Journal of Translational Medicine

REVIEW

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# Nutrient-gene therapy as a strategy to enhance CAR T cell function and overcome barriers in the tumor microenvironment

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## Abstract

Cancer immunotherapy is transforming the treatment landscape of both hematological and solid cancers. Although T-cell-based adoptive cell transfer (ACT) therapies have demonstrated initial success, several recurrent obstacles limit their long-term anti-tumor efficacy, including: (1) lack of antigen specificity; (2) poor long-term survival of transplanted T cells in vivo; and (3) a hostile tumor microenvironment (TME). While numerous approaches have been explored to enhance the antigen specificity of Chimeric Antigen Receptor (CAR) T-cell therapies, the field still lacks an effective strategy to optimize the long-term retention and in vivo expansion of engrafted T cells within the TME—a critical factor for the durable efficacy of T-cell-based immunotherapies for both blood and solid cancers. Here, we hypothesize that the success of CAR T-cell therapy can be enhanced by targeting donor T cells' ability to compete with cancer cells for key nutrients, thereby overcoming T-cell exhaustion and sustaining durable anti-tumor function in the TME. To explore this hypothesis, we first provide a comprehensively review of the current understanding of the metabolic interactions (e.g., glucose metabolism) between T cells and tumor cells. To address the challenges, we propose an innovative strategy: utilizing nutrient gene therapy (genetic overexpression of glucose transporter 1, GLUT1) to fortify the metabolic competency of adoptive CAR T-cells, deprive tumors of critical metabolites and ATP, and disrupt the TME. Altogether, our proposed approach combining precision medicine (adoptive CAR T-cell therapy) with tumor metabolism-targeting strategies offers a promising and cost-effective solution to enhance the efficacy and durability of ACT therapies, ultimately improving outcomes for cancer patients.

**Keywords** Cancer immunotherapy, Adoptive cell therapy, CAR T, TME, Metabolite, Nutrient, Glucose, GLUT1, Warburg effect, Gene therapy

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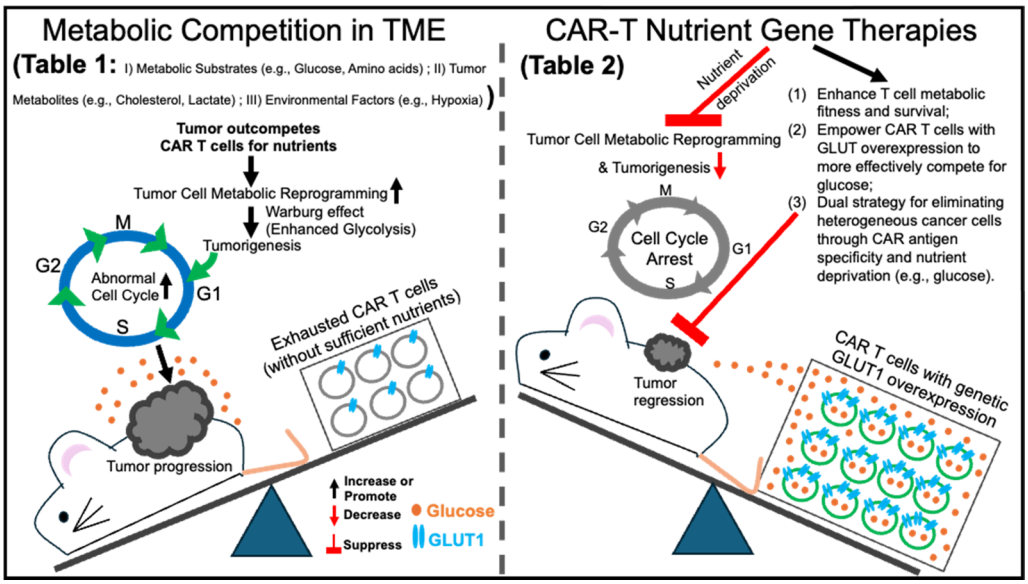
**Graphical Abstract**




## Background

Cancer immunotherapy harnesses the patient's immune system to combat cancer by targeting and eliminating malignant cells through various approaches, such as immune checkpoint blockade [1, 2]. Historically, early scientific attempts to modulate the immune systems to treat cancer can be tracked back hundreds of years [3]. The modern era of cancer immunotherapy began in 1986, when the U.S. Food and Drug Administration (FDA) approved the first immunotherapy: interferon-alpha 2 (IFN-a2), a cytokine used to treat hairy cell leukemia [4]. With the discovery of a new class of cancer therapies that work by inhibiting negative immune regulation, the FDA approved the first immune checkpoint inhibitor (an anti-CTLA-4 antibody) in 2011.

To address the impaired anti-tumor immunity of cancer patients [5], adoptive cell transfer (ACT) therapies, which involves the passive immunization of autologous or allogeneic T cells, have quickly emerged at the forefront of cancer immunotherapy development [6]. Chimeric antigen receptor (CAR) T-cell therapy, a type of ACT, has achieved remarkable clinical success by utilizing T cells engineered to target tumor antigens [7]. In 2017, the FDA approved the first CAR T-cell therapy for the treatment of acute lymphoblastic leukemia in children, a use that has since been expanded to include adult patients. The promising survival outcomes and relatively minimal long-term toxicity of CAR T-cell therapy, have fueled significant enthusiasm for the development and commercialization of cell-based therapies across the cancer research community and beyond [8].

Nevertheless, there remains major limitations to CAR T-cell therapy that prevent its widespread application and hinder its ability to achieve consistent, long-term treatment-free remission [9, 10]. First, cancer is inherently dynamic and toxic due to genetic mutations. Many cancer patients exhibit primary or secondary genomic defects, including chromosomal instability—a hallmark of cancer—that frequently gives rise to drug-resistant subclones with de novo mutations [11]. For example, acute myeloid leukemia (AML) is a heterogeneous malignancy characterized by dynamic etiologies involving somatically acquired alterations at both the DNA and RNA levels [12]. Despite advancements in immunotherapy, only less than half of AML patients respond well to CAR T-cell therapy [13, 14]. Identifying a universal antigen capable of eliciting T-cell responses across distinct tumor platforms remains a critical unmet need in the field [15]. Second, the long-term survival and functional maintenance of infused CAR T-cells within a tumor-dominated environment continue to pose challenges. Real-world evidence indicates that the maximum in vivo expansion of CAR T-cells occurs within the first few weeks post-infusion, but their durable persistence sharply declines within the subsequent six months [16, 17]. Addressing this issue requires strategies that provide CAR T-cells with a supportive microenvironment and adequate nutrients to prevent exhaustion, which is

essential for the success of adoptive T-cell therapies [18, 19]. Third, growing evidence highlights the critical role of the tumor microenvironment (TME), which is continuously shaped by local and systemic tumorigenic inputs, in each stage of cancer progression both before and post treatments [20]. For example, fibroblast-driven extracellular matrix (ECM) deposition around solid tumors and its continuous remodeling not only obstruct immune cell infiltration but also diminish their cytotoxic effects [21]. Overcoming these physical barriers within the TME is a significant challenge in the effective treatment of solid cancers [9].

