Targeting colorectal cancer and T-cell metabolism for the treatment of colorectal cancer (Review)

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Abstract. Colorectal cancer (CRC) is a malignant tumor of the digestive tract that is highly prevalent worldwide, which is associated with a poor prognosis in advanced stages and for which current treatment plans have limited efficacy. T cells serve a crucial role in immune clearance and immune evasion within the tumor microenvironment. However, tumor cells directly impair the function of T cells through nutrient competition and the release of inhibitory metabolites. Notably, targeting 'metabolic checkpoints' has emerged as a crucial strategy to enhance T-cell efficacy. The present literature review summarizes the role of reprogramming glycolysis, glutaminolysis and lipid metabolism in driving immune evasion in CRC, and discusses potential intervention strategies from two perspectives: Modulating tumor metabolism and optimizing the intrinsic metabolic functions of T cells. Finally, it is proposed that stratified precision therapy based on individual metabolic profiles represents a future direction for overcoming immune heterogeneity and drug resistance in CRC.

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1. Introduction

Colorectal cancer (CRC) ranks third globally in terms of occurrence rate among malignant tumors and is the second leading cause of cancer-related mortality (1). Early-stage CRC is typically managed with surgery combined with radiotherapy, whereas for patients with advanced colon cancer, combination therapy involving chemotherapeutic agents and targeted drugs is primarily employed, such as bevacizumab (2). Although these treatment plans have markedly improved the prognosis of patients with CRC, clinical statistical analysis in the United States has indicated that the 5-year survival rate for CRC is 65, and 14% for distant-stage (metastatic) CRC (3). CRC is a highly heterogeneous and complex disease, and patients with distinct metabolic characteristics often respond differently to the same therapeutic strategy (4,5). In particular, during cancer progression, tumor cells frequently acquire diverse features and generally become more heterogeneous (6). Consequently, although targeted therapies have improved the overall survival of patients with CRC, a substantial number of patients still lack effective targeted drugs or develop drug resistance during treatment. Given the prevalence of CRC and the limitations of current therapies, it is imperative to refine existing clinical approaches and develop novel therapeutic agents.

Tumor cells remodel their energy metabolic networks to meet the bioenergetic and biosynthetic demands associated with unlimited proliferation, invasion and metastasis. This metabolic reprogramming involves multi-level restructuring of glucose, lipid and amino acid metabolism. It not only supplies adenosine triphosphate (ATP) to tumor cells but also utilizes metabolic intermediates to participate in biosynthesis, counteract oxidative stress and modulate the microenvironment, thereby shaping the tumor microenvironment (TME) (7,8). Within the TME, tumor cells, inflammatory cells, stromal cells and cytokines form a complex immunosuppressive network that inhibits T-cell effector functions and promotes T-cell exhaustion (9,10). By remodeling the metabolic networks of glucose, lipids and glutamine to counteract malignant biological behaviors, targeting tumor metabolism has emerged as a novel strategy for cancer therapy (11).

T cell-based immunotherapy has been widely applied in the treatment of various types of cancer and has achieved notable clinical outcomes, making it a prominent research focus in the field of oncology (12). For example, chimeric antigen receptor T-cell (CAR-T) therapy has demonstrated favorable efficacy

in hematological malignancies (13). However, its effectiveness against solid tumors, including CRC, remains limited. $CD8^+$ T cells are the primary effector cells of the cellular immune response; they can specifically recognize antigens and efficiently eliminate tumor cells, thereby serving a critical role in antitumor immune responses (14). The differentiation status and infiltration proportion of intratumoral $CD8^+$ T cells are closely associated with patient clinical prognosis, which forms an essential basis for the development of T cell-based immunotherapies (15,16). Currently, metabolism has been recognized as a key mechanism regulating the antitumor activity of T cells within the TME.

Metabolic checkpoints refer to a series of cellular metabolic molecular switches that ensure the timely and accurate conversion of nutrients into metabolites. Studies have shown that metabolic checkpoints can regulate the development, differentiation and function of T cells, as well as the competition for nutrients in the TME between immune cells and tumor cells (17-21). Metabolites within the TME can impose metabolic stress on infiltrating T cells, contributing to local immunosuppression and immune evasion (22,23). Consequently, modulating the metabolic pathways of tumor cells and T cells via metabolic checkpoints to enhance the antitumor efficacy of CAR-T therapy has emerged as a promising therapeutic strategy (24). Notably, CRC exhibits tumor heterogeneity, with substantial variations in metabolic profiles and TME composition among different patients (5,6,25). Current technological advances, such as single-cell metabolomics analysis, enable the assessment of individual patient metabolic status (25). Consequently, precise immunometabolic therapy may represent a promising therapeutic direction.

The present review incorporates the latest research literature published between 2023 and 2025. Unlike previous studies, which have focused solely on either tumor metabolism regulation (3) or CAR-T optimization (26), the current review systematically elaborates on how the metabolic features of CRC drive immunosuppression. Furthermore, it discusses the potential strategies for reshaping the TME and enhancing the antitumor effects of T cells by targeting metabolic checkpoints, ranging from glycolysis and glutamine metabolism to fatty acid oxidation (FAO). Furthermore, the perspective of tailoring treatments based on distinct CRC metabolic genealogies is proposed, aiming to provide insights for developing precision immunotherapies targeting different CRC metabolic subtypes.

2. Metabolic characteristics and immunosuppressive environment of CRC

The key metabolic pathways in CRC and potential therapeutic targets are integrated and illustrated in Fig. 1.

