CAR-T-КЛЕТКИ И МЕТАБОЛИЧЕСКОЕ ПРОГРАММИРОВАНИЕ: ОБЗОР ЛИТЕРАТУРЫ

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Резюме. Терапия с применением Т-лимфоцитов с химерным антигенным рецептором (CAR-T-клетки) стала перспективным методом лечения онкогематологических заболеваний. Хотя она является успешной при системных злокачественных заболеваниях, остаются нерешенными крупные проблемы, которые надо решать для ее более широкого использования. Чтобы преодолеть эти препятствия, следует учитывать метаболические изменения, возникающие при изготовлении CAR-T-клеток, что влияет на их терапевтическую эффективность и специфичность. Поэтому продукция CAR-T-клеток с манипуляцией их метаболических путей могла бы существенно повысить их противоопухолевый иммунный ответ. В настоящем обзоре мы обобщаем последние достижения и новые стратегии, разработанные для улучшения метаболического соответствия и противоопухолевой активности CAR-T-клеточных продуктов.

Ключевые слова: рак, CAR-T-клетки, метаболизм Т-лимфоцитов, метаболическое репрограммирование

CAR T CELLS AND METABOLIC PROGRAMMING: A REVIEW

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Abstract. Chimeric antigen receptor (CAR) T cell therapy shown a promising treatment for haematological malignancies. Although it has successful achievement in hematological malignancies, there are major challenges

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that remain to be resolved to the broad application. To overcome these obstacles, changes in metabolism during the preparation of CAR T cells increase their therapeutic specificity and potency. Therefore, generation of CAR T cells with manipulated metabolic pathways could beneficially enhance antitumor immunity. Here in this review we summarize the latest advances and new strategies that have been developed to improve the metabolic fitness and antitumor activity of CAR T cells products.

Keywords: cancer, Chimeric Antigen Receptor T cells, T cell metabolism, metabolic reprogramming

Introduction

Immunotherapeutic interventions represent a groundbreaking approach in cancer treatment, significantly enhancing the immune system's inherent capabilities to combat the disease [1]. Immunotherapy through adoptive cell therapy can now lead to promising remissions. Among these, chimeric antigen receptor (CAR) T cell therapy, a form of adoptive cell therapy (ACT), has emerged as a particularly effective strategy [2, 4]. The CAR construct is a sophisticated protein design, comprising a fusion of two distinct elements: an extracellular antibody fragment, known as single-chain variable fragment (scFv), which is specific to tumor antigens, and the signaling domains derived from T cells [1, 3, 4, 6]. Chimeric antigen receptor (CAR) T cells are genetically modified to express CAR, enabling them to identify and bind to specific antigens via the single-chain variable fragment (scFv) domain. This interaction triggers T cell activation, bypassing the conventional requirement for major histocompatibility complex (MHC) molecules [9]. Despite the ability of cancerous cells to evade immune surveillance by downregulating HLA or antigen-presenting molecules, CAR T cell therapy offers a unique advantage. This approach enables the engineered T cells to identify and bind to target cell surface molecules, independent of the MHC complex [7, 10, 11]. The unique characteristics of CAR T cells, including their ability to recognize various surface antigens, have established their significance in cancer immunotherapy, leading to their approval as a viable treatment option [17].

Despite the notable success of adoptive CAR T cell therapy in managing hematological malignancies, its effectiveness in treating solid tumors remains a subject of debate within the medical community [13]. Solid tumors present unique challenges for CAR T cell therapy, primarily due to antigen heterogeneity, which hinders the precise targeting of tumor cells. This is in contrast to hematological tumors, where CAR T cells can effectively identify and eliminate cancerous cells. The physical barrier of the vascular endothelium further complicates treatment, preventing CAR T cells from infiltrating solid tumor tissue. Additionally, the presence of various immunosuppressive cell types within the tumor microenvironment, such as myeloid-derived suppressor cells (MDSCs), M2 tumor-associated macrophages (TAMs), and regulatory T cells (Tregs), contributes to the complexity. These cells promote angiogenesis, metastasis, and tumor growth, creating an inhibitory milieu that limits the efficacy of CAR T cell therapy in solid tumors [8, 14, 16, 91]. Nonetheless there are efforts to improve the function of these cells [12]. One ongoing activity focuses on metabolic reprogramming of CAR T cells in various ways [15]. The modulation of metabolic pathways, including oxidative phosphorylation and glycolysis, has the potential to influence the behavior and persistence of CAR T cells within tumor microenvironments [30]. The engineering of CAR T cells with specialized attributes, including those resembling early-memory cells, holds potential for boosting the immune system's response against tumors [12, 20].

CAR T manufacturing method are including several steps: (1) taking peripheral blood mononuclear cells (PBMCs) of patient; (2) T cells enrichment; (3) T cell activation and expansion; (4) CAR transduction into T cells; (5) CAR T cells expansion; (6) infusion into patient (Figure 1). Autologous CAR T cell therapy, derived from a patient's own T lymphocytes, is the current standard. However, an innovative approach, known as universal CAR T (UCAR T) cell therapy, utilizes allogeneic CAR T cells sourced from healthy donors. While both therapies share a common cytotoxic mechanism and metabolic profile, they differ significantly in terms of safety, production methods, and associated costs [21]. In this review, we briefly discuss studies on the manipulation of metabolic pathways in some mentioned steps for improving CAR T cell therapy.