In this study, we begin by providing a comprehensive review of the scientific literature on cancer immunotherapy, establishing the background and rationale for the proposed advancements. Special emphasis is placed on metabolic interactions (e.g., glucose metabolism) between T cells and tumor cells within the TME, which have emerged as therapeutic targets in cancer treatment [22–24]. A healthy human diet consists primarily of macronutrients such as carbohydrates and proteins, with a significant portion (50–80%) being broken down and utilized as glucose [25]. Furthermore, to meet the high energy demands of uncontrolled proliferation, cancer cells are well known for preferentially utilizing aerobic glycolysis (commonly referred to as the Warburg effect) for the majority of their ATP production, surpassing reliance on other metabolic pathways and exceeding that of normal cells [26, 27]. Therefore, targeting glucose metabolism, particularly within the TME, has emerged as a critical strategy in cancer treatment [28].

Next, building on recent achievements in reprogramming T-cell metabolism from our laboratory and other researchers [29–35], we propose an innovative nutrient-competency-based strategy (genetic overexpression of glucose transporter 1, GLUT1) to overcome these challenges and enhance ACT immunotherapy. This strategy— "CAR-T-based targeted starvation", involves a dual approach: depriving tumor cells of critical metabolites and ATP energy sources while simultaneously disrupting the TME. By combining adoptive CAR T-cell therapy (precision medicine) with tumor metabolism-targeting strategies, this approach offers a viable path forward for effectively treating cancer.

## Main text

### 1) Current literature and findings on potential of cancer immunotherapy

T-cell-based adoptive cell transfer (ACT) represents the most rapidly growing field in cancer immunotherapy. This approach involves modifying autologous or allogeneic T cells and re-infusing them into patients to target and combat their cancers [7, 36]. ACT therapies are categorized into several subtypes based on the immune cell vehicles and their cytotoxic mechanisms (Fig. 1). These subtypes include CAR T-cell therapy (broadly studied, with 23,722 research studies), tumor-infiltrating lymphocyte (TIL) therapy, engineered T-cell receptor (TCR) T-cell therapy, natural killer cell therapy, invariant natural killer T (iNKT) cell and dendritic cell therapies [37]. Most of these therapies employ a shared strategy of targeting tumor antigens to eliminate cancer cells, making ACT a promising and personalized therapeutic option for various types of cancer. Recent studies suggest that human-derived NK cells also exhibit antigen-specific responses to viruses and cytokine-induced activation, supporting their potential use in cancer immunotherapy [38, 39].

Despite its promise, several challenges hinder the long-term efficacy of CAR T-cell therapy [7]. Chief among these is the tumor microenvironment (TME), which has been the focus of 28,576 research studies (Fig. 1). The TME is a highly complex, multidimensional system characterized by cellular, molecular, and physical changes that present a wide array of challenges for T cells [40]. For example, tumor-associated macrophages (TAM), neutrophils, and myeloid-derived suppressor cells (MDSCs), create a chronic immunosuppressive environment that shield tumor cells [41, 42]. These cells secrete anti-inflammatory cytokines, such as IL-10 and TGF-β, which actively suppress T-cell activity [43, 44]. Consequently, targeting tumor-controlled cellular components within the TME is critical for the success of CAR T-cell therapy [45].

In addition to addressing these cellular challenges, we hypothesize that ensuring the durable persistence and effective anti-tumor functionality of T-cells within the hostile TME is equally vital for the success of CAR T-cell therapy [46, 47]. To explore the topic of enhancing T-cell fitness in the context of the molecular and physical characteristics of the TME [48], we conducted a comprehensive review of the scientific literature on cancer immunotherapy, adhering to the updated Preferred Reporting Items for Systemic reviews and Meta-Analyses (PRISMA) guidelines [49]. The PubMed database was searched up to January 18, 2025, using the following search terms: cancer immunotherapy, CAR T, TCR-T, tumor-infiltrating lymphocytes (TIL), natural killer cells, iNKT, tumor microenvironment (TME), metabolite, GLUT1 overexpression, GLUT3 overexpression, nutrient, TFAM. No additional filters were applied during the literature search. A total of 193,236 studies on cancer immunotherapies were identified as published between 1945 and January 18, 2025 (Fig. 1). However, this review focuses specifically on understanding the metabolic interactions between

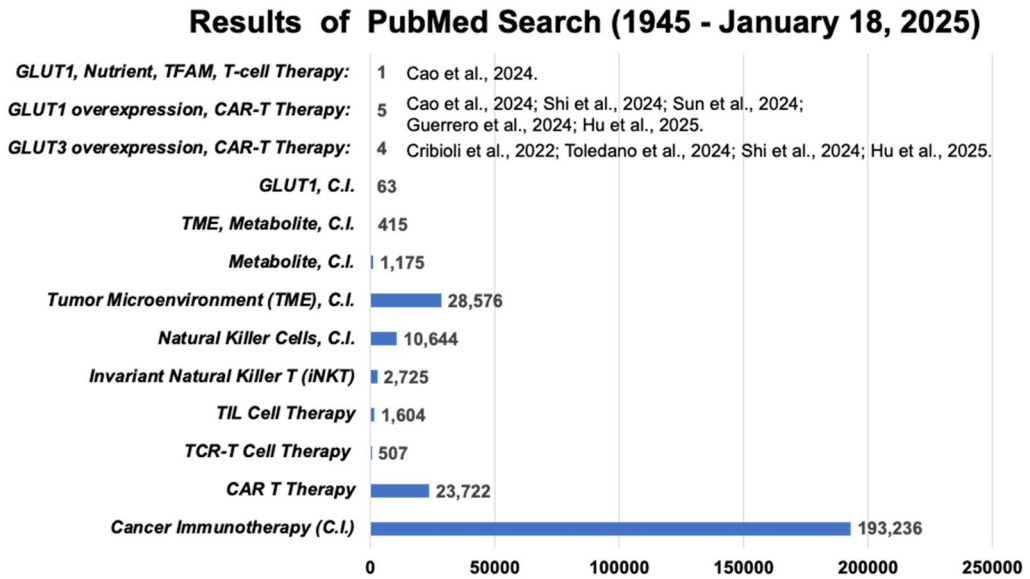



**Fig. 1** Comprehensive review of cancer immunotherapy (C.I.) studies over the last 80 years. This study highlights the potential metabolic barriers to the success of adoptive cell transfer (ACT) therapies by detailing the metabolic interactions between T cells and tumor cells within the tumor microenvironment (TME). To retrospectively examine the development of the cancer immunotherapy field, we utilized PubMed database to search all relevant studies, yielding 193,236 results between 1945 to January 18, 2025. To further narrow the scope, searches for "tumor microenvironment, cancer immunotherapy" and "metabolite, cancer immunotherapy" returned 28,576 and 1175 results, respectively. Additional searches for "TME, metabolite, cancer immunotherapy" and "GLUT1, cancer immunotherapy" yielded 415 and 63 results, respectively. These findings highlight the substantial interest in targeting TME within the cancer research field. There is significant variability in the number of studies focused on different immunotherapy techniques: CAR T-cell therapy (23,722 studies), TCR-T cell therapy (507 studies), tumor-infiltrating lymphocytes (TILs; 1604 studies), invariant natural killer T (2725 studies) and natural killer cells (10,644 studies). These numbers highlight the broad interest in CAR T-cell applications. Notably, a search for "CAR-T, metabolism-targeting" or "CAR-T, metabolite-targeting" yielded no results. However, searches for "CAR-T, GLUT1 overexpression", "GLUT3 overexpression" and "GLUT1, nutrient, TFAM (mitochondrial transcription factor A), CAR-T", returned five studies [29–32, 35], four study [31, 33–35], and one study [29], respectively. This limited number of studies underscores the novelty of our nutrient-competency-based strategy, which aims to improve the efficacy of CAR T-cells by addressing metabolic barriers within the TME