The Warburg effect. The Warburg effect, characterized by aerobic glycolysis under normoxic conditions, is a distinct metabolic feature observed in cancer cells. Despite sufficient oxygen availability, glycolysis preferentially produces lactate, thereby supporting rapid proliferation and meeting biosynthetic demands in CRC (27). Glycolysis is an inefficient energy-generating pathway, through which tumor cells competitively consume large amounts of glucose to fuel their own growth, while markedly impairing the antitumor response of immune cells (28). It has been shown that the excessive consumption of glucose by tumor cells leads to a glucose-depleted TME, which inhibits the proliferation of tumor-infiltrating lymphocytes, and suppresses mammalian target of rapamycin (mTOR) activity, glycolytic capacity and the production of effector molecules, such as interferon-γ (29). On the other hand, the enhanced aerobic glycolysis in tumor cells generates substantial amounts of metabolic byproducts, including lactate and CO_2, leading to lactate accumulation and acidification within the TME. This further imposes metabolic stress on infiltrating immune cells. The acidic extracellular microenvironment impedes lactate efflux from cytotoxic T lymphocytes, directly affecting their proliferation and cytokine secretion, ultimately resulting in impaired cytotoxic function (30,31).

Glutamine metabolism. Under the Warburg effect, the resulting hypoxic and acidic TME leads to the substantial accumulation of hypoxia-inducible factor-1α, which restricts mitochondrial aerobic activity and promotes glutaminolysis to meet the demands of tumorigenesis and progression (32). Glutamine is the most abundant non-essential amino acid in the human body. It enters cells via the transporters solute carrier family 1 member 5 (SLC1A5) and solute carrier family 7 member 5 (SLC7A5), and is converted by glutaminase (GLS) into glutamate and ammonia. Subsequently, glutamate is transformed into α-ketoglutarate (α-KG) through catalysis by glutamate dehydrogenase (GDH) or transaminases, entering the tricarboxylic acid (TCA) cycle to participate in the synthesis of nucleotides, amino acids and fatty acids (33). Concurrently, glutamine can also be converted into glutathione to maintain cellular redox homeostasis and prevent damage to biological macromolecules (34,35). Tumor cells often rely on glutamine metabolism to provide biosynthetic precursors, energy supply and maintenance of intracellular homeostasis for their rapid proliferation. The enhanced glutamine metabolism in tumor cells leads to increased ammonia release, which activates autophagy in adjacent cancer-associated fibroblasts and promotes the release of intracellular glutamine. This released glutamine can then be taken up and utilized by tumor cells to sustain their proliferative demands (36).

Early activated T cells require glutamine metabolism to initiate proliferation and immune responses. However, glutamine deficiency directly suppresses nucleotide synthesis and glutathione production necessary for early T-cell activation, leading to proliferation arrest and functional exhaustion of T cells (37). Furthermore, ammonia and α-KG produced by tumor cells can remodel the pH and metabolite profile of the TME, further inhibiting the function of $CD8^+$ effector T (Teff) and T helper (Th)1 cells, while promoting the polarization of regulatory T (Treg) cells and M2 macrophages (38). The dependence on glutamine metabolism varies markedly among already differentiated T-cell subsets. Th17 cells maintain a high level of glutamine metabolism, and their differentiation and effector functions are entirely dependent on glutaminolysis catalyzed by GLS; notably, inhibition of GLS rapidly impairs their proliferation and effector capacity. By contrast, Th1 and $CD8^+$ Teff cells gradually reduce their reliance on glutamine metabolism during later stages of activation, shifting toward