The role of the tumour microenvironment (TME) on immune cell function

One of the suppression mechanisms in TME is metabolic suppression. The microenvironment agents and tumour cells can alter immune cell function by altering their metabolic state and displaying reprogrammed metabolism for modulation of antitumor immunity [26, 27].

The characteristics of tumour cells exhibit variation based on their specific location. Within the tumour mass, reduced vascularization significantly lowers oxygen availability, thereby compelling cells to adopt alternative mechanisms for proliferation and survival, deviating from the typical oxidative process [24]. Within a low-oxygen environment, the diminished synthesis of ATP triggers an enhanced absorption of glucose, which remains unconverted into acetyl-

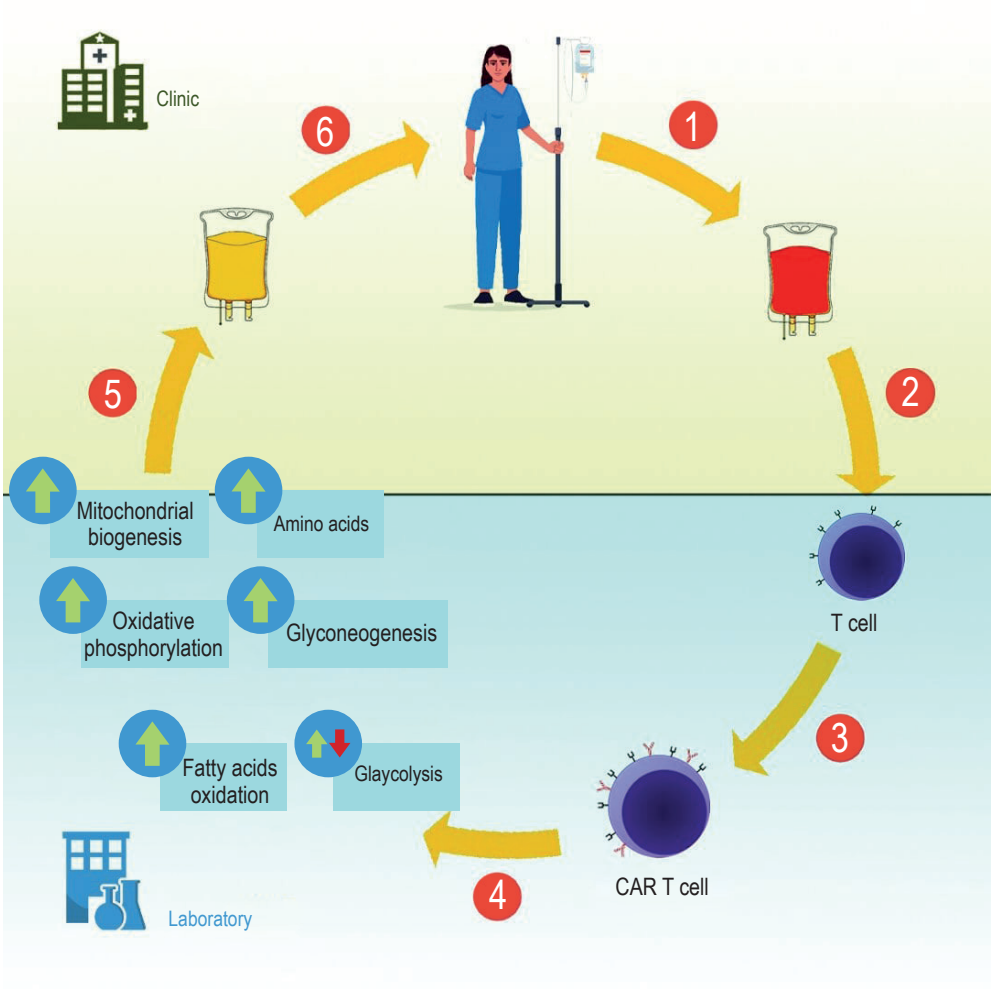

Figure 1. Schematic diagram of manipulation of metabolic pathway of CAR T cells

CoA. This surplus of glucose initiates a metabolic alteration, yielding pyruvate and subsequently lactic acid. Consequently, the shift from oxidative metabolism to lactic acid production induces an acidic transformation within the tumor [25]. Both of these events, hypoxia and acidification, are linked and enhance molecular changes capable of increasing acidosis endurance, promoting tumour growth, evolution, and metastasis, and increasing pharmacological treatment resistance [18, 22].

As well as using similar metabolism pathways and nutrients by immune and tumour cells, they create a competition that leads to cancer cell survival [19, 21, 27] effector T cell functionality occurs, leading to the disruption of memory T cell sub-populations. This decline results in the differentiation of these effector cells into a state characterized by reduced activity, termed T cell exhaustion [28, 29]. T cell exhaustion represents a condition where T cells exhibit diminished functionality, including reduced proliferation, cytokine production, and cytotoxicity. This impairment is associated with increased expression of inhibitory molecules LAG-3, PD-1, TIM-3, and CTLA-4, which collectively hinder T cell activity. Exhausted T cells also display altered energy metabolism, with decreased ATP production, reduced mitochondrial mass, and a preference for glycolysis over oxidative phosphorylation [31, 32, 33, 35, 36, 38]. Therefore, some signals that originate from the tumour microenvironment, such as acidic pH, hypoxia, nutrient deficiency, and inhibitory factors, can change the metabolic state of immune cells, thereby making changes in immune cell response and function.

