compared with memory T cells depends on the strength of signals from co-stimulatory molecules, cytokines and antigen presentation (67). Strong stimulation leads to the generation of short-lived terminally differentiated effector cells, whilst weaker stimulation promotes the differentiation of memory precursor cells, which further transform into long-lived memory cells, providing protection against re-infection (68). Certain memory T cells also arise from Teffs that survive apoptosis at the end of an immune response (69). In the AML TME, memory T cells exhibit markedly reduced metabolic adaptability and persistence. Research indicates that these cells fail to sustain critical metabolic pathways such as FAO and mitochondrial OXPHOS resulting in energy deficiency that compromises their survival and long-term effector function (6,70). AML cells exacerbate this dysfunction by competing for essential nutrients such as glucose and glutamine, further suppressing T cell metabolism. Prolonged nutrient deprivation not only impairs memory T cell function, but also promotes their exhaustion, characterized by upregulated expression of exhaustion markers such as PD-1 and thymocyte selection-associated high mobility group box protein, and diminished cytotoxic capacity (56,71). Notably, memory T cells also serve a role in modulating the response of hematological malignancies to PD-1 blockade therapy (72). Studies have reported that TNF receptor-associated factor 6 (TRAF6) influences $CD8^+$ memory T cells through lipid metabolism regulation. Mice with T cell-specific TRAF6 deficiency exhibit strong effector T cell responses but fail to form memory T cells effectively (73,74). IL-15 regulates mitochondrial spare respiratory capacity and oxidative metabolism by modulating mitochondrial biogenesis and the key enzyme carnitine O-palmitoyl transferase 1 (CPT1)a. CPT1a is critical for the rate-limiting step in mitochondrial FAO (75). Enhancing FAO through AMPK activation or mTOR inhibition can notably increase memory T cell numbers (73,76). These findings emphasize the pivotal role of lipid metabolism in T cell metabolic reprogramming.

Amino acid metabolism. Studies have reported that amino acids regulate immune responses by influencing T cell activation, cytokine production and other immune functions (77). Glutamine, the most abundant amino acid in serum, is vital for maintaining metabolic balance and cell function. Its absence in culture medium markedly impairs naive T cell activation, proliferation and cytokine production (39). In the hypoxic TME, glutamine acts as a primary carbon source, supporting the energy and metabolic needs of tumor cells (78). Amino acids and their metabolites are essential in regulating both tumor and immune cell proliferation within the TME. For instance, glutamine and its metabolic pathways are crucial for tumor cell glycolysis. Using glutamine antagonists can effectively inhibit glycolysis in tumor cells, suppressing their growth and enhancing the antitumor immune response by altering the immunosuppressive TME, thereby overcoming immune evasion (79). Besides glutamine, the metabolism of arginine and tryptophan also serves a pivotal role in immune regulation within the TME. Studies have reported that monocytes, under macrophage-stimulating factor influence, rapidly degrade tryptophan through increased IDO activity, thereby suppressing T cell proliferation. This mechanism aids tumor cells and macrophages in immune evasion. Furthermore, extracellular arginine availability in the TME directly influences T cell function and antitumor responses (80,81). Arginine deprivation leads T cells to initiate autophagy, downregulate the CD3ζ chain and ultimately undergo apoptosis. In AML, this effect is more pronounced, as AML blasts express and secrete arginase II, a key enzyme for arginine metabolism, whilst arginase I is typically low and only detectable under specific conditions. This metabolic regulation further impairs T cell function, aiding AML cells in evading immune surveillance (70). These findings highlight the crucial association between amino acid metabolism in the TME and T cell-mediated antitumor immunity.

