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REVIEW

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Metabolic checkpoints in immune cell reprogramming: rewiring immunometabolism for cancer therapy

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Abstract

Immune cell metabolism plays a pivotal role in regulating cellular proliferation, differentiation, and functional responses, collectively shaping immune responses within the tumor microenvironment (TME). Recent advancements increasingly highlight diverse metabolic phenotypes of immune cells and their complex interplay with tumor dynamics. Immune cell metabolism exhibits remarkable plasticity, enabling metabolic networks to finely tune immune cell behaviors in response to external stimuli. Furthermore, a strong correlation between metabolic profiles and immune cell fate, activation, and function has been repeatedly delineated in immunometabolism. Consequently, targeting the metabolic networks, referred to as metabolic checkpoints, to reprogram immune cell phenotypes and bolster antitumor immunity holds significant promise for clinical translation. This review summarizes the latest developments in multifaceted metabolic checkpoints, with a focus on how metabolic checkpoints modulate immunological consequences and cancer progression. Lastly, potential strategies for targeting metabolic checkpoints are explored to inspire innovative approaches in immunotherapy.

Keywords Immune cells, Metabolic checkpoints, Cancer immunotherapy, Tumor microenvironment, Metabolic reprogramming, T cell

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Introduction

Studies of immune cell metabolism have evolved significantly over the past century, and recent advances highlight how metabolic reprogramming influences immune responses and cancer progression. Immune cells exert remarked metabolic plasticity, capable of adopting distinct metabolic procedures in response to external stimuli, a central feature worth exploiting. The emerging field of immunometabolism has established that cellular metabolism fundamentally governs immune cell proliferation, activation, and differentiation [1, 2]. Aerobic glycolysis enhances phosphoinositide 3-kinase (PI3K) signaling to support the rapid energy requirements of immune cells upon antigenic stimulation [3]. This discovery challenges the traditional biochemical paradigm that views metabolism as merely a passive supporter of cellular signaling. Instead, it demonstrates that metabolic processes actively govern critical signaling pathways. Actually, there is growing evidence that targeting the immunometabolic networks, termed metabolic checkpoints, could exploit the metabolic plasticity and reprogram phenotypes of different immune cells.

The immunometabolic network within the TME encompasses a broad spectrum of genes, signaling molecules, metabolites, enzymes, and transporters that finely and dynamically regulate immune responses. According to their significance in regulating immune responses, these molecules are termed metabolic checkpoints, essential targets to exploit metabolic plasticity. Robert and colleagues demonstrated that glutamine blockade dismantled immunosuppression by limiting glycolysis in cancer and activated CD8 + T cells [4]. However, glutamine is demonstrated as a supporter of CTL effector functions in previous studies, the transporter ASCT2 of which is required for T cell receptor(TCR)-stimulated activation for subsequent metabolic signaling of proliferation [5]. This can be interpreted as T cells exhibit adaptation by supporting oxidative metabolism for energy homeostasis, boosting survival, proliferation, and effector function. While initially paradoxical, the new research reveals that context-dependent metabolic plasticity enables T cells to switch between glutamine-dependent glycolysis and oxidative metabolism, thereby maintaining antitumor functionality even under nutrient stress. In contrast, lacking plasticity in glycolysis and oxidative phosphorylation (OXPHOS), cancer cells fail to induce a hypoxic, acidic, and nutrient-depleted TME. Beyond T cells, natural killer cells (NK cells), dendritic cells (DCs), B cells, macrophages, and myeloid-derived suppressor cells (MDSCs) also exhibit metabolic plasticity and potential for reprogramming.

The field of immunometabolism traces its origins to foundational discoveries in cancer metabolism. Otto Warburg's seminal observations included the finding that cancer cells have a tendency to metabolize glucose into lactate, even with sufficient oxygen—aerobic glycolysis. Though activated effector CD8 + T cells also undergo elevated glycolysis activity, they meet the biosynthetic demands of rapid proliferation and cytokine production for tumor killing, despite yielding only 2 ATP/glucose. As revealed in mouse models, glucose consumption of cancer cells in the TME limits glycolysis and effector responses of T cells [6]. Consequently, driven by cancer cells through metabolic competition, the TME becomes nutrient-depleted, hypoxic, and acidic, resulting in metabolic and immunological dysfunction of immune cells. Moreover, depletion of key amino acids exhibited suppression of effector T cell function [7]. In a hypoxic and lactate-accumulating TME, exhaustion is a major risk for both effector T cells and NK cells, while regulatory T cells (Tregs) adapt to high lactate levels, and macrophages acquire an immunoinhibitory phenotype [8–10]. Beyond the classical Warburg effect, recent advances reveal novel dimensions of metabolic strategies employed by tumors to dysregulate immune cell function. The competition for non-essential amino acids like serine and alanine is required for T cell activation and function, where the nutrient competition further starves effector cells [11, 12]. The redox imbalance imposed by cancer cell mitochondria through ROS overproduction further induces the exhaustion of tumor-infiltrating CD8 + T lymphocytes (TILs) [13]. Additionally, cancer cell exhibits flexibility in metabolism, whereas they utilize glutamine and acetate as alternative carbon sources for acetyl-CoA production under metabolic pressure [14, 15]. In light of the heterogeneity of cancer metabolism, investigating the interaction between cancer metabolism and immune cells may hold the key to revealing metabolic crosstalk behind immune evasion and how this axis can be therapeutically targeted.

While cancer immunotherapies have made significant strides with the advent of immune checkpoint blockade (ICB) and adoptive cell therapy (ACT), resistance remains a significant challenge, as the immunosuppressive TME consistently drives effector cell exhaustion. Recently, preclinical studies have focused on targeting metabolic checkpoints combined with ICB and ACT. Targeting metabolic checkpoints expands the therapeutic landscape of ICB and ACT, potentially reducing cost and complexity while promoting the design of effector cells with enhanced metabolic fitness within the TME. Glutamine supplementation and glycolysis blockade have shown potent efficacy in enhancing PD-1 blockade and transferred CD8 + T antitumor immunity in preclinical models [16, 17]. Moving forward, clinical trials combining metabolic checkpoint inhibition with ICB and ACT

may hold the key to overcoming the limitations of current immunotherapies and achieving more durable responses in a broader cancer patient population.

Reprogramming immune cells via metabolic checkpoints represents an emerging paradigm in overcoming immunosuppression. This review comprehensively analyzes the immunometabolic landscape of the TME and intricate metabolic networks in different immune cell types, with a primary focus on T cells due to their central role in orchestrating antitumor immunity and their dynamic metabolic plasticity. By exploring multifaceted metabolic checkpoints, we emphasize novel strategies and clinical opportunities that may shape the next generation of cancer immunotherapies.

The immunometabolic landscape in the TME

The nutrient and energy requirements of various cell populations, along with their intercellular interactions, collectively influence the TME [18]. In the TME, normal metabolic pathways are usually distorted, with aberrant metabolic pathways forming a nutrient-depleted, hypoxic, acidic, and metabolite-accumulating environment, which affects immune cell functions and tumor progression (Fig. 1) [1, 19, 20]. This intricate metabolic network continuously reshapes the immunometabolic landscape of the TME, with pathways such as glucose, amino acid, and lipid metabolism collaboratively manipulating immune cell phenotypes and functional states.

Driven by oncogenic mutations (e.g., *RAS*, *MYC*), aerobic glycolysis of cancer supports rapid cellular proliferation but creates a glucose-depleted, lactate-accumulating, and hypoxic TME [21]. In preclinical studies, glucose competition and restriction directly dampened the mechanistic target of rapamycin (mTOR) activity, glycolytic capacity, and interferon-γ (IFN-γ) production of TILs, impairing antitumor responses [6]. Furthermore, glucose restriction experienced by TILs could be corrected using programmed death-ligand-1 (PD-L1) blockade, where their glycolytic activity and effector functions could be enhanced to kill cancer cells [22].

To compensate for inefficient ATP production in the Warburg effect, cancer cells increase glucose transporters protein, notably GLUT1 [23, 24], and glycolytic enzyme lactate dehydrogenase A (LDHA) expression to increase ATP production [25], producing lactate. Pathophysiological lactate concentrations could suppress multiple effective immune cells, thereby inhibiting tumor surveillance. Tumor-derived lactate transforms conventional DC into immunoinhibitory phenotypes through SREBP2 activation [26]. Moreover, lactate inhibits nuclear factor of activated T cells (NFAT) in T and NK cells, impairing IFN-γ production and promoting a hypoxia-inducible factor 2α (HIF-2α)-mediated pro-tumoral phenotype in tumor-associated macrophages (TAMs) [10, 27]. CD8 + T cell cytotoxicity is suppressed by lactate through GLUT10 inhibition as well [28]. Notably, extracellular acidosis unexpectedly induces stemness of TILs [29], which is consistent with enhanced CD8 + T cell functions after lactate treatment in a murine model bearing transplanted MC38 tumor [30]. Lactate thus emerges as a pivotal oncometabolite that orchestrates immunosuppression across the tumor microenvironment, shaping immune evasion while paradoxically preserving stem-like properties in certain T cell subsets.

Unable to obtain sufficient nutrients from the surrounding vasculature and clear metabolic waste, cancer cells initiate neovasculature formation. However, the malformed vessels remain under-perfused and exacerbate hypoxia in the TME [31], where immune cells respond through the transcriptional regulator HIF-1α. HIF-1α redirects glucose flux to aerobic glycolysis, inducing immunosuppressive effects via promoting lactate secretion. HIF-1α further drives immunosuppression in the TME by TIL exhaustion in a CD39-dependent manner, repolarization of TAMs towards a tumorigenic M2 phenotype, and elimination of tumor-targeting γδ T cells [9, 32, 33]. In conclusion, hypoxia as a metabolic outcome facilitates tumor progression.

Amino acids, essential nutrients for the survival of all cell types, are dominantly deprived from the TME by cancer cells [34, 35]. For instance, cancer cells overexpress transporter molecule SLC43A2, competing for methionine, to reduce methylation activity-induced T helper 17 cell (Th 17) differentiation and cytokine production [36]. Cancer cells and TAMs also dominate amino acid availability in the TME by upregulating enzymes like indoleamine 2,3-dioxygenase (IDO), which converts tryptophan into kynurenine, driving T cell dysfunction and Treg differentiation [37, 38]. In response to amino acid restriction, activated general control nonderepressible 2 (GCN2) kinase facilitates CD8 + T cell proliferation [39] but limits CD4 + T cell expansion [40], owing to distinct downstream metabolism. By contrast, activated T cells upregulate L-type amino acid transporter 1 (LAT1) to support proliferation by mechanistic target of rapamycin complex 1 (mTORC1) signaling [41]. The mTORC1 activity is demonstrated to be central in cellular metabolism and growth, with complex roles in shaping T cell fate. Upon T cell proliferation, inhibition of mTORC1 enhances the proliferation of stem-like T cells, while mTORC1 inhibition after exhaustion inhibits effector cell proliferation, suggesting the context-dependent role of mTORC1 activation [42].