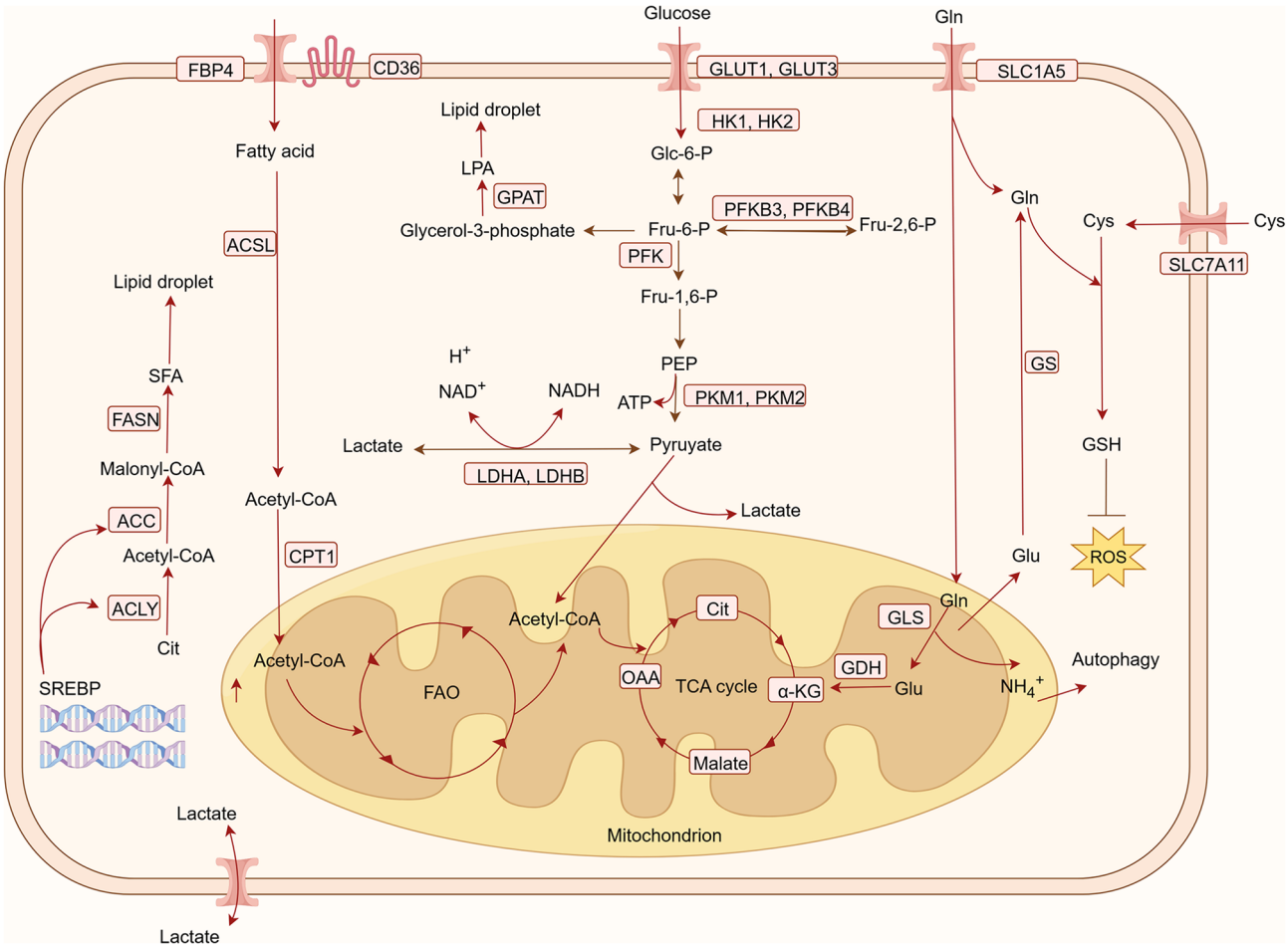

Figure 1. Overview of metabolic pathways associated with colorectal cancer cells. Schematic diagram of the major metabolic pathways contributing to malignant transformation and the corresponding metabolic checkpoints. Metabolic enzymes implicated in tumor initiation and growth are highlighted with red boxes. Created with Figdraw.com. α-KG, α-ketoglutarate; ACC, acetyl-CoA carboxylase; ACSL, acyl-CoA synthetase long-chain family member; ACLY, ATP citrate lyase; ATP, adenosine triphosphate; Cit, citrate; CPT1, carnitine palmitoyltransferase 1; Cys, cystine; FABP4, fatty acid-binding protein 4; FAO, fatty acid oxidation; FASN, fatty vacid synthase; Fru-6-P, fructose-6-phosphate; GDH, glutamate dehydrogenase; Glc-6-P, glucose-6-phosphate; Gln, glutamine; Glu, glutamate; GLS, glutaminase; GLUT, glucose transporter; GPAT, glycerol-3-phosphate acyltransferase; GS, glutamine synthetase; GSH, glutathione; HK, hexokinase; LDH, lactate dehydrogenase; LPA, lysophosphatidic acid; OAA, oxaloacetate; PEP, phosphoenolpyruvate; PFK, phosphofructokinase; PFKFB, 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase; PKM, pyruvate kinase M; ROS, reactive oxygen species; SLC1A5, solute carrier family 1 member 5; SLC7A11, solute carrier family 7 member 11; SFA, saturated fatty acid; SREBP, sterol regulatory element-binding protein; TCA, tricarboxylic acid.

FAO as the primary energy source. At this stage, inhibiting GLS does not impair their function; instead, it enhances their antitumor effects through epigenetic regulation (39). Thus, the bidirectional nature of glutamine modulation demonstrates that the timing and target of intervention are critical determinants of therapeutic efficacy.

Lipid metabolism. Alterations in lipid metabolism serve a crucial role in the occurrence and development of tumors, and are an important characteristic of CRC. Lipid metabolism provides the necessary ATP and macromolecules for tumor growth, division and survival, and disordered lipid metabolic is a typical feature of CRC, with the most notable alteration being increased *de novo* lipogenesis and subsequent massive intracellular accumulation of lipids in the form of lipid droplets (40).

Different T-cell subsets exhibit distinct lipid metabolic demands, leading to notable divergence in their sensitivity and response direction to lipid dysregulation within the TME. In the early activation phase, $CD8^+$ Teff cells rely on *de novo* fatty acid synthesis to construct new cell membranes to meet proliferation needs; however, upon entering the TME, abnormal activation of acetyl-CoA carboxylase (ACC) and CD36-mediated uptake of oxidized lipids result in substantial lipid accumulation within T cells (40,41). Concurrently, the FAO pathway in $CD8^+$ Teff cells is markedly suppressed and the large quantities of toxic lipids taken up via CD36 can damage mitochondria (41). Th17 cells depend on *de novo* fatty acid synthesis and glycolysis; enhanced FAO within the TME inhibits their differentiation, whereas lipid peroxidation directly impairs their effector functions (42,43). Increased fatty acid content in the TME favors the generation of Treg cells, which rely on exogenous fatty acid uptake to exert their immunosuppressive functions (44). Based on these mechanisms, combined strategies targeting tumor metabolic sensitization and T-cell immune enhancement can be designed to precisely reverse T-cell lipid metabolic disorders.

The efficacy of T cells in CRC is influenced by metabolic competition and the metabolic microenvironment of CRC. Theoretically, altering the competitive advantage of CRC tumor

cells for nutrients, reducing the production of immunosuppressive substances and modifying the metabolic adaptability of T cells themselves could all enhance the efficacy of T cells in CRC.