T cells and tumor cells. To refine our analysis, we conducted additional searches using the terms "TME, metabolite, cancer immunotherapy" and "GLUT1, cancer immunotherapy", which yielded 415 and 63 results, respectively. After an initial screening, we performed abstract and full-text screenings to select studies that met our inclusion criteria, which focuses on the metabolic challenges of T cells within the TME. For example, infiltrating T cells like TILs (many AML patients have ex vivo-expandable naïve T cells in both peripheral blood and bone marrow samples [50]) face unique metabolic competition with cancer cells for essential nutrients in the nutrient-depleted microenvironment [51]. This competition negatively affects T-cell function, impairing their ability to mount a robust immune response and effectively eliminate cancer cells [52].

The next section will explore the role of nutrient-like metabolites in the TME, their impact on T-cell fitness, and the significance of nutrient competition for the survival and function of CAR T-cells within the TME.

### 2) Metabolic factors in TME impact effective CAR T-cell therapy

Cancer cells rely on aerobic glycolysis, also known as the Warburg effect, to sustain the increased metabolic demand required for their rapid proliferation [53]. This metabolic process converts glucose into pyruvate and generates ATP at an accelerated rate, resulting in substantial glucose consumption [54]. In addition to local glucose depletion, other essential metabolites, such as amino acids (e.g., arginine), are also depleted due to the high metabolic demands of cancer cells, leading to a nutrient-deprived TME [55]. This heightened metabolic activity not only deprives T cells of glucose but also leads to the accumulation of lactate, which acidifies the surrounding microenvironment. Elevated lactate levels induce metabolic stress in T cells, impairing their proliferation and effector functions [56–58]. Consequently, metabolic competition between tumor cells and T cells often places CAR T-cells and TILs at a disadvantage. This nutrient deprivation is a key mechanism that allows

tumor cells to sustain their rapid proliferation during both treatment and relapse [59, 60].

Three primary categories of local factors influence T-cell metabolism and effector function within the TME: (I) Metabolic Substrates, (II) Tumor Metabolites, and (III) Environmental Factors (Table 1). The following sections detail how each of these factors impacts T-cell activity within the TME.

#### *Metabolic substrates*

I/a. **Glucose competition:** Tumor cells exhibit increased glucose uptake via upregulated glucose transporters (e.g., GLUT1) [54], whereas T cells downregulate GLUT1 expression due to leukemia-impaired activation of the Akt/mTORC1 signaling pathway, a critical metabolic pathway for T cells [59]. This bottleneck inhibits T-cell access to glucose, limiting their metabolism and functionality [59, 60]. Additionally, deficiencies in glycolytic enzymes like enolase-1 further restrict glucose utilization in T cells [61]. Acute glucose restriction may transiently enhance T-cell antitumor activity [62] but ultimately reduces nuclear factor of activated T cells (NFAT) [63], a transcription factor crucial for T-cell development and function [64]. Glucose deprivation also impairs EZH2, a histone methyltransferase that supports T cell polyfunctionality and survival [65]. Altogether, tumor cells exploit their glucose-uptake advantage to suppress T cells activation and functionality, highlighting a potential therapeutic target to enhance CAR T-cell therapy.

I/b. **Amino acid competition:** Amino acids such as methionine, glutamine, and tryptophan are critical for T-cell function. Tumor cells often outcompete T cells for these amino acids, particularly methionine, which is essential for T-cell activation, survival, and effector function, by expressing high levels of the methionine transporter SLC43A2 [66]. This competition leads to metabolic and epigenetic impairments in T cells, contributing to their dysfunction within the TME. Additionally, tumor-associated macrophages (TAM) and myeloid-derived suppressor cells (MDSCs) deplete arginine via arginase-1 (Arg1) and cationic amino acid transporter (CAT2B), impairing T-cell functionality [67]. These metabolic limitations highlight the importance of CAR T-cells with enhanced nutrient-competency to overcome these disadvantages in the TME [68].

#### *Tumor metabolites*

In contrast the historical view of tumors as deregulated and chaotic process, growing evidence suggests that cancer cells actively regulate their metabolic activity to produces extracellular metabolic byproducts. These byproducts help control the TME, induce TAM differentiation to modulate the immune response, and promote revascularization to enhance nutrient supply and blood perfusion—major obstacles to effective cancer treatment [69]. Additionally, these metabolites and their gradients act as tumor morphogens, contributing to a cancer stem cells-centered tumor organization that sustain cellular and genetic heterogeneity, facilitating adaptive survival and invasive progression [70].

II/a. **Lipid metabolism:** Tumor microenvironment is enriched with cholesterol, which induces CD8 + T cell exhaustion through ER-stress-XBP1 pathway [71]. Lipid peroxidation caused by fatty acid uptake triggers ferroptosis in CD8 + T cells, restricting their antitumor activity [72, 73]. Similarly, cholesterol absorption of CD8 + T cells activates oxidized lipid-CD36 axis-mediated lipid peroxidation and increases PD-1 expression, leading to their dysfunction [73]. Inhibiting ACAT1-mediated cholesterol esterification enhances CD8 + T-cell function by improving TCR clustering and signaling [74].

II/b. **Amino acid metabolism:** Tumor cells metabolize tryptophan via indoleamine 2,3-dioxygenase 1 (IDO1), producing immunosuppressive byproducts such as kynurenine [75], which arrests T-cell growth and limits antitumor immunity [76, 77]. Similarly, IL-2 mediated conversion of tryptophan to 5-hydroxytryptophan (5-HTP) in T cells activates the aryl hydrocarbon receptor (AhR), which promotes T-cell exhaustion [78].

Methionine, a sulfur-containing essential amino acid, plays a critical role in protein synthesis in eukaryotes [79]. In response to antigen stimulation, T cells activate the methionine cycle to support their proliferation and differentiation, highlighting the cycle's importance in T cell immunity [80]. However, tumor cells produce methionine-derived metabolites that contribute to T cell exhaustion and impair antitumor activity, presenting a barrier to both endogenous T cell responses and CAR T-cell therapy [81].

II/c. **Other tumor-derived metabolites:** Tumor cells produce metabolites like *R*-2-hydroxyglutarate, which impairs T-cell functionality [82], and 1-methylnicotinamide, which promotes TNF-α but inhibits IFN-γ production, limiting antitumor activity [83]. Additionally, lactate accumulation from aerobic glycolysis suppresses T-cell cytokine production via downregulating NFAT, a transcription factor essential for T-cell effector function [56–58]. Interestingly, under hypoxic conditions, CD8 + T cells produce *S*-2-hydroxyglutarate, which contrasts with its tumor-derived counterpart (*R*-2-hydroxyglutarate) by promoting T-cell proliferation, survival, and antitumor function [84]. The foregoing evidence highlights the dual nature of certain metabolites and the importance of environmental context in determining their effects on immune cell fate and function.