Nucleotide metabolism. Nucleotides, as essential components of genetic material, are critical for highly proliferating cells,

particularly purine and pyrimidine nucleotides. Consequently, nucleotide metabolism presents a potential target for cancer therapy (82,83). Drugs such as methotrexate, which target nucleotide metabolism, have been reported to be effective in treating acute lymphoblastic leukemia (ALL). However, non-specific targeting of nucleotide metabolism can inhibit normal cell processes, leading to severe side effects (84,85). In the AML TME, high concentrations of adenosine act as an immunosuppressive metabolite. Elevated adenosine levels suppress T cell activity by inhibiting activation, proliferation and cytokine secretion through adenosine receptor binding such as A2A receptors (56). The A2A adenosine receptor signaling pathway markedly inhibits T lymphocyte proliferation, activation and cytokine production. Additionally, this pathway activates immunosuppressive cells, such as Tregs and MDSCs, further impairing effector immune cell function (86). Activation of A2A receptors not only suppresses effector T cell activity, but also enhances Treg cell immunoregulatory function by upregulating key molecules and metabolic pathways, thus promoting immune suppression (Fig. 2) (87). Furthermore, studies have reported that LA treatment reduces nucleotide abundance in T cells, impairing proliferation and cell cycle activity. LA also disrupts several metabolic pathways, including amino acid biosynthesis and pyrimidine metabolism. NaBi itself can serve as a substrate for multiple carboxylase reactions such as pyrimidine metabolism (88,89). The application of NaBi can reverse these changes, pyrimidine metabolism increased in T cells rescued with NaBi (19).

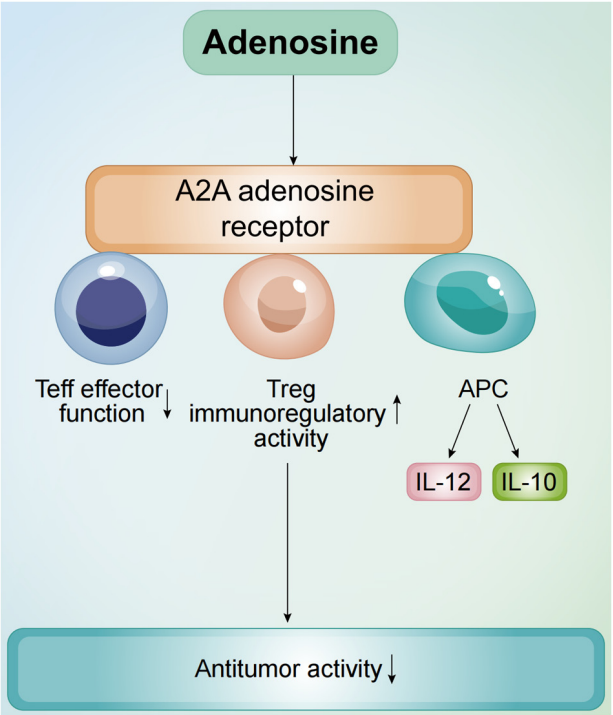

Figure 2. Adenosine binds to receptors on Teff, Treg, and APCs, suppressing Teff activation, proliferation and cytokine secretion whilst enhancing Treg-mediated immunoregulation. This signaling pathway also decreases the production of IL-12 and increases IL-10, further weakening the antitumor immune response. Treg, regulatory T cell; Teff, Tregs suppress effector T cell; APC, adenomatous polyposis coli.

4. Signaling pathways of T cell metabolic remodeling in AML TME

mTOR signaling pathway. mTOR, a serine/threonine kinase, serves a pivotal role in several cellular processes, including metabolism regulation. It is a key regulator of cell metabolism and serves as the catalytic subunit of both mTORC1 and mTORC2 complexes. mTORC1 supports effector T cell function by promoting glycolysis and protein synthesis, whilst mTORC2 regulates T cell differentiation and survival through the cytoskeleton and lipid metabolism (90). mTOR enhances glucose uptake and glycogen synthesis by modulating the insulin receptor substrate 1 (IRS1)/PI3K/Akt pathway, thereby boosting glycolysis. Inhibition of mTOR activation or its downregulation in $CD4^+$ T cells reduce glycolysis, impairing their activation (31). mTOR activation also increases GLUT1 expression, promoting T cell proliferation and cytokine production (Fig. 3) (91). Additionally, mTOR is a crucial regulator of memory $CD8^+$ T cell differentiation, with the mTOR-specific inhibitor rapamycin, an immunosuppressive drug, demonstrating an immunostimulatory effect on memory $CD8^+$ T cells (87).