3. Modulation of tumor metabolism

Inhibition of tumor cell glycolysis. Nutrient competition within the TME, particularly glucose scarcity, is a key factor impairing T-cell function (29). Therefore, targeting the aberrantly active glycolytic pathway in tumor cells to undermine their metabolic advantage has emerged as a core strategy for enhancing T-cell effector functions (45). This strategy primarily focuses on two aspects: Inhibiting glucose transporters (GLUTs) and key metabolic enzymes (46). GLUT1 is a major GLUT that serves a crucial role in cancer cells; it not only facilitates the uptake of large amounts of glucose to meet the energy demands of rapid proliferation but also protects cancer cells from oxidative stress induced by glucose deprivation, thereby enhancing their anti-apoptotic capacity (47). In CRC, upregulation of GLUT1 is strongly associated with poor patient prognosis (47). It has been demonstrated that the expression of Hes family BHLH transcription factor 1 (HES1) is markedly higher in CRC tissues compared with that in adjacent normal tissues (48), and HES1 promotes CRC progression by enhancing the stability of modified GLUT1 mRNA in an IGF2BP2-dependent manner. By contrast, knockdown of HES1 reduces aerobic glycolysis activity and inhibits tumorigenicity in CRC (49,50). Other research has revealed that the upregulation of TANK-binding kinase 1 (TBK1) in CRC is associated with disease progression. TBK1-mediated inhibition of mTOR complex (mTORC)1 induces intracellular autophagy, subsequently reducing GLUT1 degradation; this adaptive signaling cascade between TBK1 and GLUT1 provides a novel strategic avenue for CRC treatment (51). Beyond modulating gene expression to inhibit GLUT1 activity, GLUT1 inhibitors can also be employed. A recent study showed that the GLUT1 inhibitor BAY-876 can suppress CRC cell growth in both *in vivo* and *ex vivo* experiments. Its primary mechanism of action involves reducing glycolysis, thus forcing tumor cells to rely on oxidative phosphorylation for ATP production. This leads to enhanced mitochondrial respiration, reactive oxygen species (ROS) accumulation, and ultimately, apoptosis (52).

Alterations in metabolic enzymes can directly influence the glycolytic capacity of tumor cells. Current research has identified key rate-limiting enzymes in the aerobic glycolysis of tumor cells, such as hexokinase 2 (HK2), pyruvate kinase (PK), lactate dehydrogenase A (LDHA) and phosphofructokinase-1 (PFK1), as potential therapeutic targets for regulating tumor growth (53,54). The first step of glycolysis is catalyzed by HK2, the expression of which is markedly elevated in CRC. Notably, targeted inhibition of HK2 can reduce the level of glycolysis in CRC cells (55). PK is another critical glycolytic enzyme that is highly expressed in colon cancer. Changes in the PKM1/PKM2 ratio may alter glucose metabolism; specifically, a decrease in PKM1 expression coupled with an increase in PKM2 can induce the Warburg effect, thereby promoting tumor proliferation (56,57). Therefore, targeting PK expression may be an effective strategy for modulating tumor glycolysis. LDHA primarily acts in the final step of the glycolytic pathway, catalyzing the conversion of pyruvate to lactate.

A recent study, through extensive examination of 40 pan-cancer single-cell RNA sequencing cohorts, established a novel lactate metabolism-related signature, demonstrating that LDHA is a rational therapeutic target across different cancer types and represents a promising treatment strategy to enhance antitumor immune responses (58). In CRC, regenerating family member 1α (REG1α) is highly expressed and closely associated with poor prognosis. REG1α can exert its pro-tumorigenic function by inducing aerobic glycolysis in cancer cells via the β-catenin/MYC proto-oncogene/LDHA axis. The use of MYC proto-oncogene inhibitors and LDHA inhibitors can suppress the REG1α-induced increase in glycolysis, providing a basis for investigating feasible treatment plans for CRC (59).

PFK1 serves a crucial role in the conversion of fructose-6-phosphate to fructose-1,6-bisphosphate during glycolysis. Among the PFK1 family, 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3 (PFKFB3) exhibits the strongest activity and is the most important phosphokinase in the glycolytic process (60). PFKFB3 is highly expressed in CRC, and is associated with disease progression and poor prognosis (61). It has been shown that PFKFB3 is associated with the tumor immunosuppressive microenvironment and is related to the IL-2/STAT5 signaling pathway (62). Previous research has indicated that the IL-2/STAT5 pathway is essential for maintaining the homeostasis and migration of Treg cells and the exhaustion of $CD8^+$ T cells (63,64). Consequently, combining PFKFB3 inhibitors with immunotherapy holds promise for improving the response rate and prolonging overall survival in patients with CRC subjected to immunotherapy (62).

Regulation of glutamine metabolism. In tumor cells, glutamine metabolism is involved in the biosynthesis of precursors, maintains redox homeostasis and provides energy, thereby promoting cell proliferation, migration and invasion. Enzymes related to glutamine metabolism, such as GLS1/2 (65), glutamine synthetase (GS) (66), GDH (67) and transglutaminase (TG) (65), as well as protein transporters involved in glutamine transport, such as SLC1A5, solute carrier family 38 member 2 (SLC38A2) and solute carrier family 38 member 3, have regulatory roles in the TME. GLS is a mitochondrial enzyme, divided into two subtypes, GLS1 and GLS2. GLS1 exhibits high activity in CRC and is positively associated with tumor progression (68). The use of GLS inhibitors, such as BPTES and CB-839, to attenuate GLS1 expression activity in tumors can markedly inhibit tumor cell migration (69,70). In contrast to GLS1, GLS2 is generally considered a tumor suppressor in most contexts, with lower expression and activity in tumors; in addition, its expression level is negatively associated with tumor progression (71). GS catalyzes the intracellular synthesis of glutamine from glutamate and free ammonia, meeting the demands of rapidly proliferating tumor cells by intracellularly synthesizing glutamine (72). A decrease in GS activity can mediate the phenotypic transformation of tumor-associated macrophages and inhibit tumor metastasis (73). GDH catalyzes the conversion of glutamate to α-KG, which enters the TCA cycle to participate in energy supply and