Interleukin-7 (IL-7) and IL-23 have been employed as a strategic approach to enhance the longevity and anti-tumour capabilities of CAR T cells. Research has demonstrated that IL-7, in particular, plays a crucial role in preserving the less differentiated state of CAR T cells, thereby mitigating exhaustion [34, 37].

Studies shown that longer and more elevated antitumor activity of naive and memory T cells than effector T cells [41]. Although memory T cells are dependent to fatty acid oxidation (FAO) and have a slightly higher degree of oxidative phosphorylation (OXPHOS) pathways effector cells require aerobic

glycolysis and OXPHOS for energy production [39, 40]. Suitable manipulation of metabolism pathway can maintain CAR T cells in undifferentiated stage and improve theirs antitumor activity [48].

Elevated glycolytic metabolism in T cells enhances cellular proliferation and cytokine production, notably interferon γ (IFNγ). Despite their heightened invasive capabilities, these cells exhibit a brief lifespan and fail to differentiate into memory T cells due to OXPHOS metabolism. Conversely, OXPHOS facilitates memory T cell differentiation but may constrain proliferation, migration, and cytotoxic functionality [23, 43].

The optimal CAR T cell exhibits exceptional qualities, including heightened invasive capabilities, potent cytotoxicity, and prolonged viability. Within the realm of immunotherapy, our discovery of metabolic reprogramming has significantly contributed to the enhancement of immune cell functionality [43].

Strategies to enhance CAR T cell efficacy via metabolic pathways

The role of glycolysis

Inhibiting glycolysis during T cell expansion and purification

Metabolic pathway modifications have been shown to influence the proliferation and differentiation processes of T cells in laboratory settings [48]. The manufacturing of CAR T cells *in vitro* encompasses a critical stage wherein purified T cells experience a three-day growth period, leading to a significant elevation in cell numbers. This augmentation is vital prior to their administration into patients. Cytokines, including Interleukin 2 (IL-2), IL-7, IL-15, and IL-21, are introduced into the isolated T cell culture medium, stimulating cell proliferation and enhancing glycolysis [45].

In a clinical trial study for treating patients with B cell lymphomas, PBMCs obtained by leukapheresis will be cultured in the presence of aldesleukin (recombinant IL-2) and anti-CD3 (muromonab-CD3 (OKT3)) for stimulation of T cell proliferation [49].

The binding of Interleukin-2 (IL-2) to its specific receptor, IL-2R, triggers a complex signaling network, ultimately upregulating glycolysis through the Pi3K/Akt-mediated activation of mTOR. This mechanism is pivotal for the metabolic control within T cells. Likewise, IL-7 significantly contributes to the maintenance of glycolytic processes by regulating the expression of key enzymes such as hexokinase 2 (HK2) and Glucose transporter 1 (Glut1), which are fundamental for cellular energy generation. IL-15 and IL-21 exhibit a shared function in T cells, particularly $CD8^+$ memory T cells, where they stimulate oxidative phosphorylation (OXPHOS), mitochondrial development, and fatty acid oxidation (FAO) by amplifying mTOR signaling [47].

The intricate relationship between metabolic processes and the proliferation of effector cells poses a critical consideration in designing CAR T cell therapies. The introduction of 2-Deoxy-D-glucose (2DG), a glucose derivative, has the potential to disrupt glycolytic and oxidative phosphorylation pathways by targeting the initial stages of glucose metabolism [46], and the addition of 2DG during expansion by inhibition of glycolysis promotes the formation of memory T cells [28]. As well as indirectly, can inhibit glycolysis. One of the signaling pathways is PI3K/AKT, which with continuous activation has an important role in T cell activation. Inhibitors of PI3K [44] and AKT [42] by inhibition of glycolysis lead to an increase of naive T cells, central memory T cells and $CD8^+$T cell cytotoxicity. Some memory cell transcription factors that are inhibited by the mentioned inhibitors include T cell receptor (TCR) /lymphoid enhancer factor (LEF)/-catenin, signal transducer and activator of transcription 3 (STAT3), B cell lymphoma 6, forehead box transcription factors (FOXO) and transcriptional regulators [48, 57]. AKT inhibitors also promote Th2 differentiation and memory T cells [53].

Mitochondria, as vital cellular organelles, significantly influence various cellular processes, including migration, metabolic activities, proliferation, and programmed cell death. Research has established a direct correlation between T cell differentiation and mitochondrial characteristics, encompassing mitochondrial dynamics, such as fusion and fission, and mitophagy, the cellular process of eliminating damaged mitochondria [51, 55, 58]. The specialized effector T cells exhibit heightened mitotic activity and predominantly utilize aerobic glycolysis for energy production. Conversely, naive memory T cells maintain their metabolic equilibrium through oxidative phosphorylation, resulting in a higher rate of cellular fusion [50]. T cells must be in a low differentiated state prior to CAR T cell generation. Furthermore, promoting mitochondrial fusion or inhibiting mitochondrial fission could prevent T cell differentiation and increase the OXPHOS metabolism. In addition, mitophagy increases the mitochondrial integrity that prevents the differentiation of memory T cells [54, 56]. There are some mediators which could be used to inhibit glycolysis. For example, pretreatment of cells with ser/threonine Pim kinase inhibits glycolysis and promotes the efficacy of tumour cell clearance [52].