In the nutrient-depleted TME, increased utilization of lipids becomes an important source of energy and experiences metabolic reprogramming. In tumors, lipid

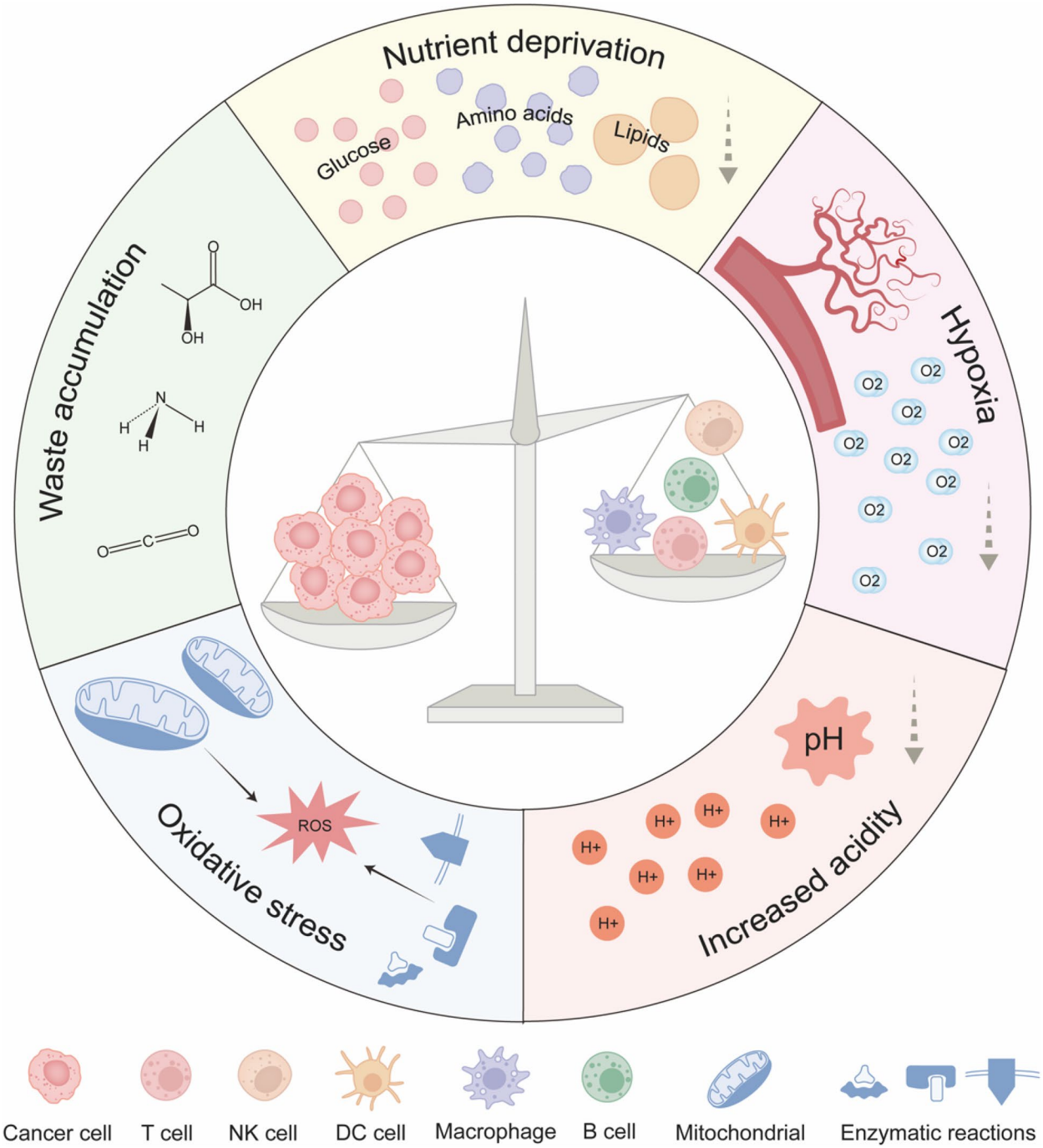

Fig. 1 Metabolic pressure in the TME. Metabolic pathways are usually dysregulated in the TME, consistently imposing tremendous metabolic pressure on both cancer cells and various immune cells. Nutrient deprivation, waste accumulation, hypoxia, oxidative stress, and increased acidity are driving forces that contribute to an immunosuppressive milieu. Nevertheless, cancer cells, with remarked metabolic plasticity, outcompete immune cells in the metabolic competition. Abbreviations: NK cell, natural killer cell; DC cell, dendritic cell; ROS, reactive oxygen species

uptake, synthesis, and fatty acid oxidation (FAO) are commonly enhanced. CD36-mediated lipid intake suppresses cytotoxic T lymphocytes (CTLs) and DCs, coupled with increased Tregs to promote tumor progression [43, 44]. In de novo lipogenesis, fatty acid synthase (FASN) could decrease T cell infiltration of the tumor by CD36-dependent lipid uptake from the TME, disrupt T cell interaction with DCs, and promote Treg functions

in ovarian carcinoma patients, which commonly overexpress FASN [45, 46]. FASN further affects NK cells and myeloid cells by affecting cyclooxygenase 2 (COX2) and eicosanoids synthesis. Besides, upregulation of the mitochondrial FAO enzyme carnitine palmitoyltransferase 1A (CPT1A) has been linked to escape signal CD47 of glioblastoma cells, thereby inhibiting phagocytosis and facilitating evasion [47].

In-depth studies of metabolic dysfunction in the TME provide a novel approach to cancer therapy: targeting metabolic checkpoints. Using a glutamine antagonist, oxidative metabolism is promoted in CTLs, favoring a persistent and highly active phenotype, which exerts potent antitumor responses in mouse models [4]. Furthermore, oxidative and glycolytic metabolism in cancer cells declines, resulting in an immunostimulatory TME with decreased hypoxia, acidity, and nutrient depletion. In other metabolic circuits, emerging metabolic checkpoints have become potential targets. Preclinical applications of these targets in cancer immunotherapies, such as ICB and ACT, have demonstrated efficacy in overcoming barriers to treatment. Glycolytic enzyme fructose-2,6-bisphosphatase 3 (PFKFB3) that highly upregulated in cancer development could be inhibited for therapeutic purposes, but inadvertently induces immune invasion through PD-L1 upregulation, whereas PD-1 blockade compensates for the unsatisfactory tumor inhibition in preclinical trials [48]. Reengineered chimeric antigen receptor-T cells (CAR-T) expressing higher arginine resynthesis enzyme levels could boost metabolic fitness in the arginine-depleted TME, improving tumor cell clearance [49]. In conclusion, numerous preclinical trials highlight that targeting metabolic checkpoints offers a transformative strategy for cancer immunotherapy. Herein, essential metabolic checkpoints are summarized to delve into the multifaceted immunometabolic networks (Table 1).

Metabolic checkpoints in different immune cells

Metabolic checkpoints in glucose, amino acid, and lipid metabolism critically shape immune cell phenotypes and functions. Among these, T cells—central orchestrators of antitumor immunity within the TME—exhibit dynamic metabolic reprogramming that dictates their activation, differentiation, and effector responses (Fig. 2). These cell-intrinsic metabolic networks offer promising therapeutic avenues to enhance cancer immunotherapy.

T cells

Glucose metabolism

Glucose restriction is known to impact T cell functions in multiple studies. Low levels of glucose could induce the AMP-activated protein kinase (AMPK) activation as well, inhibiting the mTORC1 signaling pathway [74]. Likewise, glucose restriction promotes TGF-β production in activated CD4+T cells for an immunosuppressive phenotype and inhibits TCR-dependent activation of Ca2+and NFAT signaling in TILs [50]. For therapeutic purposes, impaired glycolysis activity could be recovered by increasing phosphoenolpyruvate (PEP) levels, which induces phosphoenolpyruvate carboxykinase 1 expression and improves T cell antitumor activity in melanoma-bearing mice.

Naïve T cells utilize glycolysis and OXPHOS to generate ATP, a process where mitochondrial respiration dominates to support their long-term survival and readiness for activation. In contrast, activated effector T cells undergo higher levels of aerobic glycolysis, a less efficient but faster process of ATP production [75]. Boosted aerobic glycolysis is observed in activated T cells through TCR engagement and subsequent co-stimulation to support energy production, thus promoting effector cell expansion, and effector molecules production like IFN-γ, IL-2, and IL-17 [76, 77]. Although energy production through glycolysis is inefficient, it provides cells with access to intermediates, which in turn boost anabolism. In this context, mTORC1 activation by glucose, as well as other factors including amino acids, oxygen, and cytokines, induces necessary anabolism such as nucleic acids, protein, and lipid synthesis to support T cell effector functions. As the central metabolic regulator of cell growth and metabolism, mTOR forms two distinct multiprotein complexes, mTORC1 and mTORC2 [78]. Activation of mTORC1 and mTORC2 has been shown to upregulate PD-L1 and mediate glutamine metabolism-induced immune checkpoint resistance. TBM-1, as an mTORC1 inhibitor, leads to enhanced TIL immunity in a mouse model of Lewis lung carcinoma and B16 melanoma [79].

Following antigen recognition, TCR co-stimulation induces nuclear factor-κB (NF-κB) and NFAT activation, promoting *MYC* and HIF-1α expression [80, 81], thereby enhancing GLUT1 and hexokinase 2 (HK2) expression for glycolysis. Though highly upregulated in both cancer and T cells, HK2 is demonstrated to be dispensable for T cell activation, making it a more promising therapeutic target of selective tumor blockade [82]. Activated T cells primarily use GLUT1 for glucose uptake from the TME. Consistently, CD4+T cells lacking GLUT1 exhibit reduced glucose uptake, impeding their proliferation and ability to induce inflammatory disease [83]. GLUT1 is selectively needed in T cell differentiation, as it was found necessary for Th1, Th2, and Th17 differentiation, but not for CD8+T cells or Tregs [84, 85]. Despite GLUT1 having the highest copy number in various T cells, differentiated T cells expressed GLUT3 more similarly to

Table 1 Key metabolic checkpoints to reprogram immune cells

Cell type	Pathway	Target	Strategy	Refs
CD8 + T cell	Oxidative and glycolytic metabolism	Glutamine	Using a glutamine antagonist to suppress oxidative and glycolytic metabolism in cancer cells while fueling T cell oxidative metabolism and adaptation of a long-lived, highly activated phenotype	[4]
	Glycolysis	Ca2 + -NFAT signaling	Supplying glycolytic metabolite PEP to enhance CD8 + T cell effector function through Ca2 + -NFAT signaling against glucose restriction	[50]
	Glycolysis	HK2	Specifically inhibiting glycolysis by 2-DG in vitro to promote the formation of memory CD8 + T cells after adoptive transfer	[51] [52]
	FAO	CD36	Using blockade to suppress the oxidized lipid-CD36 axis-mediated intratumoral CD8 + T cell exhaustion	[44]
	FAO	CPT1A	Using PPARα and PPARβ/δ agonists to increase the FAO rate-limiting enzyme CPT1A for enhanced efficacy of adoptive CD8 + T cell therapy	[53]
	FAO	STAT3 signaling	Ablating T cell STAT3 or treatment with an FAO inhibitor to recover glycolysis and effector function of CD8 + T cells	[54]
	Cystine metabolism	Cystine restriction	Deleting SLC7A11 in tumor cells or supplementing intratumoral cystine to improve T cell anti-tumor immunity by enhancing glutathione synthesis and preventing CD36 upregulation	[55]
	Tryptophan catabolism	IDO, TDO and Kynurenine	Targeting IDO and TDO to inhibit the breakdown of tryptophan to kynurenine which significantly induces immunosuppression	[38] [7] [37]
	Methionine catabolism	MTA and SAM	Down-regulating SLC43A2-meduated methionine uptake by tumor cells to relieve T cell exhaustion	[56] [57]
	Arginine metabolism	Arginine restriction and CAT-2	Knocking down CAT-2 in cancer cells while supplying arginine in the TME to promote CD8 + T cell infiltration and activation	[58]
	Arginine metabolism	Arg2	specifically deleting Arg2 in CD8 + T cells to support CD8 + T cell activation, antitumor cytotoxicity, and memory formation in an OXPHOS-dependent manner	[59]
	HBP	Protein O-GlcNAcylation	Blocking O-GlcNAc transferase to inhibit T cell progenitor renewal, malignant transformation, and peripheral T cell clonal expansion	[60]
Treg	Glycolysis	PI3K-Akt-mTORC1 signaling	Manipulating the balance between TLR signaling and the transcription factor Foxp3 to control Treg proliferation and suppressive function	[61]
	Lipid synthesis	FASN and SREBPs activity	Inhibiting SREBPs-mediated lipid synthesis and inhibitory receptor signaling to suppress Treg functional maturation	[62]
	Tryptophan catabolism	AHR	Blocking AHR to suppress kynurenine-mediated immunosuppression in Tregs and TAMs	[63]
	TCA circle	ACLY	Supplying pyruvate and enhancing ACLY activity to improve metabolic fitness and antitumor potential of CD8 + T cells	[64]