biosynthesis. High expression of GDH is closely associated with clinical prognosis; GDH can promote CRC cell migration via STAT3-mediated epithelial-mesenchymal transition (EMT) and may serve as a prognostic marker for CRC metastasis (74). TG catalyzes the hydrolysis of glutamine residues within proteins or polypeptide chains and the exchange of amide groups with other amino groups. It has been reported that TG2 expression is higher in the metastatic colon cancer cell line SW620 than in primary colon cancer cell lines, and is associated with EMT progression (75). Subsequently, the developed selective small-molecule active-site-directed inhibitor of TG2, 1-155, has been shown to attenuate the ability of TG2 to induce EMT (76).

Glutamine transporters are located on the cell membrane, facilitating the uptake of sufficient glutamine from the external environment by tumor cells to meet their growth and metabolic demands. SLC1A5, also known as alanine-serine-cysteine transporter 2, is a transporter for glutamine, serine and cysteine, belonging to the sodium-dependent neutral amino acid transporter family (77). SLC1A5 has high affinity for glutamine and particularly promotes glutamine transport in tumor cells under acidic conditions (78). SLC1A5 is highly expressed in CRC, and targeted intervention using V-9302 can effectively inhibit CRC growth *in vitro* and in murine models *in vivo* (79). Solute carrier family 6 member 14 (SLC6A14) serves a crucial role in maintaining amino acid transport and cellular metabolic balance. Its primary function is to promote the unidirectional influx of amino acids such as glutamate (80,81). High expression of SLC6A14 is closely associated with metastasis and poor prognosis in patients with CRC (82). α-methyltryptophan (α-MT) is a tryptophan metabolism inhibitor and tryptophan is a substrate of SLC6A14. α-MT can inhibit the proliferation of SLC6A14-positive CRC cells but has minimal effect on SLC6A14-negative cells (83). Furthermore, compared with in primary tumors, SLC38A2 is highly expressed in metastatic CRC tissues, and the absence of SLC38A2 is beneficial for inhibiting tumor progression (84). The amino acid antiporter SLC7A5 is also crucial for tumor metastasis and development in advanced CRC; the absence of SLC7A5 can notably prolong the survival of model mice and reduce tumor metastasis (85).

Regulation of lipid metabolism. Lipid metabolic reprogramming in the TME increases the nutrient supply for tumor cells. In CRC, lipid metabolism mainly involves changes in several key genes and metabolic enzymes, including sterol regulatory element-binding proteins (SREBPs), ATP citrate lyase (ACLY) and adipose triglyceride lipase (ATGL). SREBPs are crucial transcription factors in lipid metabolism; the activation of SREBPs and their target genes, such as fatty acid synthase (FASN) and stearoyl-CoA desaturase, markedly alters cellular metabolic pathways. Knockdown of SREBP-1 or SREBP-2 in CRC cell lines leads to reduced cell numbers, decreased proliferation rates and diminished capacity to form tumor spheroids (86,87). Therefore, targeting SREBP-1 and SREBP-2 serves an important role in lipid metabolism-mediated tumor proliferation in CRC. A previous study revealed that ACLY knockdown results in a notable decrease in SREBP-1 levels in LoVo cells, leading to increased apoptosis rates. Furthermore, the apoptosis rate in cells with SREBP-1 knockdown has been shown to be higher than that in the ACLY knockdown group (88).

ACLY, the first rate-limiting enzyme in fatty acid synthesis, is associated with the metastatic potential of CRC. Knockdown of ACLY reduces the activity of β-catenin, inhibits its transcriptional activity, and consequently decreases the migration and invasion of CRC cells (89). It has been reported that zinc finger DHHC-type palmitoyltransferase 6, a palmitoyltransferase regulating fatty acid synthesis, directly palmitoylates and stabilizes peroxisome proliferator-activated receptor (PPAR)γ. This stabilization, in turn, activates ACLY transcription-related metabolic pathways, stimulates fatty acid production and is associated with CRC severity (90). Carnitine palmitoyltransferase 1A (CPT1A) is highly expressed in CRC. High CPT1A expression enhances FAO, promotes high survival rates of CRC cells and facilitates metastasis. Notably, CPT1A is not only associated with FAO activation but also interacts with the B-cell lymphoma 2 family, directly influencing metastasis (91-93). Furthermore, it has been demonstrated that ATGL is highly expressed in CRC; upregulation of ATGL promotes CRC cell proliferation and is negatively associated with patient survival (94). Glycerol-3-phosphate acyltransferase 3 (GPAT3) has been reported to promote lipid droplet generation and confer chemoresistance in CRC. Following oxaliplatin treatment, high GPAT3 expression transforms CRC cells into non-immunogenic cells, attributed to reduced cytotoxic interferon-γ release and $CD8^+$ T-cell exhaustion (95).