Increase of gluconeogenesis to improve efficacy of CAR T cell

The hypothesis posits that cells enduring prolonged acidosis could potentially harness lactate for gluconeogenesis and subsequently engage it in oxidative phosphorylation (OXPHOS). This process is facilitated by the heightened activity of phosphoenolpyruvate carboxykinase 1 (PCK1), which converts oxaloacetate (OAA) to phosphoenolpyruvate

(PEP), thereby augmenting gluconeogenesis and alleviating glucose deprivation stress within the tumour microenvironment (TME). Recent studies suggest a potential mechanism for T cell adaptation in the tumour microenvironment (TME). It has been observed that T cells may utilize lactate, a byproduct of tumour cell metabolism, by upregulating the enzyme lactate dehydrogenase B chain (LDHB). This adaptation could enhance the metabolic capabilities of CAR T cells, thereby improving their effectiveness in the TME [62].

Selecting the CAR structure that inhibits glycolysis

The downstream signaling pathways of costimulatory molecules have a role in metabolic pathways. By selection of suitable costimulatory molecules for the CAR T cell design could improve their efficacy of these cells [60, 61]. Some costimulatory domains such as ICOS [64], CD28 [59], OX40 [63, 65] stimulate glycolysis by upregulating GLUT1, PDK1 and MTOR pathways. However, another costimulatory domain such as; CD137 (4-1BB) through the AMP kinase signaling pathway are favors FAO, OXPHOS and mitochondrial biogenesis that lead to increasing the number of memory T cells [71].

The CAR framework incorporates a PI3K inhibitory domain, and the application of an additional glycolytic inhibitor, specifically a PI3K inhibitor, demonstrated efficacy in halting CAR T cell maturation during a Phase I clinical study [68]. The observed phenomenon suggests a potential elevation in memory-like T cell populations, specifically those expressing $LEF1^+$, $CD27^+$, and $CCR7^+$. The PI3K/AKT/mTOR pathway's influence on cellular differentiation via glucose metabolism requires further exploration, as the specific mechanisms underlying this interaction are not yet fully understood [68, 70]. Recent studies have demonstrated the enhanced anti-tumour capabilities of CAR T cells incorporating CD28 and 4-1BB costimulatory molecules. These cells, designed to target two distinct tumour-associated antigens with a shared CD3ζ-chain, exhibit rapid effector T cell responses and prolonged survival. This longevity is attributed to their metabolic profile, which induces glycolysis while maintaining oxidative functions, crucial for the sustained performance of CAR T cells [69].

CAR T cell maintenance in an undifferentiated stage in vitro

Through metabolic engineering of CAR T cells, mimicking the processes of T cells, these cells can be sustained in a less specialized form. This can be achieved by either suppressing glycolysis with 2DG inhibitors or by blocking the PI3K/AKT/mTOR signaling pathway, resulting in an expanded population of memory CAR T cells and enhanced anti-cancer capabilities [42, 66, 71]. Moreover, mitochondria may have an essential role in CAR T cell persistence or differentiation [67]. It seems that adjusting mitochondrial membrane potential or fusion/fission shifts the metabolism into OXPHOS and inhibits glycolysis indirectly. Despite advancements in research, the specific function of mitochondrial biogenesis in modulating metabolic flexibility remains unaddressed in current literature.

The role of CAR T and tumour cell metabolism in vivo

In vitro studies have shown that inhibiting glycolysis can prolong the survival of CAR T cells. Nevertheless, *in vivo* conditions present a different scenario due to the metabolic competition between CAR T cells and tumour cells. Consequently, augmenting both glycolytic and OXPHOS metabolic pathways in CAR T cells has been found to enhance their antitumor efficacy [77]. Some molecules in TME theoretically affect the function of CAR T cells. For example, although inhibition of the PI3K/AKT pathway *in vitro* prevents the differentiation of CAR T cells [70], activating overexpression of AKT or GLUT1 increases the antitumor activity of effector CAR T cells *in vivo* [73, 74]. The tumor microenvironment (TME) exhibits a complex interplay of cytokines, among which transforming growth factor beta (TGF-β) stands out for its inhibitory effects. This cytokine significantly influences glycolytic and OXPHOS processes. Recent studies employing CRISPR technology have revealed that blocking TGF-β can enhance glycolysis and OXPHOS in TME-specific CAR T cells. Furthermore, the metabolic competition within the TME is evident as tumor cells' glucose consumption impedes T cell glycolysis, leading to elevated phosphoenolpyruvate (PEP) levels. This increase in PEP is noteworthy due to its involvement in NFAT1 activation within T cells, a crucial component of the antitumor immune response. Nonetheless, further research is warranted to substantiate these findings and elucidate the precise mechanisms involved [76]. There is also a competition between immune cells and tumour cells in TME due to the same nutrient source (glucose) [79]. Glucose is used for glycolysis of tumour cells as well as effector activity of T cells [78]. PD-L1 is a crucial factor in tumour microenvironment regulation, as it is expressed on tumour cells and promotes glycolysis through the activation of the AKT/mTOR pathway. This process intensifies the metabolic competition between immune and tumour cells. Recent research has shown that inhibiting the PD-L1/PD1 pathway using monoclonal antibodies or engineered CARs can significantly enhance the effectiveness of CAR T cell therapy [72, 75, 80]. In addition to their direct impact on tumour cell glycolysis, certain glycolysis inhibitors also influence the metabolic processes of immune cells, presenting a dual effect. Moreover, proper approaches such as using GLUT1 inhibitors or a ketogenic diet could be used to improve CAR T cell efficacy [46]. The application of innovative techniques, such as CRISPR/Cas9, holds the potential to significantly

improve T cell receptor (TCR) signalling and bolster the effectiveness of CAR T cell therapy by targeting diacyl glycerol kinase [81].