AMPK signaling pathway. In the AML TME, AMPK, as a key energy sensor, serves a crucial role in regulating the metabolic state of immune cells, enabling them to effectively maintain their activity and function. It also serves an important role in T cell metabolic reprogramming. A previous study reported that AMPK signaling promotes lipid metabolism to generate functional memory $CD8^+$ T cells (92). Furthermore, as an upstream inhibitor of mTOR activity, AMPK can inhibit mTOR through the AMPK activator metformin, which helps reduce glycolysis in T cells (Fig. 4). This, in turn, promotes the generation of Tregs by suppressing Th1 and Th17 cells (93). Metformin also activates AMPK and inhibits the proliferation of AML cell lines and primary AML cells (94). However, future research needs to further explore the specific molecular mechanisms of AMPK activation and its potential for clinical translation.

Peroxisome proliferator-activated receptor (PPAR) family of transcription factors. The PPAR family includes PPARα, PPARδ and PPARγ. The nuclear receptor PPARγ serves an essential role in adipogenesis, immune responses and the metabolism of lipids and carbohydrates. Fatty acids can also act as ligands for PPARγ (95,96). Study have reported that in chronic lymphocytic leukemia (CLL), high doses of glucocorticoids induce the activation of PPARα and downstream FAO, leading to drug resistance (97). Moreover, it has been reported that activation of PPAR promotes the proliferation of $CD8^+$ T cells, increasing the number of functional Teffs. The activation of the PPAR pathway can also rescue PD-1 blockade-induced T cell apoptosis by upregulating anti-apoptotic proteins such as Bcl2, baculoviral IAP repeat containing 3 and apoptosis inhibitor 5. Additionally, PPAR activation can reprogram CTL energy metabolism and overcome the reduction in the number of functional Teffs associated with PD-1 blockade by reducing apoptosis or increasing proliferation (98). Therefore, targeting the PPAR signaling pathway, such as by using PPAR agonists, may serve as a potential therapeutic target for AML.