Table 1 (continued)

Cell type	Pathway	Target	Strategy	Refs
	Cholesteryl esterification	ACAT1	Using an ACAT inhibitor to increase the plasma membrane cholesterol level of CD8 + T cells for augmented tumor antigen recognition and response	[65]
	Lactate metabolism	MCT1	Inhibiting Treg adaptation to lactate through deletion of the lactate transporter MCT1	[8]
	Mitochondrial activity and biogenesis	CD36-PPAR-β signaling	Blocking CD36-PPAR-β signaling-induced mitochondrial fitness and NAD production in Tregs	[45]
TAM	Ketolysis	OXCT1	Inhibiting OXCT1 to suppress Arg1 expression and TAM polarization toward the pro-tumoral phenotype	[66]
MDSC	Arginine metabolism	Arg1	Blunting Arg1-mediated immune suppression to shift the immune landscape toward a pro-inflammatory environment	[67]
	Arginine metabolism	FFAR2	Inhibiting FFAR2 to reduce the Gαq/Calcium/PPAR-γ axis, Arg1 expression, and arginine consumption in MDSCs, which induces T cell dysfunction	[68]
	Glutamine metabolism	The glutamine metabolism/ER stress/GPR109A axis	Blocking IRE1α/XBP1 signaling or supplementation glutamine to control ER homeostasis and immunosuppressive effects of GPR109A + myeloid cells	[69]
NK cell	Glycolysis	PDHK1	Using the PDHK1 inhibitor DCA to overcome NK cell exhaustion and reduced cytokine secretion	[70]
	Lipid metabolism	PPARα/δ	Inhibiting PPAR-driven lipid accumulation to reversed NK cell metabolic paralysis and cytotoxicity	[71]
DC cell	Glycolysis	Glucose restriction and lactate accumulation	Reducing glycolysis-mediated glucose restriction and lactate accumulation in the TME to rescue antigen-presenting and mitochondrial functions of bone marrow-derived DCs	[72]
B cell	Glutamate metabolism	GAD67	Reducing GABA that is synthesized and secreted by B-lineage cells in activated lymph nodes to enhance cytotoxic T cell responses and limit anti-inflammatory TAM polarization	[73]

Abbreviations: *HK2* hexokinase 2, *FAO* fatty acid oxidation, *CPT1A* carnitine palmitoyltransferase 1 A, *IDO* indoleamine 2,3-dioxygenase, *TDO* tryptophan 2,3-dioxygenase, *MTA* 5-methylthioadenosine, *SAM* S-adenosylmethionine, *Arg2* arginase 2, *HBP* hexosamine biosynthesis pathway, *Treg* regulatory T cell, *PI3K* phosphoinositide 3-kinase, *mTORC1* mechanistic target of rapamycin complex 1, *FASN* fatty acid synthase, *SREBP* sterol regulatory element-binding protein, *TCA circle* tricarboxylic acid cycle, *AHR* aryl hydrocarbon receptor, *ACLY* ATP-citrate lyase, *MCT1* monocarboxylate transporter 1, *ACAT1 acetyl*-CoA acetyltransferase 1, *PPAR-β* peroxisome proliferator-activated receptor β, *TAM* tumor-associated macrophage, *OXCT1* 3-oxoacid CoA-transferase 1, *MDSC* myeloid-derived suppressor cell, *Arg1* arginase 1, *FFAR2* free fatty acid receptor 2, *ER stress* endoplasmic reticulum stress, *NK cell* natural killer cell, *PDHK1* pyruvate dehydrogenase kinase 1, *PPAR* peroxisome proliferator-activated receptor, *DC cell* dendritic cell, *PEP* phosphoenolpyruvate, *NFAT* nuclear factor of activated T cells, *OXPHOS* oxidative phosphorylation, *TLR* Toll-like receptor, *DCA* dichloroacetate, *TME* tumor microenvironment, *GABA* gamma-aminobutyric acid

GLUT1. In mouse models of inflammatory diseases, GLUT3-dependent glucose uptake in Th17 cells controls the inflammatory gene expression through mitochondrial glucose oxidation and adenosine 5'-triphosphate citrate lyase (ACLY)-dependent acetyl-CoA generation [86], a program to be validated and exploited in the cancer setting. In Tregs, Rathmell and colleagues found a balance between inflammatory signaling mediated by Toll-like receptor (TLR) and the transcription factor forkhead box protein 3 (Foxp3) that regulates mTORC1 activity and glucose metabolism [61], thereby molding their suppressive functions.

Glycolysis-related metabolic pathways encompass multifaceted targets in controlling the activation and function of T cells. Parallel to glycolysis, the pentose phosphate pathway (PPP) converts glucose-6-phosphate

to ribulose-5-phosphate, producing nicotinamide adenine dinucleotide phosphate (NADPH) that is critical for lipid synthesis and reactive oxygen species (ROS) detoxification [87]. Upon CD4 + T cell activation, increased glucose is shunted into the PPP, where NADPH production regulates ROS in redox homeostasis [88]. ROS fills an instrumental role in effector T cell activation by promoting IL-2 expression in an NAFT-dependent manner [89]. The hexosamine biosynthesis pathway (HBP), fueled by glucose and glutamine metabolism, branches from glycolysis and provides key substrates for protein glycosylation. Diphosphate N-acetylglucosamine (UDP-GlcNAc) produced in this pathway supports protein O-GlcNAcylation, which enhances T cell effector functions [60]. Conversely, deficiency of O-GlcNAc transferase impedes T cell progenitor renewal, malignant transformation, and peripheral clonal expansion.

Alongside glycolysis, increased tricarboxylic acid (TCA) cycle activity impacts activated T cell metabolism [77]. IL-12-stimulated CD8 + T cells utilize elevated levels of acetyl-CoA to support IFN-γ production even in the nutrient-limited TME. Enhancing acetyl-CoA in antitumor CD8 + T cells boosts their metabolic fitness and IFN-γ production, a potential approach to enhance ACT therapy.

Amino acid metabolism

To sustain proliferation, differentiation, and effector functions, immune cells within the TME rely on abundant nutrients, dominantly amino acids, as building blocks to proceed with biosynthesis.

Branched-chain amino acids (BCAAs) The BCAA family consists of leucine, isoleucine, and valine, which are transported by solute carrier family (SLC) transporters into the cytoplasm (Table 2). Induced by the TCR upon T cell activation, LAT1, encoded by SLC7A5, fosters T cell expansion and effector differentiation in the nutrient-depleted TME through c-Myc and mTORC1 activation [41]. IL-2 further upregulates SLC7A5, increasing leucine intake through LAT1 in T and NK cells to compete for survival [90]. Likewise, enhancing amino acid intake through transporters encoded by SLC7A5 or SLC3A2/SLC1A5 may be a novel approach to strengthening CAR-T and CAR-NK cell metabolic capabilities and effector functions [91]. Leucine participates in mTORC1 signaling, with Sestrin2 and SAR1B identified as necessary leucine sensors [92, 93]. Additionally, arginine and leucine are key regulators of mTORC1 in Tregs, which rely on small G proteins Rag and Rheb in supporting immunosuppressive functions [94].

Glutamine Transporters like SLC38A1, SLC38A2, and SLC7A11 are essential for glutamine intake and subsequent metabolism. SLC38A1 and SLC38A2 act as crucial regulators of mitochondrial function to support CD8 + T cell efficacy in ovarian cancer [110] and impact memory T cell responses partly through mTORC1 signaling [97], respectively. SLC7A11 acts as a cystine/glutamate antiporter essential for T cells and tumor cells. It enables cystine import for glutathione (GSH) synthesis, protecting T cells against oxidative stress. Under pseudo-starvation conditions, the upregulation of SLC7A11 mediated by the transcription factor NRF2 helps reverse Treg cell anergy to a proliferative state [100]. Tumor cells, however, overexpress SLC7A11 to outcompete T cells for cystine, preventing them from ferroptosis while driving T cell dysfunction and exhaustion [111–113]. Of note, targeting this metabolic competition by deleting tumor SLC7A11 or supplementing cystine could restore the antitumor immunity of CTLs [55].

(See figure on next page.)

Fig. 2 Metabolic networks of $CD8^+$ T cells in the TME. In interaction with numerous cell types within the TME, CD8 + T cells consistently suffer from the nutrient-depleted and toxic metabolite-accumulating environment. T cells exhibit reprogrammed metabolism, whereas the metabolic network tightly controls their immune functions. Upon activation, $CD8^+$ T cells undergo extensive metabolic reprogramming to support their effector functions. A shift toward glycolysis enhances effector activity, while the branching of HBP facilitates protein O-GlcNAcylation, further promoting T cell function. Elevated acetyl-CoA levels, resulting from enhanced glycolysis and TCA cycle activity, contribute to improved CTL metabolic fitness and functionality. In the nutrient-deprived TME, deficiencies in arginine, glutamine, leucine, methionine, and other key nutrients collectively impair $CD8^+$ T cell proliferation and effector function. mTORC1 activity, regulated by glucose, amino acids, oxygen, and growth factors, plays a central role in coordinating cellular metabolism and growth. Conversely, FAO driven by CD36-mediated lipid uptake promotes $CD8^+$ T cell dysfunction, highlighting a distinct metabolic state associated with T cell exhaustion. Consistent with this, a variety of metabolic checkpoints—including metabolites (e.g., glucose, lactate, glutamine, oxygen), enzymes (e.g., HK2, LDHA, FASN), and transcription factors (e.g., *MYC*, HIF-1α, PPARα)—collectively orchestrate the metabolic network of $CD8^+$ T cells. Abbreviations: LDHA, lactate dehydrogenase A; HK2, hexokinase 2; HIF, hypoxia-inducible factor; HBP, hexosamine biosynthesis pathway; TCA circle, tricarboxylic acid cycle; α-KG, α-ketoglutarate; ACLY, adenosine 5′-triphosphate citrate lyase; FASN, fatty acid synthase; ACC1, acetyl-CoA carboxylase 1; AMPK, AMP-activated protein kinase; FAO, fatty acid oxidation; PPAR, peroxisome proliferator-activated receptor; ER stress, endoplasmic reticulum stress; SLC family, solute carrier family; mTORC1, mechanistic target of rapamycin complex 1; PGC-1α, peroxisome proliferator-activated receptor γ coactivator 1α; MSDC, myeloid-derived suppressor cell; TAM, tumor-associated macrophage, Treg, regulatory T cell