The fatty acid-binding protein (FABP) family serves an important role in lipid metabolism in CRC. A previous study indicated that FABP6 expression is negatively associated with immune infiltration in CRC; knockdown of FABP6 increases the expression of major histocompatibility complex class I molecules and promotes the secretion of immune-related chemoattractants, suggesting enhanced immunogenicity of tumor cells (96). Upregulation of FABP4 promotes phosphorylated AKT expression to facilitate the EMT process, thereby enhancing CRC migration and invasion. Conversely, the FABP4 inhibitor BMS309403 yields opposite effects (97,98). FABP5, a transporter involved in fatty acid uptake, increases CRC cell numbers in a manner independent of the PPARβ/PPARδ signaling pathway (99). FASN is responsible for converting acetyl-CoA and malonyl-CoA into long-chain fatty acids (such as palmitic acid), and high FASN expression is negatively associated with CRC survival. Utilizing FASN inhibitors, such as cerulenin, TVB-3166, TVB-3664 and TVB-369380, can modulate the AKT and adenosine 5'-monophosphate-activated protein kinase (AMPK) pathways to inhibit CRC progression, although treatment safety must be considered (100,101). Furthermore, FASN drives cancer cell proliferation, metastasis and phosphatidylcholine metabolism via the specificity protein 1/phospholipase A2 group IVB axis. Knockdown of FASN can markedly inhibit tumor growth and the spread of CRC cells to the lungs (102). Alterations in lipid metabolism have become a key driving factor in the progression of CRC, involving multiple key molecules as aforementioned. Targeting these key genes or alterations in critical metabolic enzymes can induce apoptosis and reduce invasive capacity, with value as therapeutic targets for CRC.

4. T-cell metabolism

T cells are key components of the immune system and their metabolic status influences their functional performance (103,104). T cells in different states, such as naïve T (Tn), Teff, memory T (Tm) and exhausted T (Tex) cells, each possess distinct metabolic requirements. Tn cells exhibit a relatively low metabolic rate, primarily relying on low-level oxidative phosphorylation fueled by glucose-derived pyruvate or fatty acids to meet their energy demands (105). Upon activation of the T-cell receptor (TCR) in Tn cells, concomitant co-stimulatory signals received by receptors such as CD28 enhance TCR signaling. This triggers metabolic changes to support the anabolic processes necessary for cell proliferation and the differentiation of Teff cells, thereby enhancing effector functions (106-108). Following activation through interactions with antigens, receptors, co-stimulatory ligands and cytokine signaling, Teff cells enter a metabolically active state characterized by increased glycolytic and oxidative phosphorylation activity. They predominantly utilize aerobic glycolysis to provide energy for their rapid proliferation and functional execution (109,110). If the antigen is cleared, Teff cells can transition into a long-lived memory state with stem cell-like properties. Their metabolic profile reverts to a less active state, primarily depending on FAO and oxidative phosphorylation pathways to sustain long-term cellular survival and energy needs. Upon re-encountering their cognate antigen, Tm cells mount a rapid response, swiftly reactivating aerobic glycolysis to facilitate robust effector function and proliferation (111). In cases of persistent antigen exposure, inhibitory receptors such as PD-1 and CTLA-4, can remodel T-cell metabolism, leading to the transition of T cells towards an exhausted state. Tex cells exhibit reduced glucose and glutamine metabolism, dysfunctional mitochondria and an increased reliance on FAO (112,113). Within the TME, there exists a complex metabolic network with interactions; tumor cells engage in almost parasitic competition for nutrients and the metabolism of T cells also interacts with each other. Through regulating the metabolism of T cells, it may be possible to enhance their antitumor ability (Fig. 2).

5. Targeting T-cell metabolism

Regulating glycolysis in T cells. Fine-tuning the glycolytic pathway within T cells themselves can optimize their differentiation fate and functional state. mTOR is a shared serine/threonine kinase that exists in two distinct complexes, mTORC1 and mTORC2. Of these, mTORC1 acts as a sensor for nutrients in the microenvironment, capable of perceiving cellular nutrient status and specific needs to coordinate cellular functions, serving as a classic metabolic checkpoint molecule (114,115). Studies have shown that mTORC1 can promote glycolysis by upregulating the expression of GLUT1, GLUT3 and LDHA through upregulating hypoxia-inducible factor-1α expression in $CD8^+$ T cells, thereby promoting their effector functions (116,117). Inhibition of mTORC1 with rapamycin reduces the overall glycolytic flux in $CD8^+$ T cells, thereby increasing memory phenotype differentiation and enhancing antitumor capacity (118).

Genetic editing techniques or small-molecule inhibitors can be employed to intervene in the expression or activity of specific proteins. For example, CD38 is a single-chain transmembrane glycoprotein; knockdown of the CD38 gene or the use of small-molecule inhibitors targeting CD38 enzymatic activity can inhibit glycolysis by downregulating the CD38-cyclic adenosine diphosphate ribose-calcium ion signaling pathway and activating the CD38/nicotinamide adenine dinucleotide/sirtuin 1 axis. This, in turn, promotes memory phenotype differentiation in CAR-T cells and enhances their *in vivo* antitumor capacity and persistence (119). Mitochondrial isocitrate dehydrogenase 2 primarily mediates oxidative decarboxylation reactions. Inhibition of this enzyme in CAR-T cells with the clinical drug enasidenib shifts cellular metabolism from glycolysis to the pentose phosphate pathway, reduces ROS levels, and enhances the persistence and antitumor function of CAR-T cells (120). Suppressing overactive glycolysis can promote the formation of memory-like T cells and enhance their persistence *in vivo*. Conversely, during stages requiring rapid expansion and potent cytotoxic activity, timely promotion of glycolysis in CAR-T cells may be beneficial. This indicates that metabolic regulation of CAR-T cells to meet the functional requirements at different stages is the key to enhancing their therapeutic efficacy.

Modulation of FAO in T cells. The uptake of lipids from the TME is crucial for sustaining the effector function of $CD8^+$ T cells, as tumor cells are often deficient in glucose as an energy source. To adapt to the TME, $CD8^+$ T cells upregulate lipid transporters to acquire lipids as an energy source under nutrient stress, leading to excessive lipid accumulation within these cells, which contributes to their dysfunction and exhaustion (121). Most tumor-infiltrating lymphocytes exhibit suppressed mitochondrial biogenesis and a limited capacity to utilize FAO, further inhibiting T-cell effector function (122). Therefore, regulating T-cell lipid transporters to reduce excessive intracellular lipid accumulation may be an effective strategy to enhance the antitumor capacity of T cells.