The role of CAR T cell culture medium

The harsh conditions within the tumor microenvironment (TME), characterized by nutrient scarcity and oxygen deprivation, present a significant challenge to the effectiveness of CAR T cell therapy. To address this, a dual-strategy optimization process is required. This involves, primarily, improving the metabolic adaptability of CAR T cells by focusing on glycolysis modulation. Secondly, the precise modification of the culture medium's composition, including nutrient and cytokine content, is crucial to creating a conducive environment for the successful cultivation of CAR T cells [82]. For example, adding arginine into the medium shifts metabolism into OXPHOS and inhibits glycolysis. Furthermore, adding carnosine to TME neutralizes the acidic condition caused by aerobic glycolysis. On the other hand, IL-21 also increases the number of memory CAR T cells by shifting the metabolism of CAR T cells into FAO and OXPHOS pathways [88]. Moreover, IL-7 and IL-15 also cause metabolic adaptability and increase the number of memory CAR T cells by inhibiting glycolysis [84, 85]. However, although IL-2 is needed for the rapid proliferation of T cells, it promotes glycolysis and leads to T cell differentiation. Therefore, more studies are needed for IL-2 replacement [87].

The effects of mitochondrial biogenesis on CAR T cells

The effector T cells require mitochondrial fission that is controlled by dynamin-related protein1 (Drp1) phosphorylation and glycolysis [53]. However, the proliferation of memory T cells is dependent on mitochondrial fusion and elevated OXPHOS activity, which is facilitated by the dephosphorylation of Drp1 [58]. Thus, memory T cells have more mitochondrial mass than effector T cells [50]. Moreover, enhancing memory or effector T cell numbers by targeting mitochondrial metabolism might represent a strategy to boost CAR T cell therapy [86]. PGC1-α (Peroxisome proliferator-activated receptor gamma coactivator 1-alpha), a pivotal transcription coactivator, exerts significant control over cellular metabolic processes, particularly mitochondrial biogenesis. Upregulation of PGC1-α in T cells has been linked to enhanced cytokine secretion, mitochondrial functionality, and optimization of OXPHOS and FAO pathways, which are essential for memory T cell metabolism. This modulation may further enhance the functionality of T cells within tumor microenvironments, particularly in cases where OXPHOS is compromised [89]. PGC-1α activators and immune checkpoint inhibitors exhibit a synergistic relationship, enhancing mitochondrial metabolism and bolstering the anti-tumor capabilities of T cells through improved metabolic function [88, 89]. Advanced immunotherapy techniques have demonstrated the potential of CAR T cells when modified to enhance PGC-1 expression. This modification leads to the upregulation of critical genes such as ERR, TFAM, and NRF2, which are instrumental in metabolic reprogramming [95]. Activation of the 4-1BB costimulatory domain in CARs through a p38-MAPK-dependent pathway leads to PGC1-dependent mitochondrial fusion and biogenesis. Thus, it enhanced undifferentiated CAR T cells *in vitro* [93].

Oxidative phosphorylation and its role in improving the function of CAR T cells

Elevated oxidative metabolism is accompanied by an improvement in memory T cell population survival [94]. The engagement of 4-1BB significantly boosts T cell metabolism through mitochondrial fusion, a process mediated by peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1) and biogenesis. This enhancement is facilitated by the activation of the p38-microtubule-associated protein kinase (MAPK) signaling pathway [93, 99]. The 4-1BB co-stimulatory molecule enhances oxidative phosphorylation (OXPHOS) and subsequently augments the generation of memory T cells, which exhibit heightened survival capabilities within the organism [85, 97]. Also, The integration of the OX40 costimulatory domain within CAR T cells has been shown to enhance glycolysis, leading to the generation of memory cells. This process is mediated by the TNF receptor-associated factor 2 (TRAF2), which plays a crucial role in this metabolic reprogramming [65].