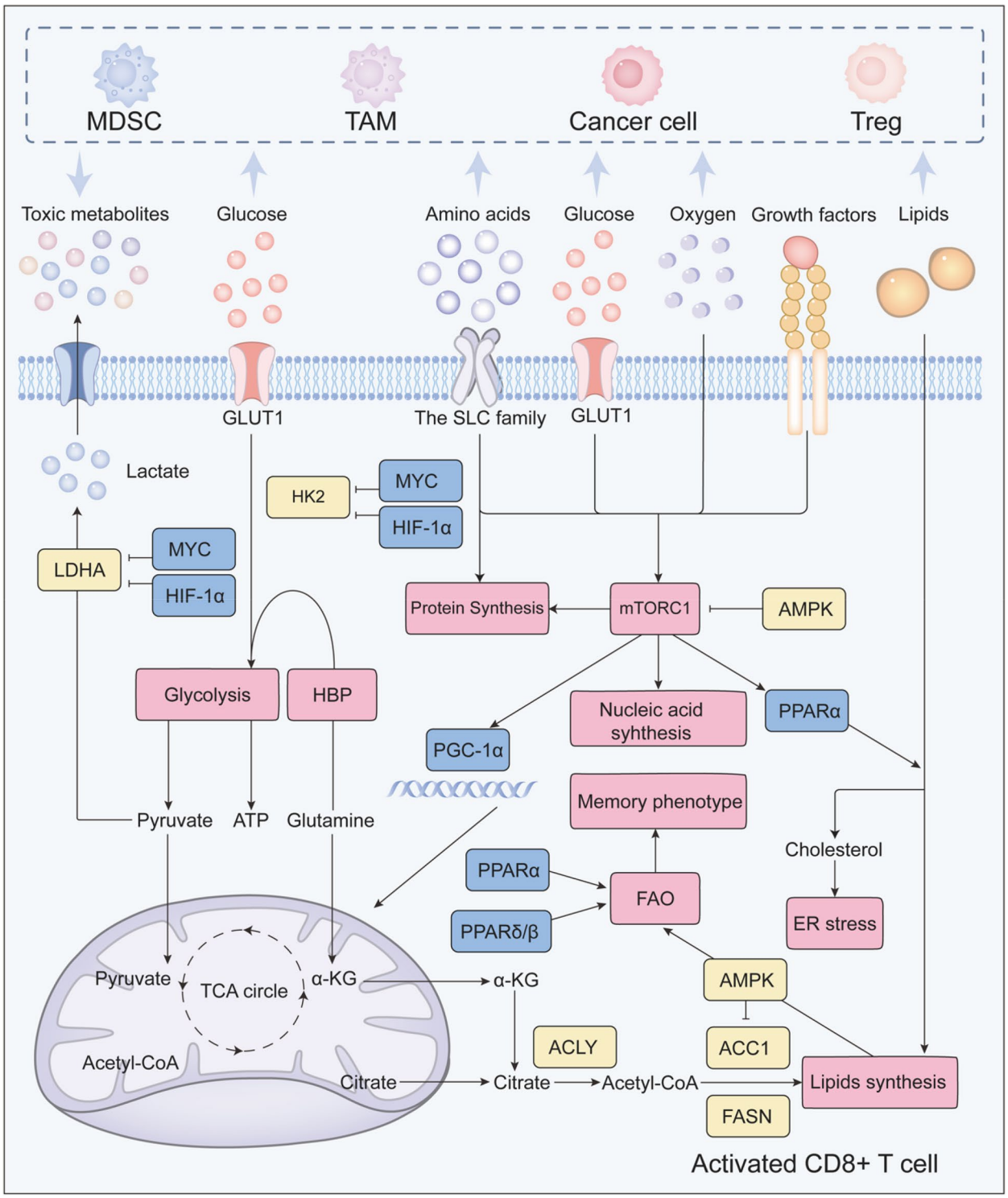

Fig. 2 (See legend on previous page.)

As a critical metabolic substrate, glutamine modulates T cell proliferation, differentiation, and redox balance. It fuels O-GlcNAcylation, which supports T cell self-renewal and even malignant transformation [60]. In T cell activation, glutaminase activity supports Th17 while limiting Th1 and CTL effector differentiation [114]. Importantly, glutamine-derived glutamate is the primary substrate for GSH synthesis, which orchestrates

Table 2 The immunometabolic function of the SLC family in various immune cells

Cell type	Gene	Synonym	Substrate	Immunometabolic functions	Refs
T cell	SLC1A5	ASCT2	Asparagine	Asparagine influx through SLC1A5 potentiates CD8 + T cell activation and anti-tumor responses by enhancing LCK activity and TCR signaling	[95]
	SLC1A5	ASCT2	Glutamine	SLC1A5 is required for TCR activation of the metabolic kinase mTORC1 in T cells	[5]
	SLC1A5	ASCT2	Glutamine	SLC1A5 expression induced by KAP1 accounts for Treg proliferation in a Foxp3-independent manner	[96]
	SLC7A1	CAT1	Arginine	SLC7A1 reduces the magnitude of memory T cell differentiation in part through mTORC1 signaling	[97]
	SLC7A5	LAT1	Leucine	TCR-dependent SLC7A5 upregulation is necessary for T cell clonal expansion or effector differentiation	[41]
	SLC7A5	LAT1	Tryptophan	CD8 + T cells fail to outcompete cancer cells in tryptophan uptake through SLC7A5 and ultimately tend to be dysfunctional	[98]
	SLC7A5	LAT1	Methionine	Reduced methionine uptake through SLC7A5 downregulation in an acidic TME facilitates T cell stemness and persistence in antitumor responses	[29]
	SLC7A5	LAT1	Kynurenine	Treg differentiation is further enhanced through LAT1-dependent kynurenine uptake in tryptophan-free conditions	[99]
	SLC7A11	xCT	Cystine and glutamate	Treg proliferation is subject to the induction of cystine/glutamate antiporter SLC7A11	[100]
	SLC38A1	SNAT1	Methionine and valine	Amino acid transporter SLC38A1 and SLC7A5 could by suppressed by cancer cells to induce mTOR inactivation and CD8 + T cell exhaustion	[101]
	SLC38A2	SNAT2	Glutamine	XBP1 inhibits SLC38A2 expression, resulting in decreased glutamine intake and CTL dysfunction	[102]
	SLC43A2	LAT4	Methionine	T cells with minimal SLC43A2 levels fail to uptake sufficient methionine and encounter dysfunction through the H3K79me2-STAT5 pathway	[103]
NK cell	SLC1A5	ASCT2	Glutamine	IL-2-mediated SLC1A5 and SLC3A2/SLC7A5 upregulation is essential for functional activation of NK cells	[104]
	SLC7A5	LAT1	Glutamine	SLC7A5 blockade reduces IL-2/IL-12-induced c-Myc activity and immunometabolic responses during NK cell activation	[105]
DC cell	SLC38A2	SNAT2	Glutamine	SLC38A2 expression in DCs is essential for T cell antitumor immunity through the glutamine–FLCN axis	[17]
TAM	SLC1A5	ASCT2	Glutamine	Macrophages provide thymic tumor cells with glutamine through the LGALS9-SLC1A5 axis in malignancy progression	[106]
	SLC6A8	CT1	Creatine	High levels of creatine in macrophages are mostly maintained through SLC6A8 and manipulates macrophage polarization	[107]
MDSC	SLC7A2	CAT2	Arginine	MDSCs rely on arginine uptake through SLC7A2 for suppressive function	[108]
B cell	SLC15A4	PEPT4	Histidine and oligopeptides	B cell SLC15A mediates TLR7-triggered IFN-I and autoantibody production by manipulating endolysosomal state and mTOR activity	[109]

Abbreviations: *TCR* T cell receptor, *mTORC1* mechanistic target of rapamycin complex 1, *Treg* regulatory T cell, *TME* tumor microenvironment, *CTL* cytotoxic T lymphocytes, *NK cell* natural killer cell, *DC cell* dendritic cells, *FLCN* folliculin, *TAM* tumor-associated macrophage, *MDSC* myeloid-derived suppressor cell

redox homeostasis and directs T cell lineage commitment. The de novo synthesis of GSH is essential for maintaining Treg suppressive function while its disruption shifts the balance toward pro-inflammatory Th17 cells, a glutamate-GSH axis that acts as a metabolic checkpoint to control the Th17/Treg equilibrium [115]. In contrast, selective glutamine metabolism inhibition in tumor cells would suppress their oxidative and glycolytic metabolism [4] and could indirectly reprogram glutamine-related metabolism in T cells, enhancing effector T cell-mediated antitumor immunity [116, 117]. Furthermore, glutaminase converts glutamine to glutamate, which, in glioblastoma patients, enhances Treg function and immune evasion, contributing to resistance against vascular endothelial-derived growth factor (VEGF) blockade [118].

Tryptophan Tryptophan metabolism has a critical immunosuppressive impact on cancer [119]. Most free tryptophan is degraded to kynurenine, a process manipulated by indoleamine 2,3-dioxygenase (IDO) and tryptophan 2,3-dioxygenase (TDO). TDO is utilized to inhibit CD8 + T cell viability, which is associated with poor prognosis in triple negative breast cancer (TNBC) [7]. Moreover, upregulated IDO1 by the polyadenylate-binding protein PABPC1L leads to T cell dysfunction and Treg infiltration, promoting immune evasion in renal cell carcinoma [38]. Tryptophan metabolism also

influences immunotherapy, as IDO inhibition induces tryptophanyl-tRNA synthetase (WARS) overexpression by accumulating tryptophan, reducing PD-1 expression in CD8 + T cells [37]. Tryptophan metabolites, derived from *Lactobacillus*, enhance CD8 + T cell production of IFN-γ to reinforce ICB efficacy [120]. Notably, tryptophan metabolism indirectly modulates T cell function since IDO-mediated kynurenine production primarily occurs in macrophages and tumor cells but not T cells. Tumor-repopulating cells also drive PD-1 upregulation in CD8 + T cells through tryptophan efflux to attenuate neighboring effector T (Teff) cell antitumor function in the TME [121].

Tryptophan restriction further induces cellular anergy and proliferation arrest, whereas GCN2 mitigates this inhibition by compensating for amino acid deficiency in T cells [122, 123]. In the context of amino acid restriction, GCN2 exhibits a dual effect in controlling immune response. GCN2 activation inhibits inflammatory Th9 cell differentiation through a HIF-1α-dependent glycolysis [124] and downregulates key enzymes in fatty acid synthesis, dampening the differentiation of CD4 + T cells [40]. Nonetheless, GCN2 is necessary for CTL proliferative fitness and trafficking [39]. In a malignant glioma mouse model, GCN2 supports CD8 + T cell survival and effector functions [125]. Moreover, the immunosuppressive axis, tryptophan-kynurenine-AHR, favors Treg cell differentiation and inhibits CD8 + T cells by inducing PD-1 [37]. Selective AHR blockade slows progression of IDO/TDO-overexpressing tumors by reprogramming interactions between Tregs and TAMs, synergizing with IDO/TDO inhibition and PD-1 blockade [63].

Methionine Following T cell activation, the methionine transporter SLC7A5 is upregulated to import methionine, essential for synthesizing S-adenosylmethionine (SAM), a key methyl donor [36]. In contrast, cancer cells overexpress SLC43A2 to compete for methionine, depleting SAM levels and reducing methylation activity in T cells [103]. The SAM shortage leads to diminished histone H3K4 methylation (H3K4me3) at promoters of genes critical for Th17 proliferation and cytokine production [126]. Methionine restriction also decreases H3K79me2, downregulating AMPK signaling and increasing PD-1 expression, thereby impairing CD4 + T cell antitumor immunity [127]. In this context, AMPK serves as a methionine-dependent checkpoint in regulating PD-1 expression and preventing exhaustion. Paradoxically, elevated levels of 5-methylthioadenosine (MTA) and SAM would induce T cell exhaustion [56], likely through altered methylation or feedback mechanisms. Activated Tregs depend on high methionine uptake and usage for survival, in conditions of IL-2 deprivation [128]. A recent study employing CRISPR/Cas9-based SLC43A2 downregulation relieves methionine competition in the tumor microenvironment, thereby restoring TIL function and reversing immune suppression [57]. However, the antitumor effect of methionine restriction has been demonstrated as it reduces the expression of immune checkpoints including YTH domain-containing family protein 1 and PD-L1, suppressing immune escape [129]. For modulating methylation activity and reprogramming T cell functions, methionine restriction and related metabolism represent a promising aspect to be delved into.

Arginine Tumor cells and MDSCs highly express arginase 1 (Arg1) and nitric oxide synthase (NOS), leading to arginine depletion and suppressed T cell activation and proliferation [130–132]. Upon arginine deficiency, TCR ζ chain (CD3ζ) expression is reduced, impairing TCR signaling and subsequent activation [133, 134]. This immunosuppressive environment also hinders aerobic glycolysis in activated T cells and promotes MDSC accumulation [135]. Additionally, arginine depletion triggers GCN2 activation and mTORC2 signaling while inhibiting mTORC1, causing T cell cycle arrest [136, 137]. In the arginine-depleted TME, arginine transporter SLC7A1 (CAT-1) is critical for sustaining T cell activation and proliferation, particularly in naïve, memory CD4 +, and CD8 + T cells [138]. In vivo CRISPR screening also revealed that mTORC1 signaling, regulated in part by SLC7A1, restricts memory T cell differentiation [97]. Further regulation of mTORC1 activity depends on opposing roles of arginine sensors, as SLC38A9 promotes mTORC1 activation upon arginine uptake while CASTOR1 inhibits mTORC1 under arginine scarcity [139, 140]. Together, these pathways shape T cell fate in the arginine-depleted TME.