**Table 1** Metabolites and metabolic competition within the tumor microenvironments (TME)

| Metabolite/signaling molecule | Effect on T cells in TME | Organism | Article/review | References |
|---|---|---|---|---|
| **(I) Competition with tumor cells** | | | | |
| Glucose restriction | Acute restriction may increase antitumor effect of T cells. Overall reduced NFAT activity | Mouse | Article | Ho et al., [62] |
| | | Mouse | Article | Geltink et al., [63] |
| Decreased Methionine | Low expression of STAT 5 impairs T cell immunity | Human/mouse | Article | Bian et al., [66] |
| Decreased Glutamine | Reduced T cell accumulation/function in TME, Increased glucose uptake beyond basal levels | Human/mouse | Article | Reinfeld et al., [68] |
| **(II) Tumor metabolites** | | | | |
| Cholesterol | Increases PD-1 expression, and causes CD8 + T cell exhaustion through ER-stress XBP1 pathway | Human/mouse | Article | Ma et al., [71] |
| Fatty acids/oxidized lipids | Ferroptosis, limited antitumor function | Human/mouse | Article | Ma et al., [72] |
| | | Human/mouse | Article | Xu et al., [73] |
| 2-hydroxyglutarate (2-HG)<br>R form predominantly from tumor cells; S form predominantly from T cells | R-2HG impairs T cell functionality; S-2HG improves proliferation, survival and antitumor function of T cells | Human/mouse | Article | Bunse et al., [82] |
| | | Human/mouse | Article | Tyrakis et al., [84] |
| Tryptophan deprivation or conversion via IDO1 to kynurenine and quinolinic acid | T cell growth arrest, limited antitumor immunity; mouse models show T cell apoptosis | Human/mouse | Article | Sadik et al., [75] |
| | | Human/mouse | Article | Uyttenhove et al., [76] |
| | | Human | Article | Terness et al., [77] |
| | | Human/mouse | Article | Liu et al., [78] |
| Methylglyoxal | Inhibits T cell function | Human/mouse | Article | Baumann et al., [86] |
| 1-methylnicotinamide (MNA) | Promotes TNF-alpha, reduces IFN-gamma and limits tumor activity in vitro | Human | Article | Kilgour et al., [83] |
| Methionine metabolites | Promotes T-cell exhaustion, inhibits antitumor response | Human/mouse | Article | Hung et al., [81] |
| Lactate | Dampens proliferation, impairs effector T function and cytotoxic T cell activity, diminishes cytokine production in vitro | Human | Article | Fischer et al., [56] |
| | | Human/mouse | Article | Brand et al., [57] |
| | | Human | Article | Rostamian et al., [58] |
| GABA | Immune exclusion and T cell exhaustion | | Review | Peng et al., [23] |
| **(III) Environmental factors and stressor** | | | | |
| Impaired glucose metabolism | Poor antitumor immunity due to decreased EZH2 | Human/mouse | Article | Zhao et al., [65] |
| IL-2 stimulated 5-hydroxytryptophan formation | Limits antitumor immunity | Human/mouse | Article | Liu et al., [78] |
| NO | Induces cell cycle arrest and blocks cytokine production | Mouse | Article | Mazzoni et al., [85] |
| ROS | T Cell apoptosis, exhaustion, hyporesponsiveness | Human | Article | Matarrese et al., [87] |
| | | Human | Article | Cemerski et al., [88] |
| | | Human/mouse | Article | Yu et al., [89] |
| | | Human/mouse | Article | Trama et al., [90] |
| PGE2 | Blocks activation, impairs cytokine secretion capacity, suppresses survival, enhances exhaustion | Mouse | Article | Chen et al., [91] |
| | | | Review | Wu et al., [92] |
| | | Mouse | Article | Sinha et al., [93] |
| Low pH | Reversible T cell damage, dampens CD25, TCR, STAT5 | Human/mouse | Article | Calcinotto et al., [94] |
| Elevated potassium | Promotes stem-like programs, long-term persistence | Human/mouse | Article | Vodnala et al., [96] |
| Hypoxemia | Upregulates TIL effector function, promotes cytotoxic T lymphocyte differentiation | Mouse | Article | Doedens et al., [98] |
| Hypoxia | Indirect effect via adenosine limits TCR-mediated activation and expansion of effector T cells | Mouse | Article | Deaglio et al., [99] |

#### *Environmental factors and stressors*

Beyond metabolic challenges (the metabolic stress discussed in all the sections above), the TME imposes additional stressors and immunosuppressive conditions that impair T-cell function.

III/a. **Oxidative stress:** Myeloid-derived suppressor cells (MDSCs) convert arginine to nitric oxide (NO) via inducible nitric oxide synthase (iNOS), causing T-cell cycle arrest and inhibiting cytokine production [85]. Similarly, methylglyoxal produced by MDSCs suppresses T-cell function [86]. Glucose deprivation and hypoxia generate reactive oxygen species (ROS), inducing T-cell apoptosis and reducing proliferation through mitochondrial dysfunction [87]. Chronic ROS exposure decreases nuclear factor-kappa B ($NF_KB$) activation, leading to T-cell hyporesponsiveness and exhaustion [88]. Elevated mitochondrial ROS levels further exacerbate T cell exhaustion [89, 90].

III/b. **Immunosuppressive molecules:** Prostaglandin E2 (PGE2) in the TME binds to T-cell receptors, impairing cytokine secretion, survival, and effector function of T cells [91, 92]. PGE2 also promotes MDSC accumulation, further suppressing T-cell activation [93].

III/c. **TME physiology:** The acidic environment of the TME inhibits T-cell activity by dampening T-cell receptor (TCR) activation and cytokine secretion [94]. Proteins like VISTA (V-domain Ig suppressor of T cell activation) specifically inhibit T cells in acidic conditions [95]. Elevated potassium levels in the TME impair T cell effector function by limiting T-cell nutrient uptake; however, increased potassium can preserve T-cell stemness and long-term survival [96].

III/d. **Hypoxia:** Hypoxia is prevalent in the TME and can adversely affect therapeutic outcomes [97]. However, hypoxia has dual effects on T cells. On one hand, it promotes TIL differentiation and effector function via HIF1α and HIF2α activation [98]. On the other hand, it indirectly suppresses TCR-mediated T-cell activation and expansion through adenosine stimulation [99]. Thus, the effects of hypoxia on T cells depend heavily on the specific microenvironment, making it an attractive target for mitigating T-cell exhaustion and immunosuppression in the TME [100].

#### *Glucose transporters (GLUTs) and their role in T cell metabolism*

Among the various metabolites in the TME, glucose stands out as the dominant nutrient critical for cancer metabolism and disease progression. The *SLC2* family (solute carrier family 2) of genes encodes a family of GLUT transporter proteins, which are transmembrane carriers responsible for glucose influx and efflux [101]. There are 14 glucose transporters (GLUT1-GLUT14), which cooperatively supply glucose to fuel cellular metabolic processes while maintaining physiological blood glucose levels [102]. GLUT transporters are classified into three classes based on genetic sequence similarities: Class 1 consisting of GLUT1-GLUT4 and GLUT14; Class II including GLUT 5, 7, 9, and GLUT 11; and Class III comprising GLUT 6, 8, 10, 12, and GLUT13 [103]. In recent years, GLUT transporters have been increasingly characterized for substrate specificity, tissue distribution, and crystal structures—particularly GLUT1 (also known as solute carrier family 2, facilitated glucose transporter member 1, SLC2A1) [104] and GLUT3 [105]. This growing body of research highlights the potential therapeutic value of targeting GLUT proteins [106].