CD36, a scavenger receptor responsible for transporting fatty acids and oxidized lipids, is highly expressed in tumor-infiltrating $CD8^+$ T cells and impairs their function (123). Knockout of the CD36 gene in $CD8^+$ T cells has been shown to markedly inhibit tumor growth in CRC (41,124). Notably, anti-CD36 blocking antibodies can also target metastasis-initiating cells, inhibiting metastasis in both immunodeficient and immunocompetent mouse models without marked side effects (125). Consequently, CD36 represents a promising drug target, and the development of novel CD36 inhibitors, particularly in combination with CAR-T therapy, holds potential for advancing cancer therapies. Tumor-infiltrating $CD8^+$ T cells exhibit increased lipid storage due to elevated ACC activity. Restriction of ACC activity can reprogram T-cell metabolism, enhance survival and polyfunctionality, and suppress tumor growth (126). FASN, a critical enzyme in fatty acid synthesis, serves a marked role in the function and survival of memory $CD8^+$ T cells. These cells rely on fatty acid synthesis to achieve long-term persistence, and inhibition of FASN leads to decreased survival of memory $CD8^+$ T cells, whereas effector $CD8^+$ T cells remain largely unaffected (127). However, the specific role of FASN in tumor-infiltrating $CD8^+$

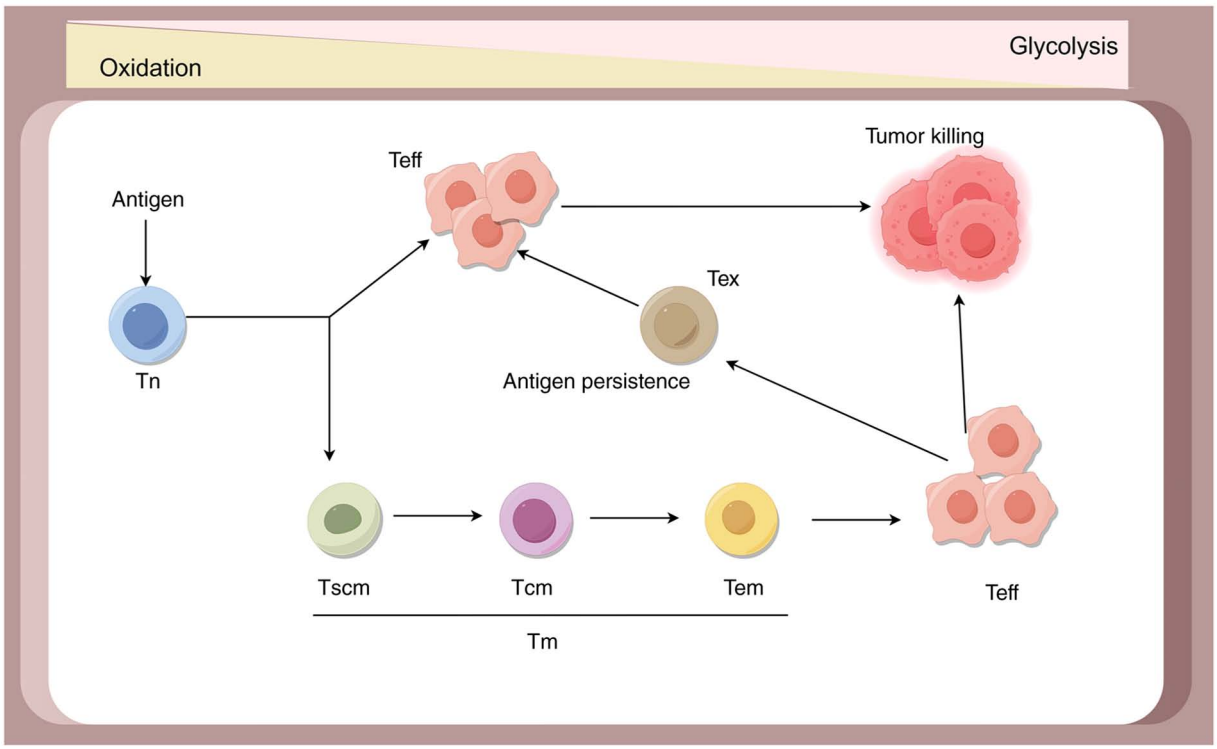

Figure 2. Differentiation and functional evolution of Tn cells upon antigen stimulation. Following antigen stimulation, Tn cells undergo proliferation and expansion, differentiating into Teff cells that kill tumor cells. The persistent presence of tumor cells can drive the conversion of Teff cells into Tex cells. Created with Figdraw.com. Tn, naïve T; Tscm, stem cell-like memory T; Tcm, central memory T; Tem, effector memory T; Teff, effector T cells; Tex, exhausted T cells.

T cells remains unclear, and further investigation is required to determine its impact on antitumor function.

In summary, in the TME, the continuous nutritional stimulation of $CD8^+$ T cells may lead to the excessive accumulation of lipids within the cells, which in turn causes cellular dysfunction and exhaustion. Therefore, targeting lipid transport proteins to reduce the accumulation of harmful lipids may be an effective strategy for restoring and enhancing the antitumor efficacy of T cells.