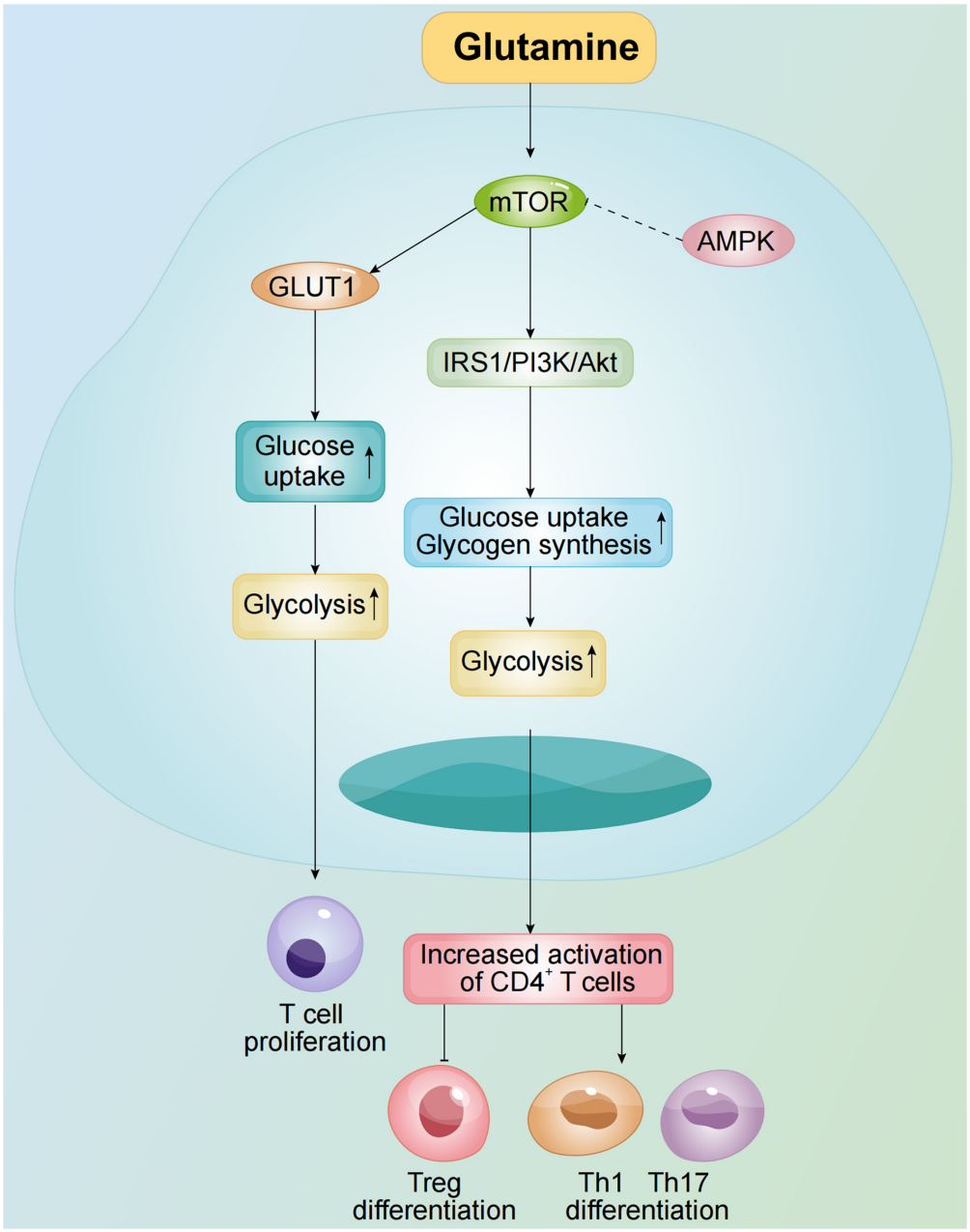

Figure 3. mTOR enhances glucose uptake and glycolysis in $CD4^+$ T cells by increasing GLUT1 expression and regulating the IRS1/PI3K/AKT pathway. This promotes glycogen synthesis, T cell proliferation and activation, favoring Th1/Th17 differentiation whilst reducing Treg generation. Inhibition of mTOR impairs glycolysis and $CD4^+$ T cell activation. GLUT1, glucose transporter 1; IRS1, insulin receptor substrate 1; Treg, regulatory T cell; AMPK, AMP-activated protein kinase; Th, Helper T cell.

HIF-1α and hypoxic response. HIF-1α is a central transcription factor in hypoxic cells and a hallmark of TME. It is also a downstream target of GLUT-1 (99). It facilitates Treg migration by promoting glycolysis and FAO. Elevated glucose uptake by cancer cells stabilizes HIF-1α, thereby suppressing antitumor immunity (100,101). Moreover, HIF-1α-driven transcription enhances glycolysis in T cells, supporting Th17 differentiation whilst inhibiting Tregs (91). Mitochondrial dysfunction and HIF-1α-mediated metabolic reprogramming contribute to T cell exhaustion, a process reversible through glycolysis inhibition (102). Treatment with digoxin or acriflavine, both inhibitors of HIF-1 expression and function, in subcutaneous tumor mice has been reported to limit tumor growth (103). Therefore, targeting HIF-1 in the TME may be an effective therapeutic strategy for AML.