In recent studies, it was demonstrated that co-stimulation of OX40 and 4-1BB domains in CAR T cells also improved glucose uptake, glycolysis, and OXPHOS [100]. Also, the transcription factor BATF, in conjunction with NFAT and IRF4, plays a pivotal role in $CD8^+$T cell dysfunction. This collaborative mechanism inhibits metabolic processes and induces exhaustion, resulting in a diminished capacity for cytokine production, notably TNF, IL-2, and IFNγ [102]. JQ1, a bromodomain and extra-terminal motif (BET) protein inhibitor, has been observed to downregulate BATF expression, leading to enhanced glycolytic and OXPHOS activity. This metabolic shift promotes the maintenance of $CD8^+$T cells with a central memory phenotype and stem cell-like characteristics. Furthermore, combining JQ1 with CAR T cell therapy significantly augments their anti-tumor capabilities and persistence *in vivo* [96]. Another strategy to decrease BATF effect on T cell exhaustion is overexpression of the C-Jun transcription factor in CAR T cells. Interestingly, C-Jun seems to compete with BATF/IRF and switch off BATF transcriptional functions at the promoter of the genes [92]. Moreover,

inhibition of lactate dehydrogenase (LDH) causes internalizing of pyruvate into the tricarboxylic acid (TCA) cycle [101]. LDH inhibition by NCI-737 treatment combined with IL-21 increases mitochondrial fusion and the production of memory T cells while suppressing programs of exhaustion T cells. These findings demonstrated metabolic states in T cells with improving anti tumour immunity [101].

Amino acid metabolism and CAR T cells

Within the tumor microenvironment (TME), both tumor and associated cells demonstrate the expression of specific amino acid-metabolizing enzymes. These enzymes facilitate the utilization of essential amino acids, which are crucial for the functionality of local T cell populations. Notably, arginine, a vital amino acid for T cell activity, is metabolized by enzymes such as inducible nitric oxide synthase (iNOS) and arginase, which are expressed by tumor-associated macrophages (TAMs). This enzymatic activity leads to a decrease in arginine availability within the TME [103]. The culture medium's nutritional composition has the potential to enhance T cell metabolic activity, offering a significant advantage in adoptive T cell therapy. This can be achieved by incorporating L-arginine, which effectively reduces glycolysis while promoting OXPHOS, thereby optimizing T cell function. Consequently, a proposed strategy involves pre-treating CAR T cells with specific metabolites, including L-arginine, prior to their introduction into the patient's system [82]. Moreover, constructing CAR T cells to express the arginine resynthesizing enzymes such as; ornithine trans carbamylase (OTC) and arginine succinate synthase (ASS), are another way to overcome low arginine levels *in vivo* [103]. As well as researchers developed an lead-guide RNA (dgRNA)-based CRISPR screen in $CD8^{+}$T cells and introduced knocked in or overexpressed proline dehydrogenase 2 (PRODH2) as a new approaches for improving CAR T-based killing. PRODH2 reprograms proline metabolism in primary $CD8^{+}$T cells and enhances CAR T cell therapy in multiple cancer models [98]. The conversion of ATP to adenosine within tumour cells presents a significant challenge, as it depletes the essential ATP required for the optimal functioning of CAR T cells [106]. The presence of adenosine analogues (SCH58261) significantly augments the anti-neoplastic capabilities of CAR T cells by suppressing specific alterations [105]. A proposed method involves the engineering of a CAR (chimeric antigen receptor) that responds to adenosine by fusing the intracellular costimulatory domain of CARs with the extracellular domain of an adenosine receptor. This innovative approach transforms a typically suppressive signal into an activating one, offering a unique strategy in CAR design [104]. The immune metabolite 2-hydroxyglutarate (2HG) exists in two forms, with the S-enantiomer (S-2HG) being the focus of this discussion. S-2HG production is linked to HIF-1 stabilisation within the body. Notably, CAR T cells enriched with S-2HG demonstrate an increased presence of central memory T cells. In mouse xenograft studies, these S-2HG-treated CAR T cells display heightened anti-tumour capabilities and suppress tumour growth. This metabolite inhibits various a-ketoglutarate (a-KG)-dependent enzymes, including demethylases and hydroxylases. Among these, the demethylase Ten-eleven translocation 2 (TET2) is a known target, and its inhibition by S-2HG correlates with reduced tumour progression and the promotion of central memory CAR T cells, ultimately enhancing the therapeutic potential of CD19-targeted T cell therapies [107]. In addition, it has an inhibitory role in T cell differentiation into effector cells [109]. Indoleamine 2,3-dioxygenase (IDO) is a crucial enzyme present in tumour cells, facilitating the metabolic conversion of tryptophan into kynurenine [103]. Kynurenin exhibits potent immunosuppressive properties, specifically targeting CAR T cells. This compound suppresses the production of IFN and IL-2, crucial cytokines for T cell function, and induces apoptosis in these cells. Interestingly, inhibiting the enzyme responsible for Kynurenin production, through the use of 1-methyl-tryptophan, appears to rejuvenate CAR T cell activity, offering a potential therapeutic strategy [108]. As well as, shown that kynureninase modified CAR T cells through targeting kynurenine have anti tumour activity in the metabolic immunosuppressive TME with high kynurenine [110]. The metabolite tetrahydrobiopterin (BH4), synthesized by activated T cells, exhibits a regulatory role in mitochondrial bioenergetics and iron homeostasis. Notably, BH4 can counteract the immunosuppressive properties of kynurenine, thereby enhancing anti-tumoral immune responses [113].