T cell activation, differentiation, and functions also rely heavily on glucose metabolism [107, 108]. Glucose enters T cells primarily through the high-affinity transporter GLUT1, which plays a central role in the metabolic and activation processes of CD4 + T cells [109]. Other GLUT transporters also play specific metabolic role in T cells. GLUT2, a low glucose-binding transporter, regulates CD8 + T cells by enhancing glucose uptake, glycolysis, and glucose storage in glucose-deprived inflammatory environment [110]. This highlights GLUT2's potential utility in improving CAR T-cell therapies in nutrient-depleted conditions such as the TME. GLUT3 is essential for the effector functions of Th17 cells in autoimmune disease models [111], supporting the idea that individual GLUT transporter may play differential roles in lymphocyte subtypes. GLUT4, an insulin-responsive transporter is enriched in the membrane structures of skeletal muscle fibers and adipocytes, distinguishing it as a tissue-specific transporter [112]. In rodent pancreatic islets, GLUT2 is the primary glucose transporter in insulin-secreting β-cells [113], further demonstrating the specific location and function of each GLUT protein. These distinctions in the affinity, tissue distribution, and roles of GLUT transporters make them attractive potential targets of tissue- or cell-specific therapeutic strategies in cancer treatment.

In summary, the tumor microenvironment presents numerous challenges for T-cell functionality, including nutrient competition, tumor-derived immunosuppressive metabolites, and environmental stressors (Table 1). These factors collectively limit the durable efficacy of adoptive cell therapies, such as CAR T-cell therapy. To address these challenges, we propose innovative metabolic engineering approaches to enhance CAR T-cell nutrient competency and resilience in the following section. These strategies aim to improve the efficacy of CAR T-cell therapies for the treatment of both blood and solid cancers.

### 3) Nutrient-competency-based gene therapy can enhance the durable efficacy of CAR T-cells for the treatment of both blood and solid cancers

With the advancement of new biochemical technologies revolutionizing the field of cancer metabolomics [114], therapeutically targeting metabolites in cancer medicine has garnered significant attention in recent years, particularly in the context of glucose metabolism [23, 115–117]. However, the number of preclinical studies specifically investigating the feasibility of combining metabolite-targeting strategies with adoptive T-cell immunotherapies remains unexpectedly limited (Table 2). Out of 193,236 published studies of cancer immunotherapy conducted over the last 80 years (from 1945 to January 18, 2025) (Fig. 1), only seven peer-reviewed research articles have been dedicated to exploring glucose transporter (GLUT)-based metabolite targeting for treating in vitro and in vivo human cancer models (Table 2). These studies span cancers such as acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), and solid tumors including renal cell carcinoma, glioblastoma, hepatocellular carcinoma, melanoma and Lewis lung carcinoma [29–35].

The metabolic states of T cells and the metabolite dynamics of tumor cells represent critical targets for optimizing adoptive cellular interventions [118]. Evidence suggests that targeting these factors could significantly enhance treatment effectiveness when combined with existing cancer therapies [119]. Therefore, we will next discuss how a nutrient-competency-based strategy can improve the efficacy of CAR T-cells in cancer treatment.

### 3/a (Approach 1 for blood cancers): Developing a dual therapeutic strategy combining CAR T-cells with GLUT1-overexpression gene therapy to metabolically starve leukemia cells of energy can significantly enhance the efficacy of adoptive cell therapies

Recently, we engineered T cells with a competitive glucose uptake advantage by overexpressing the GLUT1 transporter, enabling them to outcompete leukemia blasts for glucose and demonstrating superior therapeutic potential in in vitro AML blast models [29]. As a result of energy depletion and inhibition of glycolysis (1.g., the Warburg effect) in leukemia blasts, their proliferative capacity is reduced, while GLUT1-overexpressed CAR T-cells become more resistant to apoptosis via activation of the PI3K/Akt pathway compared to controls in in vivo studies (Fig. 2) [32]. Furthermore, when co-cultured with GLUT1-overexpressed T cells, leukemia blasts exhibited decreased glucose uptake, confirming that cancer cells can be deprived of essential nutrients, leading to increased apoptosis [29]. In contrast, T cells with enhanced glucose uptake display increased glycolic activity and biosynthetic potential. This metabolic reprogramming promotes the expression of key cytokines, such as IL-2, IFN-γ, IL-17F and IL-22 which promote T cell differentiation along with further recruitment and activation of additional cytotoxic T cells to perform anti-leukemia functions [29, 30].

GLUT1 is the most widely studied glucose transporter in immune cells and plays a vital role in T cell effector function [109]. Studies show that GLUT1 overexpression decreases the transcription exhaustion signature (including GNLY, Nur77 and TNFRSF9), which is associated with T cell dysfunction [29, 30]. GLUT1 overexpression has also been found to enhance resistance to reactive oxygen species (ROS) accumulation. In the presence of ROS, such as $H_2O_2$, GLUT1-overexpressed T cells were resistant to oxidative stress, as evidenced by increased IL-2 secretion, a marker for T cell homeostasis and growth. Subsequent chemical challenge tests further revealed that GLUT1 overexpression activates antioxidant-promoting pathways, enabling resistance to ROS-induced suppression and cellular damage [30].

Although GLUT3 has a higher affinity for glucose and its overexpression can enhance T cell metabolic fitness and antitumor effector function in vivo [33], RNA sequencing revealed that GLUT1 overexpression in CAR T-cells increases the expression of genes involved in glycolysis, mitochondrial respiration, and T stem cell-like memory formation—benefits not observed with GLUT3 overexpression [31]. Interestingly, GLUT1 overexpression was also found to upregulate the GLUT3 gene expression in CAR T-cells, thereby enhancing glucose consumption, supporting metabolic reprogramming and protecting against ROS imbalance [30]. As a result, GLUT1-overexpressed T cells not only deprive leukemia blasts of essential nutrients, thereby reducing the overall leukemia burden, but also demonstrate enhanced dual-killing potential by preserving their cytotoxic functionality (Fig. 2B).

Another significant challenge of CAR T-cell therapies is "antigen escape", a prominent cause of AML relapse after CAR T-cell therapy [16]. AML is heterogeneous and characterized by primary or secondary mutations caused by chromosomal instability, which enables leukemia blasts to evade immune system recognition [120]. This genomic plasticity presents a major hurdle for CAR T-cell therapies, as the dominant clone in a refractory leukemia population can develop antigen variants post-treatment [12], a phenomenon that is also observed in solid cancers [121]. These rapidly evolving antigen profiles lead to an insufficient T-cell response, allowing the emergence and proliferation of new subclones that drive relapse.