5. Metabolic features of the AML microenvironment and their impact on immunotherapy

Immune checkpoint (IC) inhibitors. ICs are molecular mechanisms that regulate immune system activity, comprising co-stimulatory receptors such as CD40 and CD80 and inhibitory receptors such as cytotoxic T-lymphocyte-associated protein 4 and PD-1. These checkpoints maintain immune tolerance, protect normal tissues from excessive immune responses, or, in certain cases, enable cancer cells to evade immune surveillance (34). The advent of IC inhibitors has

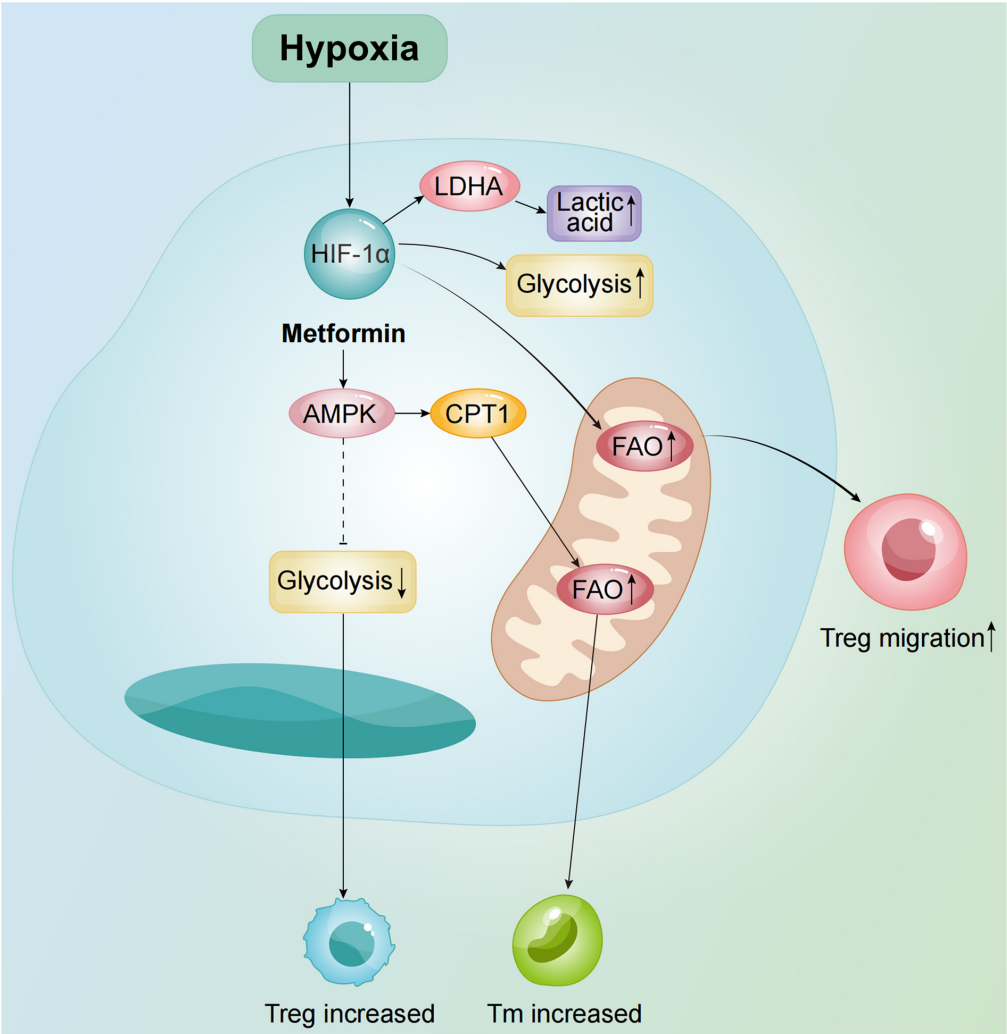

Figure 4. As an mTOR inhibitor, AMPK suppresses mTOR activity via metformin, reducing glycolysis and promoting Treg generation whilst suppressing Th1/Th17 differentiation. AMPK also upregulates CPT1, enhancing FAO and supporting T cell metabolic reprogramming. Additionally, HIF-1α promotes Treg migration by upregulating glycolysis and FAO. AMPK, AMP-activated protein kinase; Th, Helper T cell; Treg, regulatory T cell; CPT1, carnitine O-palmitoyl transferase 1; HIF-1α, hypoxia-inducible factor 1α; LDHA, lactate dehydrogenase A; FAO, fatty acid oxidation; Tm, memory T cell.