Glutamine, an essential amino acid, plays a dual role in cellular processes. It is a prerequisite for the growth of cancer cells, yet simultaneously, it is integral to the functioning of T cells, which are vital components of the immune system [111, 112]. It seems that there is amino acid competition between the T cells and tumour cells [26]. A recent study has identified a glutamine antagonist, JHU083, which exhibits a unique mechanism of action by targeting tumour cell metabolism. This compound effectively inhibits glycolytic and oxidative processes, leading to reduced acidosis and hypoxia within the tumour microenvironment. Consequently, this metabolic modulation enhances the oxidative capacity of effector T cells and promotes their persistence, potentially improving anti-tumour immune responses [114]. This research reveals that intratumoral T cells can exhibit metabolic plasticity with attention to glutamine metabolism deletion and may be a promising direction to pursue in combination with CAR T cells [114]. As

well as demonstrated that glutamine inhibition by glutamine antagonist 6-Diazo-5-oxo-l-norleucine (DON) enhanced mitochondrial OXPHOS utilizing fatty acids and reduced glycolysis of CAR T cells. DON retains more na ve T cell or central memory T cell subsets and exhibited stronger killing activity *in vitro* and *in vivo* [115]. Additionally, a promising strategy that causes CAR T cell metabolism adaption to TME is imitating the TME metabolic stresses during ex vivo development. For example, in mouse models, adding T cells in a medium with glutamine inhibitors or in glutamine-depleted culture improves the $CD8^+$T cell antitumor activity [117]. Carnosine, a naturally occurring dipeptide, exhibits the ability to neutralize extracellular protons (H^+) originating from lactate within the media. This process facilitates the redirection of metabolic pathways in CAR T cells, promoting a shift from glycolysis to an oxidative phenotype [116].

Lipid metabolism regulation of CAR T cell

It is considered that lipid metabolism reprogramming is an important feature of malignant tumors. In acidic, hypoxic, and nutrition-deficient TMEs, immune cells and cancer cells use lipids for their energy needs [119]. Some studies demonstrated that the incubation of specific cytokines in the culture medium improved CAR T cell therapy through lipid metabolism. For example, IL-7 increased expression of triglyceride synthesis and glycerol transporters and promoted FAO in CAR T cells [121]. IL-15 also upregulates the carnitine palmitoyl transferase enzyme and increases FAO [106]. IL-21 and IL-9 seem to have the same effects and improve FAO [83]. By using IL-7, IL-15, or IL-21 in conjunction with CAR T cells, aerobic glycolysis is switched to FAO and metabolic reprogramming, which enhances mitochondrial fusion and fitness [118].

Recent study has demonstrated that the activation of the NOTCH1 receptor enhances the effectiveness of CD19-targeted CAR T cell immunotherapy. This enhancement is attributed to the upregulation of fatty acid synthesis, heightened OXPHOS activity, and the induction of mitochondrial biogenesis, which collectively support the preservation of a stem cell-like memory T cell population [120]. The study elucidates the mechanism of NOTCH1's impact on T cell function, revealing its role in metabolic reprogramming and the subsequent upregulation of FOXM1, a transcription factor. This process enhances the anti-tumor capabilities of CAR T cells in leukemia models, providing a novel insight into the therapeutic potential of NOTCH1-mediated cellular responses [120]. The connection between cholesterol and its impact on solid cancers and T cell activity is an area of ongoing research. Recent investigations have revealed that suppressing the cholesterol esterification enzyme, ACAT1, leads to elevated cellular cholesterol levels. This, in turn, enhances the accumulation of TCR on the plasma membrane, resulting in heightened $CD8^+$T cell functionality [122]. Nonetheless, other work shows that high cellular cholesterol inhibits glycolysis and upregulates inhibitory markers, leading to exhaustion of tumour infiltrating lymphocytes [124]. Furthermore, inhibition of the Akt pathway by MK2206 increases the FAO pathway in CAR T cells and improves their antitumor activity [20, 42, 123].

miRNA targeting in CAR T cell therapy

MicroRNAs (miRNAs) and chimeric antigen receptors (CARs) have the potential to synergistically enhance adoptive T cell therapy through various mechanisms. The integration of miRNAs with CAR T cells presents a powerful approach to cancer treatment. Notably, the IDO enzyme and its derivative, kynurenine, are identified as upstream regulators of miR-143, with IDO substantially elevating its expression. Glut-1 has been confirmed as the target gene of miR-143, which inhibits Glut-1 activity, impedes T cell differentiation, and disrupts glycolysis and glucose uptake. Furthermore, miR-143 upregulation stimulates carnitine palmitoyl transferase 1A (CPT1A) expression, augmenting FAO and diminishing reliance on glycolysis. This study demonstrates that the overexpression of miR-143 enhances the effectiveness of HER2-CAR T cells against the TE-7 esophageal cancer cell line [125, 126]. High levels of IDO1 are related to the low survival rate of colon cancer (CC) patients. Interferon (IFN) can increase IDO1 expression, resulting in tryptophan degradation and kynurenine formation in TME. In 2018, Huang et al. clarified that miR-153 blocks IDO1 expression in tumour cells, which further improves the CAR T cell therapy against CC. It is a tumour suppressor miRNA that improves the effectiveness of CAR T cell treatment in solid tumours [127]. $CD8^+$T cells express HIF-1 and therefore, may induce glycolysis and enhance effector T cell activity. The evidence demonstrates that miR-17-92 targets HIF-1. Overexpression of this miRNA enhances the development of terminal effector T cells and reduces memory T cell formation by improving mTOR function. Therefore, downregulation of miR-17-92 is needed for memory T cell differentiation [128]. In contrast to this study, other research shows that miR-17-92 expression improves interferon (IFN) production and T cell survival. They reported that miR-17-92 expression is decreased in T cells derived from glioblastoma patients, and they assumed that co-expression of miR17-92 in CAR T cells could enhance the efficacy of treatment against this disease [129].