CAR T-cells are typically designed to possess specific antigen receptors (or multiple receptors with new

**Table 2** List of preclinical studies and literature review of cancer immunotherapies targeting TME metabolites

| Name of study | Objective | Organism | Article/review | References |
|---|---|---|---|---|
| Development of a competitive nutrient-based T-cell immunotherapy designed to block the adaptive Warburg effect in acute myeloid leukemia | T cells overexpressing GLUT1 and TFAM (mitochondrial transcription factor A) exhibited greater anti-leukemia effects in acute myeloid leukemia (AML). Engineering the T cells with enhanced mitochondrial biogenesis facilitates a metabolic homeostasis in transcriptionally reprogrammed T cells | Human | Article | Cao et al., [29] |
| GLUT1 overexpression in CAR-T cells induces metabolic reprogramming and enhances potency | Enhancing glucose availability via GLUT1 overexpression could augment antitumor immune function in acute lymphoblastic leukemia (ALL) | Human/mouse | Article | Guerrero et al., [30] |
| GLUT1 overexpression enhances CAR T cell metabolic fitness and anti-tumor efficacy | CAR-T cells overexpressing GLUT1 exhibited greater antitumor effects in acute lymphoblastic leukemia (ALL), renal cell carcinoma (RCC), and glioblastoma (GBM) | Human/mouse | Article | Shi et al., [31] |
| GPC3-targeted CAR-T cells expressing GLUT1 or AGK exhibit enhanced antitumor activity against hepatocellular carcinoma | CAR-T cells overexpressing GLUT1 exhibited greater CD8 + T-cell persistence in vivo and better antitumor effects in hepatocellular carcinoma (HCC) | Human/mouse | Article | Sun et al., [32] |
| Enforcing GLUT3 expression in CD8 + T cells improves fitness and tumor control by promoting glucose uptake and energy storage | CD8-T cells overexpressing GLUT3 exhibited improved metabolic fitness and greater antitumor effects in melanoma tumors | Mouse | Article | Cribioli et al., [33] |
| Genetically engineering glycolysis in T cells increases their antitumor function | Engineered human T cells expressing phosphofructokinase and GLUT3 demonstrated improved in vivo therapeutic potential in a xenograft model of human melanoma tumor | Human/mouse | Article | Toledano Zur et al., [34] |
| Glut3 overexpression improves environmental glucose uptake and antitumor efficacy of CAR-T cells in solid tumors | GLUT3-overexpressing CAR-T cells demonstrated increased tumoricidal efficacy in multiple xenografts and syngenetic mouse models | Human/mouse | Article | Hu et al., [35] |
| The glucose transporter 5 enhances CAR-T cell metabolic function and anti-tumor durability | GLUT5 enhances CAR-T cell anti-tumor function in vivo | Human/mouse | Article | Valentic et al., [133] (Preprint) |
| NSUN2 is a glucose sensor suppressing cGAS/STING to maintain tumorigenesis and immunotherapy resistance | Glucose-activated NSUN2 drives cancer growth and immunotherapy resistance by maintaining TREX2, inactivating cGAS/STING | Human/mouse | Article | Chen et al., [141] |
| Targeted glucose or glutamine metabolic therapy combined with PD-1/PD-L1 checkpoint blockade immunotherapy for the treatment of tumors—mechanisms and strategies | The study explores the impact of glucose and glutamine metabolism on tumor immune escape and proposes strategies for targeting glucose or glutamine metabolism in combination with PD-1/PD-L1 checkpoint blockade immunotherapy | | Review | Ma et al., [140] |
| Metabolic barriers to cancer immunotherapy | Examined the T cell metabolism in cancer immunotherapies and explore new combination approaches | | Review | DePeaux et al., [116] |
| Metabolic programming and immune suppression in the tumor microenvironment | The study explores the role of metabolic programming in tumor progression and metastasis, suggesting that targeting metabolic heterogeneity could potentially enhance immunotherapies and overcome immune suppression | | Review | Arner et al., [115] |
| Effects of glucose metabolism, lipid metabolism, and glutamine metabolism on tumor microenvironment and clinical implications | This study explores the impact of metabolism on tumor cells and effector cells, highlights recent research on metabolic effects on tumor microenvironment, and introduces applications of metabolic features in clinical oncology | | Review | Zhu et al., [142] |

**Table 2** (continued)

| Name of study | Objective | Organism | Article/review | References |
|---|---|---|---|---|
| Enhancing immunotherapy in cancer by targeting emerging immunomodulatory pathways | This review explores the potential of agents targeting co-stimulatory and co-inhibitory T cell receptors, their mechanisms of action, and ongoing clinical trials. It also discusses novel immunomodulatory (ICI) agents, including those targeting LAG3, TIM3, TIGIT, BTLA, GITR, OX40, 41BB, and ICOS. The review suggests further efforts to optimize timing of combination ICI approaches and individualize immunotherapy based on patient and tumor characteristics | | Review | Kraehenbuehl et al., [117] |
| O-GlcNAcylation in cancer development and immunotherapy | This review explores the biological functions and molecular mechanisms of OGT- or O-GlcNAcylation-mediated tumorigenesis, its potential role in tumor immunotherapy, and compounds targeting O-GlcNAcylation to suppress oncogenesis, suggesting a promising strategy for human malignancy treatment | | Review | He et al., [143] |