improved the prognosis for numerous solid tumors and certain lymphomas by blocking inhibitory signals such as the PD-1/PD-L1 pathway, thereby enhancing antitumor immunity (104). However, their efficacy in AML remains limited, particularly with PD-1/PD-L1 inhibitors (105), for reasons that are not yet fully understood. In the AML TME, competition for nutrients between AML cells and T cells restricts T cell access to glucose and glutamine, impairing their metabolic function and antitumor response. Consequently, IC inhibitors fail to enhance T cell-mediated antitumor effects (22). Furthermore, the PD-1/PD-L1 interaction serves a critical immunosuppressive role in the TME, promoting regulatory T cell function and inhibiting the activation and proliferation of Teffs, thereby further dampening the antitumor immune response (106).

Limitations of adoptive T cell therapy (ACT). ACT enhances immune responses against tumors or infections by modifying or expanding autologous or donor-derived T cells *ex vivo*. This includes engineering T cells with chimeric antigen receptors (CARs) or TCRs to recognize specific tumor antigens. Following expansion, these Teffs are re-infused to mediate targeted immune responses (107,108). However, unlike in ALL, CAR-T cell therapy shows limited efficacy in AML, largely due to the immunosuppressive TME (29). Lymphodepleting chemotherapy prior to CAR-T cell infusion can enhance therapeutic outcomes by reducing Tregs in the TME and alleviating their suppressive effects, thereby improving CAR-T cell proliferation and persistence *in vivo* (109). In AML, expanded Tregs secrete immunosuppressive cytokines such as IL-10 and TGF-β, which impair CAR-T cell function (57). Additionally, AML cells secrete arginase II, disrupting T cell metabolism and promoting immune evasion (41). Inhibition of arginine metabolism has been reported to enhance the efficacy of CD33-CAR T cells in preclinical AML models (110). Similarly, blocking the adenosine A2A receptor (A2AR), a downstream mediator of adenosine signaling, improves CAR-T cell efficacy in solid tumors (111). Adenosine suppresses T cell proliferation, activation and effector function via A2AR, whilst promoting Treg expansion, thereby dampening antitumor immunity (112). However, whether this mechanism extends to hematologic malignancies such as AML and CLL remains unclear.

Potential therapeutic strategies for metabolic regulation. In patients with AML, elevated intracellular and plasma arginase activity markedly inhibits T cell proliferation, contributing to immune dysfunction. This effect is largely mediated by increased expression and activity of arginase II in AML cells, identifying it as a potential biomarker for immune status and disease progression. Inhibition of arginase II has been reported to restore T cell proliferation and enhance antitumor immunity (110,113). When PD-1 binds to its ligand PD-L1, activated T cells are unable to continue glycolysis and normal amino acid metabolism, which results in insufficient energy production to support their effector functions. In addition to inhibiting glycolysis and amino acid metabolism, PD-1 may also impair T cell oxidative detoxification capacity, reducing their ability to cope with oxidative stress (114). Thus, elucidating the PD-1 signaling axis is crucial for understanding T cell dysfunction and identifying novel therapeutic targets.

6. Future research directions and challenges

Key areas for further exploration in T cell metabolism in AML TME. Although the role of T cell metabolism in the AML TME has been preliminarily elucidated, further in-depth exploration is needed in the following key areas.

Metabolic reprogramming and personalized therapy. In future research, individualized treatments targeting T cell metabolic reprogramming in the TME of patients with AML should focus on the impact of metabolic heterogeneity on treatment responses. Differences in metabolic characteristics between patients with AML may profoundly influence the metabolic state of T cells and their antitumor capabilities. For example, variations in glycolysis, FAO or amino acid metabolism across different patients could lead to notable differences in therapeutic efficacy. Utilizing metabolomics and single-cell analysis techniques could uncover individual differences in T cell metabolic reprogramming and provide a basis for precise metabolic interventions. However, this approach faces several challenges, such as the ways to integrate multidimensional data to accurately identify key metabolic nodes, implement personalized metabolic regulation of targets in clinical applications and minimize potential side effects of metabolic interventions on systemic metabolic homeostasis. In the future, combining advanced technological methods and large-scale clinical studies will be necessary to explore the feasibility of personalized metabolic interventions, with the goal of achieving precision treatment for patients with AML.