Conclusion

A new era in cancer has begun in recent years with the use of CAR T cell therapy. In spite of promising results in hematological malignancies, these ap-

proaches have encountered some complications in solid tumors. The success of CAR T cell therapy for patients depends on the CARs' performance, which is influenced by the metabolic fitness of the CARs and the metabolic status of the tumour cells, complexity and high heterogeneity of tumor microenvironment. The efficacy of this immunotherapy appears to be optimized by improving the metabolism of the CARs and harnessing the tumour cells' metabolic state by using of transcriptomic, proteomic, metabolomics and the identification of specific markers for designing the more effective CAR T cells. Numerous studies support the idea that metabolic reprogramming of CAR T cells, including modifying glycolysis, increasing of OXOHOS, gluconeogenesis, mitochondrial biogenesis, and lipid or amino acid metabolism using various generations of CARs or other methods, may be a useful strategy for production of best CAR T cell and improving clinical outcomes (Table 1). Therefore, more investigation of the metabolic fitness of CAR T cells in response to TME is necessary to improve the

TABLE 1. SOME STUDIES OF MANIPULATING THE METABOLISM TO IMPROVE EFFICACY OF CAR T CELLS

Metabolic alteration	Intervention	Outcome/ result	Year	Reference
Glycolysis	Second-generation of CARs with CD28 domain	Early domination of the effector T cells	2018	[29]
	Second-generation CARs with ICOS domain	Shift to the lipogenesis and glycolysis path and Glut-1 induction	2016	[31]
	Second-generation CARs with CD27 domain	Enhanced T cell anti-tumor function and survival *in vivo*	2010	[35]
	Using second-generation CAR that co-expressed with T-bet	Up-regulates the expression of glycolytic pathway genes	2018	[36]
	IL-2 used in generating CAR T cells	Effector T cell growth via PI3K/ mTOR path	2020	[46]
	IL-7 used in generating CAR T cells	STAT5 pathway elevates glucose uptake	2008	[44]
	Using of LY294002 (PI3K inhibitor)	Reduce exhaustion of effector T cells	2018	[28]
	Using inhibitors against AKT pathway	Increase glucose uptake and reduce the expression of pro-apoptotic gen	2017	[87]
	Using CRISPR/Cas9 technology and TGFB2R Knockdown	Deleting the negative effect of TGF-β and reducing the CAR T cells exhaustion	2020	[50]
	Blocking the PD-L1/PD1 axis	Diminish the tumor cell glycolysis	2013	[45]
	Inhibition of mTOR function	Block aerobic glycolysis	2017	[49]
OXPHOS	Using second-generation CARs with the 4-1BB domain	Induces a more OXPHOS and memory T cells with a higher resistance	2015	[54]
	Co-stimulation of OX40 and 4-1BB domains in CAR T cells	Improved glucose uptake, glycolysis and OXPHOS	2016	[61]
	Diminish in BTAF expression after JQ1 treatment or with C-Jun over-expression in CAR T-cells	Diminish exhaustion and increase glycolysis and OXPHOS	2017	[64]
	LDH inhibition by NCI-737 treatment combined with IL-21	Interning pyruvate into the tricarboxylic acid (TCA) cycle and improve metabolic programming in CARs		

Metabolic alteration	Intervention	Outcome/ result	Year	Reference
Amino acids metabolism	Adding L-arginine in culture medium or constructing CARs to express the arginine resynthesizing enzymes	Compensating arginine deficiency for immune cell	2016	[68]
	Using adenosine analogues	Inhibiting convertion of ATP to adenosine by tumor cells	2015	[69]
	Using CAR T cells with S-2HG	Elevate proportions of memory cells	2020	[67]
	Inhibition of enzyme controls converting tryptophan to Kynurenines (indoleamine 2,3-dioxygenase)	Inhibiting immune-suppressive effect of Kynurenines	2015	[77]
	Using glutamine antagonist (JHU083)	Has suppressive activity on both glycolytic and oxidative metabolic path in tumor cells	2019	[79]
	Carnosine existence in culture media	Neutralize protons (H^+) from lactate and improve converting pathway to OXPHOS in CARs	2020	[75]
Lipid metabolism	Adding IL-7,IL-15,IL-19 in the culture medium	Switching aerobic glycolysis towards FAO and improve mitochondrial fitness	2020	[82]
	AKT pathway inhibition	Increases FAO pathway in CAR T cells	2019	[37]
Mitochon-drial biogenesis	Activation of the NOTCH1 receptor	Boost fatty acid synthesis, OXPHOS and mitochondrial biogenesis	2020	[83]
	IL-15 used in generating CAR T cells	Improves mitochondrial fitness	2019	[20]
	4-1BB co-stimulated CAR T cells through p38-MAPK dependent pathway	Improves PGC1α-dependent mitochondrial biogenesis	2018	[29]

function of CAR T cell therapy and its application in clinical trials.

Authors' contributions

Mohammad Reza Atashzar and Shekoufeh Hatami designed the project; Fatemeh Kazemi, Faezeh Ataei, Sahar Shomeil shushtari, collaborated in writing the paper. The final manuscript went through review and approval by all authors.

Competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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