Extracellular arginine depletion by Arg1 has emerged as a hallmark immunosuppressive mechanism in the TME, while arginase inhibitor CB-1158 could reverse this suppression, restoring T cell proliferation in vitro and reducing tumor growth in mouse models [67]. Compared to CB-1158, a novel approach exhibits enhanced efficacy by selectively knocking down the CAT2 transporter in cancer cells, thereby limiting their arginine uptake while supplying alkaline l-arginine to support immune cell function [58]. Beyond extracellular arginine regulation, mitochondrial Arg2 serves as an intracellular suppressive checkpoint in CD8 + T cells, suppressing activation, antitumor cytotoxicity, and memory formation independently of extracellular arginine levels [59]. Specific deletion of Arg2 in CD8 + T cells remarked synergized with PD-1 blockade to reduce tumor growth [59]. Kinetic metabolome analysis revealed that elevated arginine levels shift metabolism from glycolysis to OXPHOS,

a process crucial for effective antitumor responses [141]. This metabolic switch may underlie Arg2-mediated suppression of T cell activity.

Other metabolic checkpoints in amino acid metabolism are also identified as critical for T cell function. Serine metabolism supports T cell division by fueling nucleotide biosynthesis via one-carbon metabolism and glycine production, while serine deprivation or pathway inhibition impairs purine biosynthesis and T cell proliferation [11], which can be restored with glycine and formate supplementation [142]. In the TME, cancer cells often exhibit serine addiction, particularly in p53-mutant tumors where inhibition of the serine synthesis pathway could suppress tumor growth [143]. However, Tregs rely on glutathione to suppress serine metabolism and preserve their suppressive capacity, possibly revealing novel directions for manipulating serine-related immunometabolism [144].

While massive studies focus on amino acid metabolism, further studies need to decipher the interplay between major metabolic checkpoints that have significant control over T cells in the TME.

Lipid metabolism

Lipid metabolism dynamically regulates immune cell function in the TME, with CD36, a scavenger receptor and fatty acid translocase, emerging as an important modulator of lipid metabolism across immune cell subsets [145, 146] [44, 145, 146]. CD36 orchestrates immunometabolic crosstalk in the TME mainly through its dual roles in Tregs and CTLs. As the primary fatty acid translocase upregulated by AMPK during energy stress, CD36 potentiates Treg immunosuppression through supporting mitochondrial fitness in the TME [45]. In cytotoxic CD8 + T cells, CD36-mediated uptake of oxidized lipids triggers p38 activation and ferroptosis, driving cellular dysfunction reversible by glutathione peroxidase 4 overexpression [44]. This lipid peroxidation axis contrasts sharply with the CD28-mTORC1 pathway, where TCR co-stimulation redirects lipids toward anabolic processes that fuel CTL expansion and antitumor activity [147, 148]. The dichotomous regulation of Treg suppression versus CTL exhaustion positions CD36 as a pleiotropic metabolic checkpoint whose therapeutic targeting requires cell-type-specific strategies.

Activated by sterol regulatory element-binding protein 1 (SREBP1) and SREBP2, CD8 + T cells upregulate lipid synthesis and cholesterol intake to support membrane structure, immune receptor signaling, and effector functions [65, 149]. The cholesterol esterification enzyme acetyl-CoA acetyltransferase (ACAT1) partly regulates the membrane cholesterol levels of CD8 + T cells during activation. ACAT1 knockout leads to increased membrane cholesterol levels, enhanced TCR signaling, and more efficient immunological synapse formation in mouse models [65]. However, excess cholesterol induces endoplasmic reticulum (ER) stress, promoting immune checkpoint expression and CD8 + T cell exhaustion in the TME [150]. Notably, cholesterol biosynthesis is essential for CD8 + T cell antitumor function, where ACAT1 inhibition suppresses cholesterol esterification and facilitates enhanced tumor killing [151, 152].

In fatty acid synthesis, the first rate-limiting enzyme acetyl-CoA carboxylase 1 (ACC1), which converts acetyl-CoA to malonyl-CoA, affects T cell differentiation, where its inhibition diminishes Th17 differentiation but enhances memory CD4 + T cell formation [153–155]. Inhibition of ACC1 further favors histone and protein acetylation, and FoxP3 transcription in Treg differentiation, remarkably causing an imbalance that limits Th17-dependent inflammation in the TME [156]. Upon reprogramming the Th17/Tregs balance in cancer immunotherapy, a broader spectrum of ACC1-related metabolic networks should be investigated. Another essential enzyme in fatty acid synthesis is FASN, which is required for long-chain fatty acid synthesis. It supports Treg cell maturation, lipid accumulation in hepatocytes, and inflammatory cytokine production in CD4 + T cells [62, 157]. Additionally, the PI3Kα-specific inhibitor CYH33 boosts CD8 + T cell fatty acid metabolism and, when combined with FASN inhibitor C75, synergistically activates CD8 + T cells for enhanced effector functions [158].

In addition to lipid uptake and synthesis, FAO is highly active in immune cells, accounting for memory T cell generation predominantly [159]. FAO, also called β-oxidation, is the mitochondrial process that breaks down fatty acids, serving as a critical energy source under nutrient-limited conditions and playing specialized roles in immune cell function. Activation of peroxisome proliferator-activated receptor α (PPARα) and PPARδ/β increases key FAO-related enzymes expression in T cells, sustains memory phenotypes, and enhances IFN-γ production, thereby supporting their functionality and persistence [53]. However, increased FAO through the obesity-linked leptin-STAT3 pathway limits glycolysis and T cell antitumor functions. Furthermore, PD-1 ligation could activate STAT3 for FAO, consequently impeding glycolysis in CD8 + T cells, facilitating tumor progression [54]. These insights into lipid metabolism in T cells highlight the dual role of FAO in promoting memory phenotypes while potentially impairing effector responses, suggesting that context-specific modulation of lipid metabolism may be required for optimal antitumor immunity.

Macrophages

Among various myeloid cells, macrophages critically modulate innate immunity and antitumor responses due to their functional diversity and plasticity. Previous studies classified macrophages into inflammatory (M1) and immunosuppressive (M2) phenotypes [160], with opposite roles in antitumor immunity. Induced primarily by HIF-1α, M1 macrophages rely on glucose uptake and glycolysis to accumulate succinate for energy and IL-1β production [161]. The PPP is simultaneously activated to generate NADPH, which maintains redox homeostasis and supports ROS production [162]. In contrast, M2 macrophages rely on FAO and mitochondrial respiration, resembling Tregs [163]. Enhanced FAO in M2 macrophages was achieved mainly by triacylglycerol (TAG) uptake mediated by PPAR and liver X receptor (LXR) [164], and peroxisome proliferator-activated receptor γ coactivator 1β (PGC-1β) triggered by the IL-4-STAT6 axis, whereas the FAO inhibitor [165], etomoxir, blocked IL-4-induced M2 macrophage polarization [164]. Interestingly, FAO attenuation alone doesn't fully inhibit IL-4-induced polarization, suggesting M2 polarization was orchestrated by alternative metabolic pathways and transcriptional networks [166].

During different stages of tumor progression, TAMs exhibit phenotypic plasticity and display a spectrum of functional states beyond a strict M1 or M2 dichotomy [167]. M2 macrophages could express high levels of Arg1, creating an immunosuppressive TME through arginine depletion, while M1 macrophages require arginine to produce NO via inducible nitric oxide synthase (iNOS) [168]. While M1 macrophages typically rely on glycolysis for their pro-inflammatory functions, recent work in pancreatic ductal adenocarcinoma models reveals a context-dependent exception: GLUT1 deletion in TAMs reduces their glycolytic activity but unexpectedly enhances antigen presentation capacity. This metabolic rewiring increases glucose availability for infiltrating NK and CD8 + T cells, thereby boosting their tumor killing activity [169]. Importantly, this effect appears specific to the tumor microenvironment, as other studies show that promoting glycolysis remains essential for classical M1 polarization in non-malignant settings [170]. Some studies also focused on nanomaterial-based repolarization of M2 macrophages into the M1 phenotype [171], highlighting macrophage-centered immunotherapy of immune engineering.

Myeloid-derived suppressor cells

Another fundamental executor of immunosuppression is MDSCs, named for their myeloid origin and immunosuppressive functions (Fig. 3). Unlike peripheral MDSCs, tumor-associated MDSCs exhibit increased glycolysis and OXPHOS [172], leading to elevated PEP production, which prevents excess ROS production and facilitates MDSC survival in the TME. Inhibiting glycolysis with 2-DG reduces MDSC resistance to ROS-mediated apoptosis in the TME [173].

Arginine metabolism in MDSCs actively molds the immunosuppressive milieu in the TME, as Arg1-mediated arginine depletion contributes to Teff dysfunction [132]. The Arg1-induced T cell dysfunction may be subject to the immunosuppressive Gαq/Calcium/PPAR-γ axis, signaling modulated by free fatty acid receptor 2 (FFAR2) as well [68]. Blocking PPAR-γ or supplementing arginine reverses FFAR2-induced immune suppression in mouse models and overcomes resistance to ICB. iNOS cooperates with Arg1 to upregulate SLC7A2 for arginine uptake, a process essential for MDSC suppressive function, as SLC7A2 deletion diminishes this activity in mice. Interestingly, the suppressive effect of MDSCs on T cells primarily depends on direct cell contact rather than Arg1 activity, remaining effective even with PD-L1 blockade or SIRPα deficiency [174]. Furthermore, the immunosuppressive effect of MDSCs could be enhanced by STAT3-induced IDO upregulation, supporting Treg and Breg differentiation to promote immune evasion [175, 176].

Key metabolic signaling, like GCN2, was found to facilitate MDSCs maturation and macrophage polarization through CREB2/ATF4 signaling [177]. ATF4 and GCN2 deficiency limited tumor progression as expected, indicating a dependence of cancer cells on myeloid GCN2 signaling to survive. Targeting innate immunity via myeloid cells has demonstrated improved outcomes in cancer cases [178]. However, a deeper mechanistic understanding of reprogrammed metabolism is essential for translating these findings into clinical success.

NK cells

As a crucial effector of innate immunity, NK cells eliminate tumor cells via multiple mechanisms, such as the release of perforin and granzyme, independent of tumor antigens. Upon stimulation with cytokines like IL-12 and IL-15, NK cells utilize aerobic glycolysis and OXPHOS to support activation [179]. The transcription factor SREBP essentially mediates cytokine-driven metabolism in NK cells, beyond its function in lipid synthesis [180]. Inhibition of SREBP in an adoptive NK cell model significantly impaired metabolic reprogramming, cytokine production, and cytotoxicity against cancer cells in vitro. Additionally, fructose-1,6-bisphosphatase (FBP1) activation suppresses glycolysis and impairs NK cell cytotoxicity, while 2-DG-mediated glycolysis blockade not only directly compromises NK cell function but also counteracts FBP1-induced suppression [181].