Application of emerging technologies. In future research on T cell metabolic reprogramming within the AML TME, emerging technologies will provide crucial support for uncovering metabolic regulatory mechanisms and therapeutic potential. The application of single-cell metabolomics and spatial metabolomics can capture the dynamic changes and spatial heterogeneity of T cell metabolism in the AML microenvironment with high resolution, offering a new perspective on the role of metabolic reprogramming in tumor immune evasion. Moreover, metabolic flux analysis can track the dynamic changes in key metabolic pathways within T cells in real-time, revealing the flow and regulation patterns of metabolites under different conditions. By contrast, CRISPR screening technology can precisely identify key genes and metabolic nodes involved in T cell metabolic reprogramming, providing specific targets for developing intervention strategies. The combination of these technologies will not only deepen the understanding of T cell metabolic regulation mechanisms but also advance the design of personalized metabolic treatment plans. However, the application of the aforementioned technologies in AML still faces challenges, such as integrating multidimensional data, high costs and unclear clinical translation pathways. Future multi-disciplinary collaborations will be required to further optimize their application.

Challenge of clinical translation. There are still notable obstacles and challenges in translating the research on T cell metabolic reprogramming within the AML TME into clinical application. A key obstacle from basic research to clinical use is the way to simplify complex metabolic mechanism studies into clear clinical targets, whilst ensuring these targets have broad applicability across heterogeneous patient populations. Moreover, although certain preliminary progress has been made in clinical trials of metabolic interventions in AML, such as improving the immune microenvironment through the regulation of glycolysis, FAO or amino acid metabolism, issues such as individual variability in efficacy, long-term treatment side effects and resistance remain prominent. Metabolic interventions may affect systemic metabolic homeostasis leading to unpredictable toxic reactions, and the adaptive metabolic mechanisms of tumor cells may induce resistance. Therefore, future research needs more precise targeting strategies to achieve efficient regulation within specific metabolic pathways, whilst minimizing systemic effects. The combination of advanced technologies, such as metabolomics and single-cell analysis for personalized treatment design, along with the development of combination therapies to mitigate resistance, may be key approaches to overcoming these challenges.

7. Conclusions

The present review explored the key mechanisms of T cell metabolic reprogramming in the TME of AML and its notable impact on antitumor immune responses. The AML microenvironment, through the synergistic effects of high LA levels, hypoxia, nutrient competition and chemokines, markedly suppresses critical metabolic pathways in T cells, such as glycolysis, lipid metabolism and amino acid metabolism, weakening their proliferation, effector functions and antitumor capabilities. Additionally, the accumulation of metabolic waste products from AML cells, as well as abnormalities in adenosine and potassium ion metabolism, further promotes the establishment of an immunosuppressive state. Furthermore, although the mechanisms of T cell metabolic reprogramming are preliminarily understood, designing personalized treatment strategies based on the metabolic characteristics of patients remains a major challenge. Emerging technologies, such as single-cell metabolomics and metabolic flux analysis, provide new research directions for uncovering metabolic mechanisms and developing metabolic-targeted therapies.

At the same time, future clinical translation needs to balance efficacy with side effects, optimizing metabolic intervention strategies to enhance the effectiveness of immunotherapy.

In summary, in-depth research on T cell metabolic reprogramming in the AML microenvironment will provide important theoretical support for improving AML immunotherapy strategies, whilst also offering new insights for the clinical application of metabolic intervention therapies.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

Not applicable.

Authors' contributions

XYZ designed and conceived the study. YHL wrote the manuscript. JL and MY revised the manuscript. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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