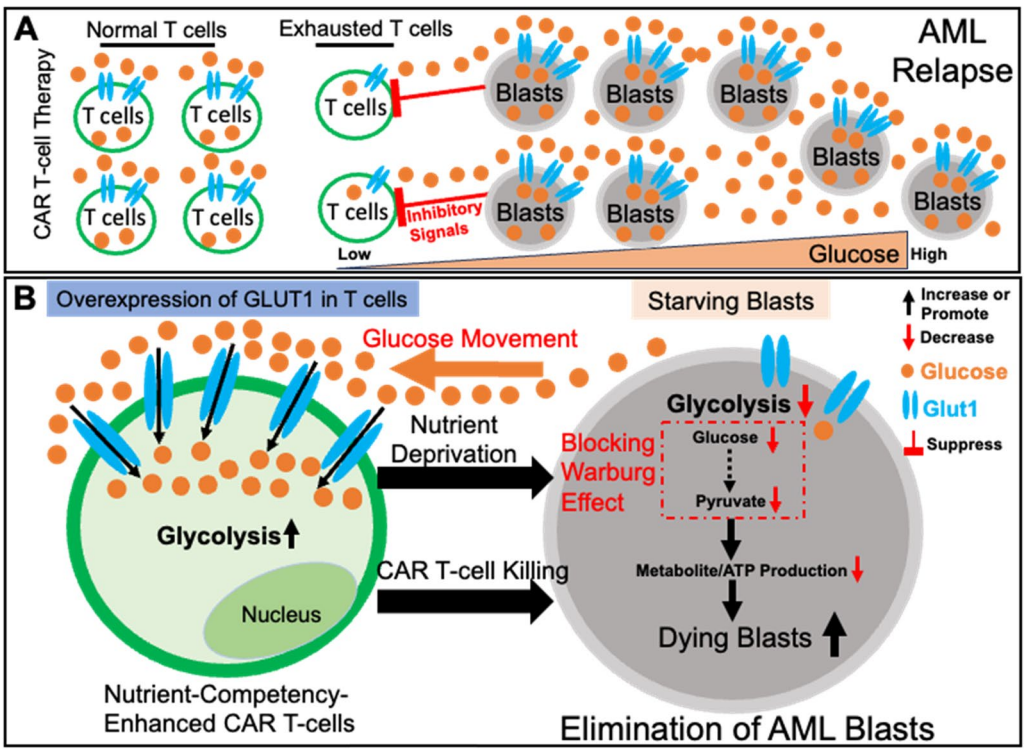



**Fig. 2** A schematic diagram (Approach 1 for blood cancers) illustrating the strategy of developing a nutrient-competency and metabolism-enhanced CAR T-cell therapy for AML. **A** In current CAR T-cell therapies, adoptively transferred T cells may fail to compete with leukemia blasts for glucose uptake. Blasts are known to suppress T cells through inhibitory signals (e.g., PD-L1) and by depriving glucose from T cells, leading to T-cell exhaustion. Simultaneously, blasts exploit the Warburg effect (increased glycolysis) to fuel their uncontrolled proliferation and drive AML relapse. As a result, various cellular populations are present during AML relapse, including normal T cells, exhausted T cells and relapsed blasts. **B** To improve CAR T-cell therapy for AML, T cells can be genetically engineered to overexpress the *GLUT1* transgene. GLUT1 overexpression enhances CAR T cells' metabolic fitness and competitive glucose-uptake capabilities. By depriving blasts of glucose, the Warburg effect is reduced, potentially resulting in increased blast cell death (dual cytotoxicity) and improved therapeutic outcomes

techniques) (Fig. 3A) [122]. However, the high mutation rates of leukemia blasts create a diverse and dynamic antigen presentation profile [123]. This diversity means that CAR T-cells targeting a specific antigen may be unable to effectively treat heterogeneous cancers (Fig. 3B), as the antigen targets may be polymorphic or expressed at insufficient levels to stimulate an adequate T-cell response (both CAR T and TCR T cells) [124].

Our GLUT1 overexpression-based strategy addresses this limitation by equipping T cells to outcompete leukemia blasts for nutrients and utilizing a nutrient deprivation approach to target a universal vulnerability of all cancer cells who rely on glucose as a primary source of energy in the tumor microenvironment, regardless of tumor antigen heterogeneity (Fig. 3C, D). Therefore, GLUT1 overexpression has been associated with improved tumor clearance across multiple murine tumor models in both in vitro and in vivo settings [29–32].

In summary, by tackling both metabolic and antigen-related challenges, our nutrient gene therapy approach represents an innovative and alternative strategy to improve the efficacy of CAR T-cell therapy in the treatment of heterogeneous AML.

**3/b (Approach 2 for solid tumors): Developing a dual therapeutic strategy combining CAR T-cells with GLUT-overexpression gene therapy to metabolically starve tumors and their tumor microenvironment (TME) stromal components could disrupt physical barriers, enabling CAR T-cells to penetrate tumors more effectively and target cancer stem cells and tumor organization for destruction**

To date, the success of CAR T-cell therapy for hematological malignancies has not been translated to efficacy for solid tumors. This discrepancy is partly due to the hostile TME and the physical barriers surrounding solid tumors, which interfere with the ability for CAR T-cells to properly infiltrate into the tumor microenvironment (Fig. 4A). Also, solid tumors often contain low $O_2$ levels, leading to upregulation of GLUT1 and glycolysis in tumor cells via hypoxia-inducible factor-1α (HIF-1α) and subsequently leading to increased glucose fermentation

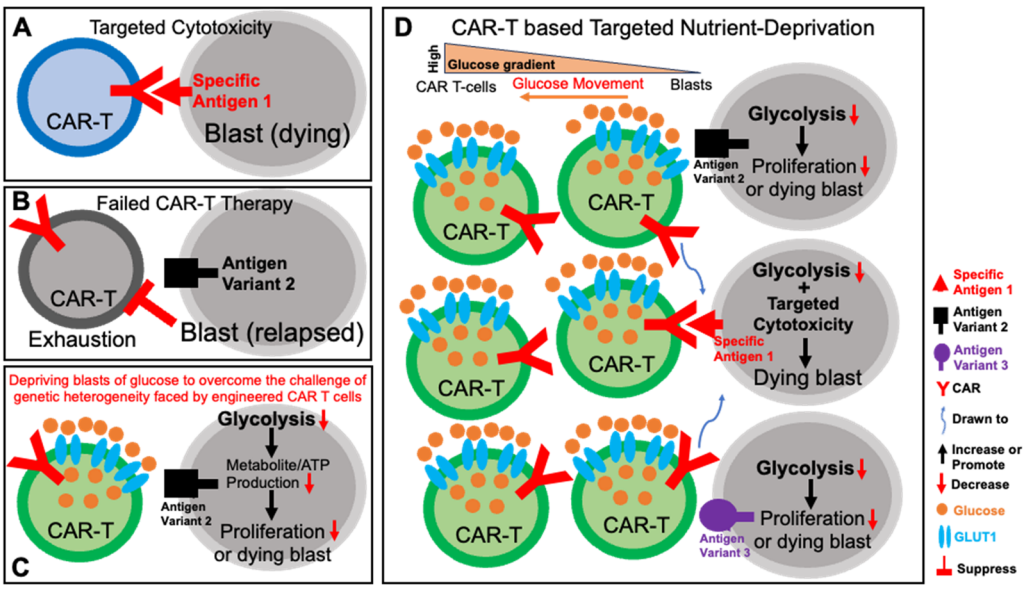



**Fig. 3** A schematic diagram illustrating the strategy of starving blasts to overcome the challenge of genetic heterogeneity in pre-designed CAR T-cell therapy for AML. **A** CAR T-cells bind to matched specific antigen 1 and induce targeted cytotoxicity in leukemia blasts. **B** Due to genetic heterogeneity, CAR T-cells engineered for specific antigen 1 fail to mount a cytotoxic response against leukemia blasts expressing antigen variant 2, leading to disease relapse and T-cell exhaustion. **C** CAR T-cell with GLUT1 overexpression deprive blasts of glucose, disrupt the Warburg effect, and inhibit uncontrolled blast proliferation. This approach provides an alternative strategy to circumvent the challenge of genetic heterogeneity in pre-designed CAR T-cell therapies. **D** In heterogeneous AML, engineered CAR T-cells with GLUT1 overexpression are drawn to a leukemia population composed of both blasts with a specific antigen 1 and blasts with antigen variants 2 or 3. These CAR T-cells exert dual cytotoxic effects: directly targeting antigen-specific leukemia blasts while simultaneously depriving both specific blasts and nearby non-specific blasts of glucose, thereby inhibiting uncontrolled blast proliferation