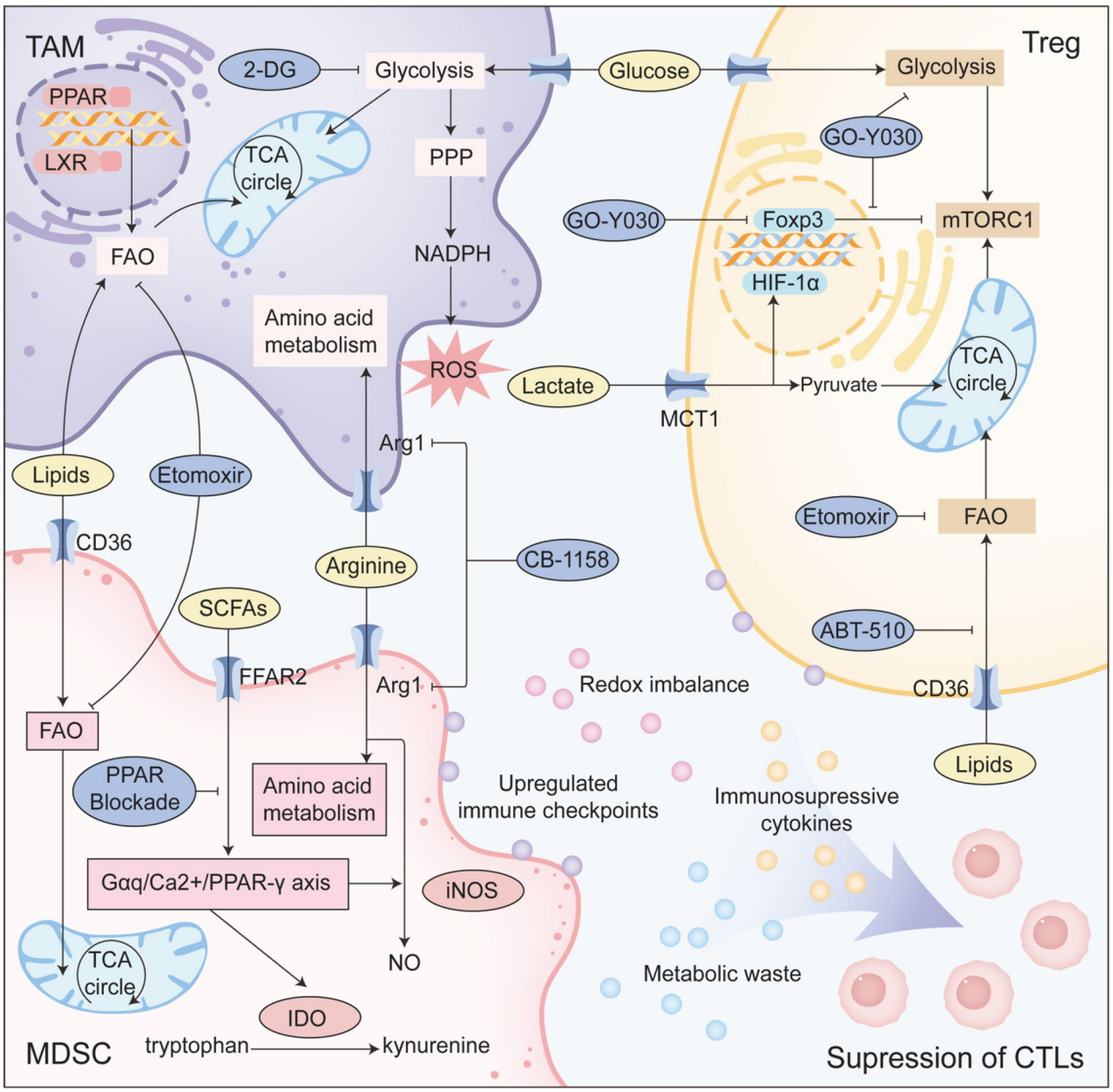

Fig. 3 Suppression of immunometabolism on CD8 + T cells. In the immunosuppressive TME, multiple immunoregulatory cells—including TAMs, MDSCs, and Tregs—exert profound metabolic control over CTLs, thereby dampening antitumor immunity. For instance, arginine metabolism in TAMs and MDSCs actively molds the immunosuppressive milieu in the TME, as Arg1-mediated arginine depletion contributes to Teff dysfunction. The upregulation of IDO in TAMs and kynurenine production significantly impairs T cells. Tregs rely heavily on lipid metabolism for suppressive function, where CD36, AMPK, CPT1a, the PI3K-AKT-mTOR axis, etc. serve as key regulators. Of note, the therapeutic blockade of Arg1, IDO, and FAO has shown promising potential in reversing immune suppression within the TME. Abbreviations: TAM, tumor-associated macrophage; PPAR, peroxisome proliferator-activated receptor; LXR, liver X receptor; PPP, pentose phosphate pathway; TCA circle, tricarboxylic acid cycle; FAO, fatty acid oxidation; NADPH, nicotinamide adenine dinucleotide phosphate; ROS, reactive oxygen species; Arg1, arginase 1; MDSC, myeloid-derived suppressor cell; SCFAs, short-chain fatty acids; FFAR2, free fatty acid receptor 2; PPAR-γ, peroxisome proliferator-activated receptor γ, IDO, indoleamine 2,3-dioxygenase; iNOS, inducible nitric oxide synthase; Treg, regulatory T cell; mTORC1, mechanistic target of rapamycin complex 1; HIF, hypoxia-inducible factor; MCT1, monocarboxylate transporter 1

NK cells are subject to metabolic pressures from the TME. In malignant pleural effusions, TME caused a remarked deficiency in NK cell mitochondrial activity, while IL-15 could rescue mitochondrial integrity for sustained OXPHOS activity and effector function [182]. In patients with metastatic breast cancer [183], TGF-β

contributed to metabolic dysfunction and exhaustion of circulating NK cells. In a lipid accumulation TME, twisted PPAR signaling blunted antitumor responses of NK cells by inhibiting mTOR-mediated glycolysis, whereas PPAR inhibition or blocking the transport of lipid to mitochondria rescued their deficient metabolism and cytotoxicity [71]. A comprehensive investigation of NK cell metabolism and strategic targeting of related targets may advance NK cell-based immunotherapy.

Other immune cells

Intratumoral DCs with antigenic cross-presentation have been a crucial component of antitumor immunity. Mediated by HIF-1α, DCs undergo a metabolic switch from OXPHOS to aerobic glycolysis, fundamental for DC survival, stimulatory cytokines production, and T cell activation [184]. However, pharmacologic activation of AMPK, essential signaling for OXPHOS, could block DC maturation in vitro [185]; further research should examine whether specific metabolism exerts a dominant effect on DC function. Low glucose and high lactate levels in the TME suppress the antigen-presenting capacity and mitochondrial functions of DCs [72], highlighting the significant impact of nutrient competition on DC functionality. Furthermore, DC functions of stimulating allogeneic T cells and antigen presentation could be impaired by elevated triglyceride levels observed in tumor-bearing mice and cancer patients [186].

B cells encompass various metabolic processes closely linked to their bidirectional functions, depending on activation state and subsets. Activated B cells rely on SREBP for metabolic reprogramming necessary for antibody responses, and generation of germinal centers, memory B cells, and bone marrow plasma cells [187]. Fumarate was shown to suppress B cell activation and function through inhibition of tyrosine kinase LYN directly [188], while 25-hydroxycholesterol could inhibit IL-2-mediated B cell proliferation to dampen IgA production [189]. B cell metabolism also impedes antitumor immunity. B cell-derived gamma-aminobutyric acid (GABA) promotes anti-inflammatory macrophage differentiation and secretion of IL-10 to suppress CTL functions, while inhibition of GABA-generating enzyme GAD67 could enhance T cell effector function [73]. Leucine-tRNA-synthase-2 (LARS2) expression was shown to reprogram NAD + regeneration and oxidative metabolism in a leucine-dependent manner, resulting in an immunosuppressive phenotype of B cells [190]. A comprehensive review of metabolic pathways and associated phenotypes is necessary to define the metabolism-function axis in B cell biology, in essence.

Targeting metabolic checkpoints for cancer immunotherapy

Targeting metabolic checkpoints offers multifaceted strategies for improving cancer immunotherapy, with the promise of clinical translation (Table 3). Mechanistically, it is optimal to enhance effective responses while reducing suppression. Moreover, strengthening immunotherapies, including ICB and ACT, through metabolic checkpoints provides a synergistic avenue to improve treatment efficacy and overcome resistance.

Enhancing effector immune cells to boost antitumor immunity

Manipulation of metabolite levels in the TME to alleviate effector cell dysfunction includes regulating lactate production, ROS production, and amino acid levels. In a murine melanoma model and a humanized mouse model of TNBC, lactate oxidase nanocapsules induce decreased lactate levels and increased immunostimulatory hydrogen peroxide, enhancing CD8 + T cell efficacy without disrupting healthy cell metabolism [194]. Signaling through the APOL3-LDHA axis induces IFN-γ production and decreases lactate concentration, facilitating tumor ferroptosis and the cytotoxic ability of CD8 + T cells [219]. Intracellular pyruvate dehydrogenase also serves as a target for recovering cytotoxicity of CD8 + T cells from the lactate-enriched TME [220]. This strategy may help recover DC cell function as well, for DC cells are illustrated as inhibited by low glucose and high lactate [72].

Apart from lactate, ROS as a metabolic byproduct in T cells, manipulates their function tightly. Recent studies demonstrated that Venetoclax, a Bcl-2 inhibitor for acute myeloid leukemia (AML) treatment, could fulfill therapeutic functions by increasing ROS production to enhance T cell effector function [196]. Moreover, Venetoclax achieved a breakthrough for AML ineligible for intensive chemotherapy in combination with Azacytidine [195, 197, 221, 222].

The strategy of reprogramming effector cell function through supplementing amino acids is receiving increasing attention. In particular, arginine supplementation, in combination with nutrients or chemotherapy, shifts activated T cells from glycolysis to OXPHOS with a memory-like phenotype and enhanced effector function [141], leading to improvement in patient pathology [223]. Arginine also synergizes with the chemotherapeutic agent Docetaxel to promote DC cell proliferation and function [224]. However, a recent study also identified a link between dietary restriction and optimized innate antitumor immunity to rewire NK cells metabolically [225], where NK cells enhance CPT1A-mediated fatty

Table 3 Metabolic checkpoints of translational significance

Target	Representative agents	Monotherapy or in combination	Tumor types	Clinical trials	Refs
Glutamine	JHU083	Monotherapy	MC38 colon cancer, B16 melanoma, etc	NA	[4]
	redox-DON	Monotherapy	Colon cancer CT26 and MC38, melanoma B16F10, and mammary carcinoma	NA	[191]
	Glutamine supplementation	In combination with fatty acid supplementation	Colorectal cancer	[192]	NA
GAPDH	DMF	Monotherapy	Cutaneous T cell lymphoma	[193]	NA
Lactate	Nanocapsules of lactate oxidase	In combination with PD-L1 blockade	Melanoma and triple-negative breast cancer	NA	[194]
ROS	Venetoclax	In combination with azacytidine	Acute myeloid leukemia	[195]	[196, 197]
Arginine	Arginine supplementation	In combination with fatty acids and nucleotides supplementation	Head and neck cancer	[198]	NA
	Arginine supplementation	Monotherapy	Prostate cancer	[199]	NA
Arg1	CB-1158	In combination with PD-L1 blockade	Advanced or metastatic solid tumors	[200]	NA
IDO1	Epacadostat	In combination with BN-brachyury, M7824, and N-803	Castration-resistant prostate cancer and other metastatic cancers	[201]	NA
	Epacadostat	In combination with PD-L1 blockade	Advanced solid tumors	NA	[202, 203]
IDO1 and TDO2	AT-0174	Monotherapy	Non-small cell lung cancer	NA	[204]
	AT-0174	In combination with temozolomide	Glioblastoma	NA	[205]
AMPK	Metformin	In combination with PD-L1 blockade	MC38 colon carcinoma and B16 melanoma	NA	[206]
	Metformin	In combination with PD-L1 blockade	Refractory MSS colorectal cancer, small cell lung cancer, and non-small cell lung cancer	[207] [208] [209]	NA
mTORC1	Metformin	Monotherapy	Fibrosarcoma, radiation leukemia, and melanoma	NA	[210]
mTOR-S6 axis	GO-Y030	In combination with PD-L1 blockade	B16-F10 melanoma	NA	[211]
PI3Kδ/γ	RP6530	Monotherapy	Hodgkin lymphoma	NA	[212]
PI3K/PKB	Nanocapsules of d-lactate	Monotherapy	Hepatocellular carcinoma	NA	[213]
One-carbon metabolism	Formate supplementation	In combination with PD-L1 blockade	B16 melanoma	NA	[214]
GLUT1	Overexpression of GLUT1	In combination with CAR-T therapy	Nalm6-GL leukemia	NA	[215]
Glycolysis and NAD production	Fc-IL-4	In combination with CAR-T therapy	B16F10 melanoma, MC38 colon cancer etc	NA	[216]
FOXO1	Overexpression of FOXO1	In combination with CAR-T therapy	MC38 colon cancer, E0771 breast cancer, etc	NA	[217]
OXPHOS and ATP synthesis	Venetoclax	In combination with CAR-NK therapy	Acute myeloid leukemia	NA	[218]

Abbreviations: *GAPDH* glyceraldehyde 3-phosphate dehydrogenase, *DMF* dimethyl fumarate, *PD-L1* programmed death-ligand-1, *ROS* reactive oxygen species, *Arg1* arginase 1, *IDO1* indoleamine 2,3-dioxygenase 1; *TDO2* tryptophan 2,3-dioxygenase 2, *AMPK* AMP-activated protein kinase, *MSS colorectal cancer* microsatellite stable colorectal cancer, *mTORC1* mechanistic target of rapamycin complex 1, *PI3K* phosphoinositide 3-kinase, *CAR-T therapy* chimeric antigen receptor-T cell therapy, *CAR-NK therapy* chimeric antigen receptor-natural killer cell therapy

acid metabolism. Additionally, removing dietary tryptophan reduced the activity of TAM AhR, a tryptophan sensor, and increased TILs [226]. Still, the lack of specific therapeutic targets and obvious efficacy in monotherapy suggests amino acid manipulation as an adjunct to immunotherapy.