Engineering T-cell metabolism via CAR molecular design. During the *ex vivo* activation and expansion of T cells, precise control can be achieved through engineering, enabling targeted intervention in T cells without affecting tumor cells or other normal tissue cells (128). By incorporating specific signaling transduction domains or functional domains of special structural proteins into the CAR construct, CAR-T cells with enhanced effector functions or greater persistence as memory-type CAR-T cells can be generated (129,130). For example, CD28 and 4-1BB signaling domains are introduced into the CAR structure to optimize the therapeutic efficacy of CAR-T therapy. The incorporation of the 4-1BB domain promotes the differentiation of T central memory cells, markedly enhancing cellular respiratory capacity, FAO and mitochondrial biogenesis levels (131). By contrast, CAR-T cells harboring the CD28 domain tend to differentiate more towards T effector memory cells with enhanced glycolytic capacity (107). This phenomenon aligns with the downstream signaling pathways of these two co-stimulatory molecules: 4-1BB activates AMPK, promoting FAO and mitochondrial biogenesis, whereas CD28 typically promotes glycolysis by activating the PI3K/AKT/mTORC1 pathway and modulating mitochondrial morphology and function. This strategy of prospectively optimizing T-cell metabolism through molecular design represents a key direction for improving the antitumor efficacy of CAR-T therapy.

6. Discussion

The present review systematically elucidates the complex mechanisms underlying the interplay between immunity and metabolism in CRC. Tumor cells actively shape an immunosuppressive TME through metabolic reprogramming, thereby compromising the efficacy of T-cell therapy. Through an in-depth analysis of these mechanisms, it may be hypothesized that dual breakthroughs are required at the fundamental conceptual and technical levels.

While traditional research has predominantly focused on the roles of cytokines and immune checkpoint molecules within the TME, the current review highlights the pivotal role of metabolic regulation in fostering immunosuppression (22,23,132). The interaction between tumor cells and T cells extends beyond competition for physical space and signaling pathways to encompass the regulation of nutrient acquisition and metabolic pathways. Lactate, the end product of glycolysis, not only contributes to an acidic milieu but can also directly regulate the expression of immune-related genes (such as Foxp3) by inducing histone lactylation, thereby stabilizing the functional state of immunosuppressive cells, such as Treg cells (31,32). Conversely, aberrant lipid metabolism leads

to the accumulation of oxidized lipids within the TME, which can directly impair mitochondrial function in $CD8^+$ T cells and promote the development of an exhausted phenotype (41,124). Consequently, effective therapeutic strategies must address two key aspects: Improving nutrient availability within the TME and actively clearing or neutralizing these bioactive immunosuppressive metabolites.

Notable metabolic heterogeneity exists among patients with CRC, forming a crucial basis for differential therapeutic responses (4,24). For example, intervention strategies targeting glutamine metabolism are effective only in tumors with high GLS1 expression (68,69), showing limited efficacy against tumor subtypes with metabolic compensation mechanisms and potentially affecting normal T-cell function, which also relies on glutamine (39,133). Therefore, future clinical practice necessitates the establishment of a patient stratification system based on metabolic profiles. By integrating metabolic imaging techniques with single-cell metabolomic analyses (4,134,135), the metabolic landscape of a patient can be systematically assessed prior to treatment, facilitating the development of individualized combination strategies. The precise identification of tumor-specific metabolic dependencies is a prerequisite for achieving precision immunometabolic therapy.

A reason for the limited functionality of current T cells within the TME is their insufficient metabolic adaptability (29,136). Future technological developments should focus on enhancing the metabolic adaptability of CAR-T cells, improving metabolic plasticity, regulating key metabolic regulatory factors through genetic engineering, or introducing heterologous metabolic enzymes to enable CAR-T cells to utilize multiple energy substrates and adapt to nutrient-limited conditions within the TME (17,131). The construction of metabolic resistance can be achieved by utilizing gene editing technologies to knock out specific receptors, thereby reducing the sensitivity of CAR-T cells to inhibitory metabolic signals within the TME (121,122,137). Furthermore, by using exogenous small molecules to regulate metabolic pathways, researchers can precisely control when and where the CAR-T cells change their metabolic state. For example, glycolytic capacity can be enhanced during the expansion phase, whereas a shift toward oxidative phosphorylation can be promoted during the effector phase to facilitate the formation and maintenance of memory subsets (107,131).

The simple combination of metabolic modulators with T cells is unlikely to achieve optimal synergistic effects (54,72). A sequential treatment strategy is therefore proposed: Prior to T-cell infusion, the TME could be pre-conditioned with metabolic modulators to improve the metabolic milieu; following CAR-T cell infusion, a metabolic support regimen centered on sustaining T-cell function could be implemented (62,72). Furthermore, the combined application of metabolic interventions with epigenetic regulators may induce a deeper synergistic antitumor effect by remodeling the transcriptional states of both tumor and immune cells (73,103).

7. Conclusion and prospects

The application bottleneck of T-cell therapy in CRC is fundamentally a problem of mismatch between therapeutic cells and the metabolic characteristics of the TME. The solution should shift from mere targeted killing to the systemic remodeling of the TME and the precise optimization of the metabolic functions of CAR-T cells. This necessitates the establishment of a patient stratification system based on multi-omics analysis and the development of next-generation CAR-T cells with metabolic adaptability. This research direction represents a notable developmental trend in cancer immunotherapy, namely immunometabolic precision therapy aimed at breaking metabolic constraints. Its advancement will provide a novel breakthrough pathway for the treatment of solid tumors such as CRC.

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Authors' contributions

QY contributed to conceptualization, project administration, writing the original draft, reviewing and editing. PL contributed to investigation, supervision, reviewing and editing. JL contributed to investigation, reviewing and editing. LW contributed to conceptualization, supervision, reviewing and editing. Data authentication is not applicable. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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