Beyond metabolite manipulation, strategic inhibition of key immunometabolic enzymes offers powerful opportunities to reinvigorate antitumor immunity. In CD8 + T cells, inhibition of glycolytic enzymes such as HK2 with 2-DG promotes a metabolic shift from glycolysis to OXPHOS as evidenced by increased OCR/ECAR ratios and boosts cytotoxicity functions [51], though its clinical translation requires more selective strategies of targeting to control systemic effects [227]. Disrupting glutamine metabolism through JHU083 demonstrates dual benefits. While cancer cells succumb to metabolic stress, CD8 + T cells maintain functionality by utilizing acetate to fuel the TCA cycle, showcasing their metabolic plasticity [116, 228]. Notably, JHU083 also enhances NK cell activity by stabilizing c-Myc to boost both glycolytic and oxidative metabolism [4]. NK cell function can be further augmented through glycogen synthase kinase-3 (GSK3) inhibition that stabilizes c-Myc in AML patients [105, 229], or via CISH deletion that activates JAK/STAT and mTORC1 signaling for enhanced metabolic fitness and antitumor responses [230].

In studies targeting metabolic enzymes involved in amino acid metabolism, IDO and TDO-related blockade exhibit remarkable clinical potential. Since Munn et al. first identified the immunosuppressive role of IDO in the TME, targeting IDO has been a major focus of cancer immunotherapy research. Similarly, TDO, which is primarily expressed in the liver, controls tryptophan metabolism in suppressive cells, dampening T cell efficacy. Early clinical trials focusing on blocking either IDO or TDO are ongoing, aiming to restore effector T cell function to combat cancer [201, 231, 232], but their clinical efficacy remains limited. Epacadostat, a selective IDO1 inhibitor, showed promising preclinical data, but clinical trials combining it with PD-1 blockade failed to achieve the anticipated improvement in patients [202, 203]. The limited efficacy may be attributed to the compensatory role of unblocked TDO [233], as well as complex escape mechanisms by upregulation of PD-L1 and other immune checkpoints within the TME. Notably, therapies targeting IDO and TDO simultaneously or in combination with ICB have been developed in recent years as a novel strategy for clinical testing [204, 205]. Following tryptophan degradation, kynurenine metabolism could be inhibited through PEGylated kynureninase and targeting kynurenine-3-monooxygenase (KMO), thereby enhancing CD8 + T cell and NK cell antitumor activity [234, 235].

Targeting immunosuppressive cells to alleviate suppression

Tregs

Treg depletion through direct targeting of immunosuppressive molecules like Foxp3 and Cytotoxic T-Lymphocyte Antigen-4 (CTLA-4) is known to exert systemic toxicity, particularly severe autoimmunity [236–238]. Thus, novel strategies may focus on exploiting Tregs' metabolic vulnerability within the TME for more precisely targeted effects. The metabolic vulnerability represents a relative dependency or weakness that can be exploited for therapeutic purposes. Tregs exert remarked reliance on specific metabolic pathways in the TME (Fig. 3). The PI3K-AKT-mTOR axis is the most crucial regulator of glucose metabolism in intratumoral Tregs. Previous studies demonstrated that the PI3K-AKT-mTOR signaling facilitated glycolysis in Tregs and limited their differentiation and functions. Pharmacological inhibition of PTEN, which stabilizes Tregs, stimulates the PI3K-AKT axis and deprives their immunosuppressive phenotype, leading to an inflammatory TME and improved immunotherapy efficacy in mouse models of melanoma [239]. Metformin, activating mTORC1 through reducing Foxp3 expression, attenuated Treg differentiation and enhanced antitumor responses in the TME [210]. However, some studies indicated that Tregs rely on glycolysis for suppressive functions as well, with TLR8 signaling, an inhibitor of mTORC1 activity, reducing HIF-1α-induced glucose metabolism and disrupting their suppressive roles in cancer models [240, 241]. Recent research identified that Glut3-dependent O-GlcNAcylation supports intratumoral Treg function mediated by the NF-κB signaling [242], providing novel insights for Treg-targeted cancer immunotherapies.

Targeting Tregs' heavy liability on lactate and lipid metabolism offers potential therapeutic strategies to counteract immunosuppression. Tregs adapted to extracellular lactate in the TME to support suppressive ability, whereas GO-Y030 treatment inhibited lactate production and limited the mTOR-ribosomal S6 kinase pathway, counteracting PD-1 blockade-induced Treg proliferation [211]. Selective inhibition of the lactate transporter monocarboxylate transporter 1 (MCT1) reduced the metabolic fitness and abundance of intratumoral Tregs in the TME as well [8]. As intratumoral Tregs rely on FAO heavily, CD36, an upregulated scavenger receptor, could be blocked by ABT-510 to restrict lipid metabolism, thereby reducing Treg metabolic fitness. Limiting FAO through the CPT1a inhibitor etomoxir also reduced Treg populations in suppressing glioblastoma progression

[45]. Nonetheless, further research to identify key transcription factors and enzymes of Treg lipid metabolism in preclinical models is needed to further exploit their metabolic vulnerability.

TAMs

TAMs are regarded as suppressing effector cells and promoting tumor evasion, with the absolute majority of them exerting an immunoinhibitory phenotype like M2 (Fig. 3). Thus, current strategies focus on the depletion of TAMs and repolarization of them towards an M1-like phenotype. Targeting glucose metabolism seems practical, with 2-DG and deletion of LDHA exerting efficacy through reducing glycolysis and lactate production that favor suppression of TAMs [243, 244]. Moreover, the dual PI3Kδ/γ inhibitor Tenalisib (RP6530) repolarizes TAMs into an inflammatory phenotype by inhibiting the aerobic glycolysis enzyme PKM2, a determinant in Hodgkin lymphoma tumor cell-induced M2 polarization, in addition to reducing lactate production and killing cancer cells [212]. Notably, tenalisib further exerts therapeutic efficacy by modulating PI3Kδ/γ-related metabolism to limit malignant T cell and cancer cell proliferation directly [245].

Notably, the above strategies modulate shared metabolic circuitries in the TME, making therapeutic outcomes hard to predict. Nanomaterials, a novel approach, have been fabricated for their ability to be easily internalized by phagocytosis to repolarize TAMs. For instance, the delivery of NO into M2 macrophages impaired mitochondrial and TCA cycle activity, facilitating the expression of M1 markers and inflammatory cytokines [246]. Nanoparticles loaded by D-lactate (a gut microbiome metabolite) promote the polarization of M2 macrophages to M1 via inhibition of PI3K/AKT pathway and activation of the NF-κB pathway, retarding HCC development in mouse models [213]. Blocking Arg1 also serves as a novel approach to reprogramming TAMs, as TAMs and MDSCs rely on Arg1 to facilitate suppression. The arginase inhibitor CB-1158 significantly reduced myeloid cell-mediated suppression and tumor growth [67]. However, the clinical efficacy of arginase inhibitor monotherapy as well as its combination with ICB therapy has not met expectations [200]. Overall, while TAMs exhibit significant metabolic and functional plasticity, further in-depth studies are required to pinpoint determinant metabolic pathways that shape their functions.

Strengthening immunotherapy through metabolic checkpoint modulation

Enhancing immune checkpoint blockade

ICB therapies, targeting brake molecules of immune responses, have revolutionized cancer treatment by reactivating suppressed effector cells. However, resistance to ICB remains a major obstacle, driven by the TME, which imposes metabolic challenges such as hypoxia, lactate accumulation, nutrient depletion, and suppressive cells with high metabolic fitness [247]. For example, melanoma cells with deregulated oxidative metabolism deplete intratumoral oxygen, creating hypoxic conditions that drive T cell exhaustion and resistance to PD-1 blockade [248].

To overcome these barriers, metabolic interventions have emerged as a hopeful adjunct to ICB therapies. Metformin reduces oxygen consumption in tumor cells, alleviating intratumoral hypoxia and thereby boosting T cell effector function and tumor killing in combination with PD-1 blockade [206]. In HCC mouse models with non-alcoholic steatohepatitis (NASH) that limits ICB efficacy, metformin could rescue the efficacy of PD-1 blockade to reverse resistance, but the precise immunologic mechanisms remain unclear. Despite its potential, the clinical outcomes of metformin in combination with PD-1 blockade have been modest [207–209, 249]. Reprogramming metabolic profiles of T cells for enhanced antitumor phenotypes seems beneficial, as glutamine antagonists combined with PD-1 blockade could induce a dramatically improved antitumor effect mediated by a metabolic shift supporting OXPHOS [4]. Small molecule agonism of the PPP without acute glycolytic impairment contributes to a progenitor-like T cell state, promoting ICB efficacy in patient-derived tumor organoids [250]. Supplementing formate to support one-carbon metabolism could enhance CD8 + T cell fitness in anti-PD-1 therapy [214]. In addition, *Lactobacillus johnsonii* and the tryptophan-derived metabolite indole-3-propionic acid (IPA) have been reported to enhance the efficacy of CD8 + T cell-mediated PD-1 blockade [251].

Mitochondrial function is a determinant of ICB efficacy. Impaired mitochondrial function induced by continuous hypoxia stimulation, often linked to the loss of PGC-1α, results in exhausted T cells unable to sustain effective antitumor responses [252]. Interventions aimed at restoring mitochondrial activity, such as agonists of mTOR, AMPK, or PGC-1α, could synergize with PD-1 blockade to enhance CTL function [253]. Bezafibrate, a PGC-1α/PPAR complex agonist, has been shown to activate mitochondria, upregulate OXPHOS and glycolysis, and FAO, thereby improving the efficacy of PD-1 blockade [254]. Likewise, stimulation of the costimulatory molecule 4-1BB enhances mitochondrial capacity and activates PGC-1α signaling, yielding robust antitumor responses when combined with PD-1 blockade [255]. These findings underscore the importance of targeting key metabolic checkpoints of immune cells to boost the therapeutic efficacy of ICB.

Augmenting adoptive cell therapy

Adoptive cell therapy, such as TIL, CAR-T, and TCR-T therapies, has emerged as a novel paradigm of cancer therapy by directly harnessing and enhancing the tumor-targeting capabilities of patient-derived or engineered immune cells. However, as previously discussed, the efficacy of ACT is often limited by the immunosuppressive TME, whereas similar strategies, such as overcoming arginine and glucose deficiency, have exerted obvious efficacy [49, 215].

Chimeric antigen receptor (CAR) T cell therapy has exhibited potent efficacy in hematological malignancies such as acute lymphoblastic leukemia [256, 257], B cell lymphoma [258, 259], and multiple myeloma [260, 261]. However, its efficacy in solid tumors remains limited due to the suppressive properties of the TME, which drives T cell exhaustion. Metabolic modulations have shown promise in engineering T cells for a more durable phenotype. Typically, T cells undergo a metabolic shift from glycolysis to support OXPHOS for a memory phenotype, whereas 2-DG was shown to support T cell self-renewing capacity [51]. The type 2 cytokine Fc-IL-4 was shown to induce STAT6 and mTOR signaling, increasing glycolysis and NAD levels to reinvigorate exhausted CD8 + T cells for enhanced CAR-T therapy [216]. Furthermore, replacing the CD28 signaling domain in CAR T cells with a 4-1BB domain leads to better therapeutic outcomes in ACT through increased mitochondrial metabolism and FAO [262]. Mitochondrial metabolism could be enhanced through FOXO1 for sustaining T cell stemness, thereby improving their therapeutic efficacy in vivo [217], however, the precise role and mechanisms of mitochondrial activity in CAR-T therapy remain to be elucidated and nuanced.

Apart from CAR-T cells, other adoptive cells bear obvious promise in metabolic modulation as well. Attenuating PGE2 signaling promotes TIL expansion and functionality partly through restored mitochondrial and metabolic fitness, enhancing tumor control [263]. Venetoclax could function through NF-κB signaling to promote mitochondrial respiration and ATP synthesis in NK cells, augmenting CAR-NK therapy for AML [218]. Collectively, these findings highlight metabolic reprogramming as effective in enhancing the persistence, functionality, and antitumor efficacy of various ACT modalities.

Bridging metabolic checkpoints with emerging technologies

Cutting-edge technologies that enhance immune function and surmount therapeutic barriers are transforming the evolving landscape of metabolic checkpoint-targeted immunotherapy. Leveraging tools such as CRISPR-based gene editing, single-cell metabolomics, and microbiome modulation holds immense potential to overcome current limitations and propel the field forward.

CRISPR-Cas9 and base-editing technologies enable precise genetic modifications to disrupt cancer cell metabolism. A CRISPR-Cas9 system that knocks down LDHA expression synergizes with metabolic blockade of nutrients and energy production in cancer cells, converting the hypoxia and acidic TME into an immunocompetent state to boost antitumor immunity in TNBC [264]. Given the growing demand for CRISPR-based immune cell engineering, further advancements in this field hold immense potential. Integrating metabolic reprogramming with personalized immunotherapy could ultimately redefine cancer treatment paradigms. Complementing genetic approaches, advanced analytical tools may enable precise deciphering of the metabolic heterogeneity of immune cells within the TME. Single-cell metabolomics and multi-omics approaches could provide a high-resolution map of TILs to identify novel metabolic checkpoints and advance the development of customized therapeutic interventions [265]. Equally important is harnessing the gut microbiome-immune axis. Microbial-derived metabolites have been shown to enhance T cell differentiation and function, where probiotic interventions and dietary strategies that modulate the gut microbiome can improve the metabolic fitness of effector T cells to enhance immunotherapy outcomes [266, 267].

Conclusion and perspective

Metabolic reprogramming is a shared hallmark of immune cells and cancer cells in the TME. In multiple metabolic pathways such as glycolysis, amino acid metabolism, lipid metabolism, OXPHOS, etc., in immune cells, remarkable plasticity was shown (Fig. 4), shaping the immune contexture of the TME jointly. Targeting metabolic checkpoints promotes antitumor phenotypes in effector cells, reprograms immunoinhibitory cells to reduce suppression, and establishes a TME with immunostimulatory properties. Consistent with the notion, metabolic barriers of immunotherapies like ICB and ACT may be tackled through gene modulation, pharmacological blockade, dietary therapy, and other metabolic modulations, exerting more profound and extensive effects. Herein, targeting metabolic checkpoints, especially combined with ICB and ACT, opens a novel direction for cancer immunotherapy.

As research continues to elucidate the intricate nexus between metabolism and immune function, there remain some issues: 1) Different classes of immune cells and cancer cells are metabolically connected. For instance, TAM-derived L-carnitine synergizes with CPT1A in lung cancer stem cells to promote ferroptosis resistance and CD8 + T cell inactivation [268].

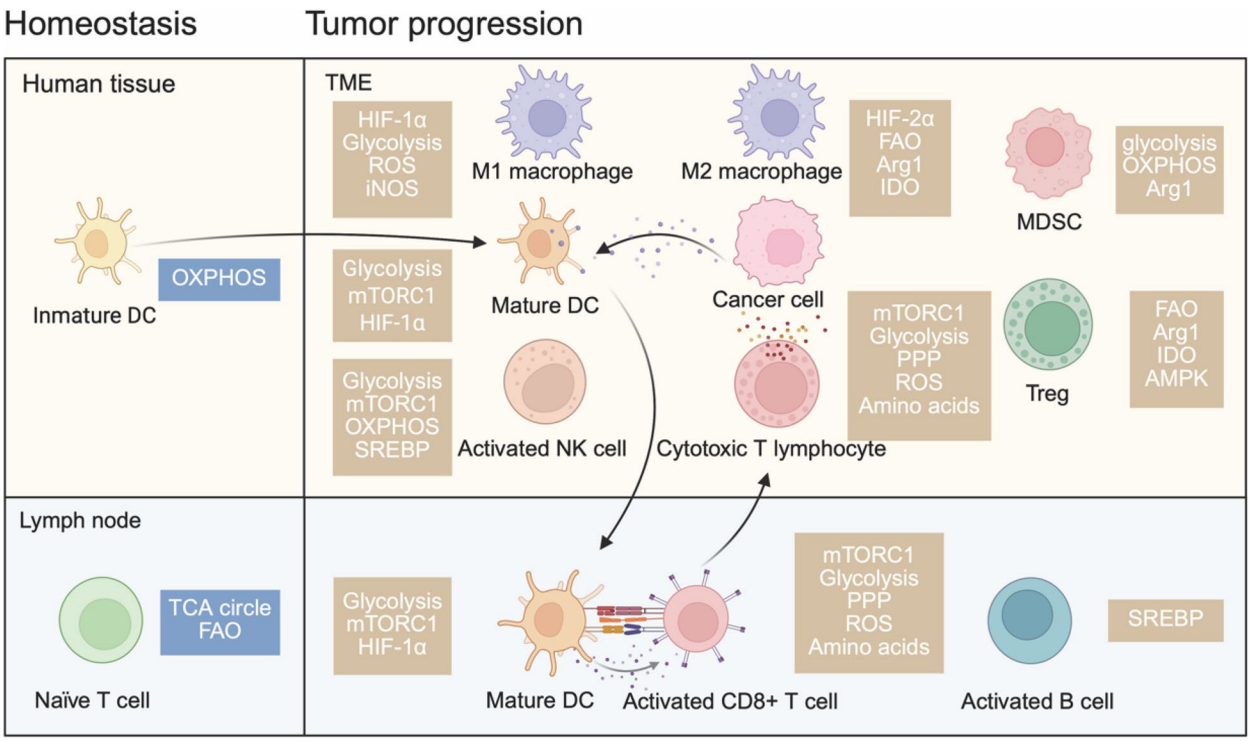

Fig. 4 Metabolic profiles of immune cells. Immune cells adopt distinct metabolic programs in response to environmental cues. During tumor progression, the immunometabolic landscape of the TME dynamically reprograms immune cell metabolism, contributing to functional reprogramming and immune dysregulation. Abbreviations: TME, tumor microenvironment; DC, dendritic cell; MDSC, myeloid-derived suppressor cell; Treg, regulatory T cell; OXPHOS, oxidative phosphorylation; HIF, hypoxia-inducible factor; ROS, reactive oxygen species; TCA circle: tricarboxylic acid cycle; iNOS, inducible nitric oxide synthase; mTORC1, mechanistic target of rapamycin complex 1; FAO, fatty acid oxidation; IDO, indoleamine 2,3-dioxygenase; Arg1, arginase 1; PPP, pentose phosphate pathway; AMPK, AMP-activated protein kinase; TCA circle, tricarboxylic acid cycle; SREBP, sterol regulatory element-binding protein

Simply targeting a specific immune cell type may not be potent in manipulating immune responses. A novel direction is to map such metabolic networks to identify leverage points. 2) The immunometabolic network operates through complex, interconnected pathways rather than isolated checkpoints. Leveraging advanced technologies, such as the Nobel Prize-winning invention AlphaFold and the novel single-cell transcriptomics tool PERCEPTION, could aid in identifying checkpoint structures and predicting drug responses [269, 270]. 3) In the process of TCR recognition, co-stimulating, and cytokine release, the role of cellular metabolism remains to be elucidated in a comprehensive review to deepen insight into immunometabolism mechanisms. 4) The shared metabolic machinery among immune cells poses significant off-target risks. Targeting a single checkpoint with molecules such as 2-DG, metformin, etomoxir, or JHU083 may inadvertently affect the global immune system. Identifying distinct and dominant checkpoints expressed in a certain or a slim range of immune cells should attract enough attention. 5) A critical challenge lies in the bi-directional effects of metabolites like lactate. While lactate inhibits T cell function through direct metabolic effects or lactylation to modify critical proteins [271–273], it also enhances CD8 + T ability of tumor killing in certain cases. Another example is mTOR signaling, its dual role in promoting effector T cell activation and Treg stability complicates targeting outcomes. These dualities underscore the need for temporally and spatially precise interventions, such as stage-specific inhibition of metabolic checkpoints, or in combination with immune checkpoint blockers. Overall, multi-dimensional approaches will be essential to overcome the current limitations and unlock the full potential of metabolism-focused cancer immunotherapies.

Abbreviations

TME	Tumor microenvironment
PI3K	Phosphoinositide 3-kinase
OXPHOS	Oxidative phosphorylation
NK cells	Natural killer cells
DCs	Dendritic cells
TAMs	Tumor-associated macrophages
MDSCs	Myeloid-derived suppressor cells
Tregs	Regulatory T cells

ICB	Immune checkpoint blockade
ACT	Adoptive cell therapy
PD-L1	Programmed death-ligand-1
LDHA	Lactate dehydrogenase A
mTOR	Mechanistic target of rapamycin
mTORC1	Mechanistic target of rapamycin complex 1
TILs	Tumor-infiltrating CD8 + T lymphocytes
NFAT	Nuclear factor of activated T cells
HIF	Hypoxia-inducible factor
TAMs	Tumor-associated macrophages
IDO	Indoleamine 2,3-dioxygenase
GCN2	General control nonderepressible 2
LAT1	L-type amino acid transporter 1
FAO	Fatty acid oxidation
CTLs	Cytotoxic T lymphocytes
FASN	Fatty acid synthase
CPT1A	Carnitine palmitoyltransferase 1A
CAR-T	Chimeric antigen receptor T cells
AMPK	AMP-activated protein kinase
NF-κB	Nuclear factor-κB
HK2	Hexokinase 2
Th1	T helper 1 CD4 + T cell
TCR	T cell receptor
PPP	Pentose phosphate pathway
ROS	Reactive oxygen species
TCA circle	Tricarboxylic acid cycle
SLC	Solute carrier family
TDO	Tryptophan 2,3-dioxygenase
SAM	S-adenosylmethionine
Arg1	Arginase 1
NOS	Nitric oxide synthase
SREBP1	Sterol regulatory element-binding protein 1
PPARα	Peroxisome proliferator-activated receptor α
AML	Acute myeloid leukemia
PGC-1α	Peroxisome proliferator-activated receptor γ coactivator 1α

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ZQL, YYZ, XWH, and YYL provided overall conceptual guidance and strategic direction throughout the development of this review. XWH supervised the project and secured funding support. ZSL and YYL were primarily responsible for drafting and revising the manuscript. YYL conducted critical review and made substantial intellectual contributions to manuscript refinement. XWH, ZKZ, and ZQL contributed to the critical revision and refinement of the content. JLS provided detailed guidance on the modification and refinement of the figures. STL, JLS, YHB, SYW, YYZ, ANZ, HX, PL, QC, CHZ, JYN, and YKC contributed through discussions, provided feedback during the preparation process, and assisted in the administrative or coordination aspects of the review.

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