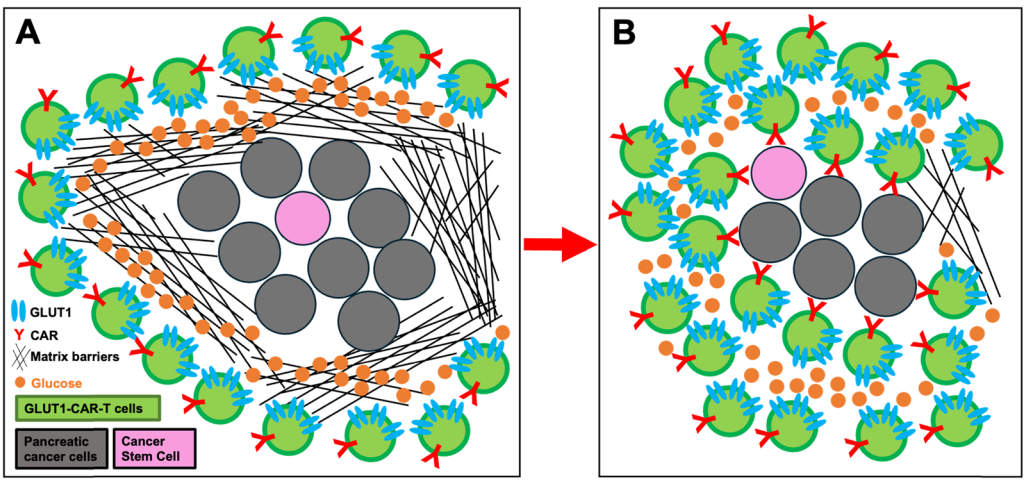



**Fig. 4** A schematic diagram (Approach 2 for solid tumors) illustrating the action of metabolically starving tumor cells and their TME stromal components to disrupt the matrix barrier surrounding tumors. This disruption enhances the penetration of CAR T-cell therapies, enabling them to target and eliminate cancer stem cells more effectively, thereby improving outcomes in the fight against cancers

to lactate, which suppress T cell activity [125]. Since the TME heavily depends on nutrient and metabolite availability [23], we hypothesize that depriving tumor cells and their TME stromal components of these resources could reduce TME stress, weaken the structure integrity of the matrix, and enable CAR T-cells to overcome these physical barriers.

For example, pancreatic cancer cells actively maintain the integrity of the extracellular matrix (ECM), making it challenging for CAR T-cells to infiltrate and target cancer

stem cells and progenies (Fig. 4A). We hypothesize that therapeutically starving both cancer cells and their TME stromal cells of metabolites and ATP energy will force them to undergo nuclear reprogramming and gene transcription aimed at survival [126]. This reprogramming could inadvertently compromise the structural integrity of the ECM, reducing the physical barrier to T-cell infiltration (Fig. 4B).

The matrix metalloproteinase (MMP) family of enzymes plays a key role in ECM degradation [127]. MMP-1, also known as collagenase-1, has a unique ability to cleave the triple helix of collagen, unwinding it and making it more susceptible to further degradation by other MMPs [128]. Increased expression of MMP-1 has been associated with enhanced tumor cell survival and resistance to treatments [129]. Also, under survival stress such as glucose starvation, cancer cells underwent metabolic adaptation by activating LKB1-AMPK-regulated MMP-9 axis to overcome the unfavorable growth condition [130], consequently leading to proteolytic cleavage of connective tissues and disruption of the ECM [131]. Yet, this breakdown of the protective matrix may allow CAR T-cells to infiltrate the tumor, reach cancer stem cells, and exert their cytotoxic effects, potentially causing significant tumor shrinkage (Fig. 4B).

In summary, metabolically weakening the ECM and other physical barrier components could reshape the tumor landscape, leaving cancer cells more vulnerable to CAR T-cells and therapeutic drugs, rather than allowing them to remain isolated within a protective microenvironment. Although cancer cells are well known for their metabolic plasticity and ability to scavenge nutrients under adverse conditions [126, 132], our nutrient gene therapy-based metabolic depletion strategy not only enhances CAR T-cell infiltration but may also maximize their anti-tumor efficacy by enabling them to more effectively engage and eliminate cancer cells.

## Discussion

In this review, we present the background and rationale for our innovative strategy to enhance adoptive cellular therapies by targeting metabolic pathways that tumor cells rely on for survival within the tumor microenvironment. Strategies such as our proposed GLUT transporter gene therapy exploit key vulnerabilities discussed throughout this review. Our key conclusions from this study are as follows:

There is a growing body of literature supporting the notion that the tumor microenvironment (TME) is a major obstacle to the success of immunotherapy (Fig. 1). The TME often promotes tumor growth while simultaneously hindering the effectiveness of immune-based therapies. For example, in solid tumors, cancer cells are frequently encased within a stromal matrix, which creates a physical barrier that prevents immune therapies from reaching and targeting the tumor cells. Tumor cells often evolve to meet the metabolic demands of rapid proliferation and survival in the hostile TME. The predominant reliance on aerobic glycolysis, known as the Warburg Effect, is perhaps the most well studied metabolic adaption utilized by tumor cells. As we have discussed, this also results in local glucose deprivation for tumor infiltrating lymphocytes (Fig. 2), which may result in impaired T-cell functionality. A multitude of other metabolic changes are also likely to impair the effectiveness of immunotherapy (Table 1). While targeting the TME and its various phenomena, like nutrient competition, holds promise in cancer treatment, the development and clinical application of such therapies have lagged behind. Therefore, there is considerable need to investigate this further to improve clinical outcomes.

To address the existing and emerging barriers, we proposed a combination approach—nutrient gene therapy to overexpress GLUT1 in CAR T-cells—for hematological malignancies (Fig. 2) and for solid tumors (Fig. 4). This strategy has the potential to inhibit cancer metabolism and reverse the metabolic shift (e.g., glucose) towards the benefit of CAR-T cells, thereby demonstrating promising therapeutic efficacy in preclinical studies across various tumor models [29–32]. Moreover, this approach can be further adapted to include additional metabolic receptors or GLUT transporters (e.g., GLUT3 [33–35] or GLUT5 [133]). The goal of this strategy is to promote a sustained and robust T-cell immune response while simultaneously depriving cancer cells of critical metabolites and ATP, thereby significantly impairing their proliferation.

Among the recurring challenges in cancer immunotherapy, primary and secondary genetic heterogeneity as well as the high mutation rate of cancers pose substantial obstacles to identifying optimal tumor antigens for T-cell-based therapies capable of achieving long-term clinical remission. Given that cancer cells require large amounts of glucose for ATP production to sustain their uncontrolled proliferation, our nutrient-competency-based therapy targets this fundamental dependency by depriving them of environmental glucose. In the absence of glucose, cancer cells cease to proliferate and tend to undergo increased apoptosis under such conditions [134]. Therefore, our approach, which exploits the cancer cell's reliance on glucose for ATP production, has the potential to address genetic heterogeneity by delaying the emergence of mutations and preventing the formation of new subclones (Fig. 3). It may also enhance the efficacy of CAR T-cell therapies in cancer patients. However, further studies are required to determine the mechanism by which GLUT1 overexpression in CAR T-cells impacts

the mutation rate of cancer antigens. (As mentioned previously, transplantation-related safety issues and side effects, such as cytokine release syndrome, are beyond the scope of the current review).

Although there is a risk that nutrient-competency-based therapy may affect normal cells, there is reason to believe that cancer cells are more likely be impacted. Since normal cells are not undergoing mitosis at the same accelerated rate as cancer cells and have lower energy demands, nutrient deprivation is expected to have a lesser effect on them, whereas cancer cells rely heavily on glucose for survival and proliferation [135]. Furthermore, our CAR T-cells-mediated nutrient-competency-based therapy is typically confined to tumor cells within the TME due to the antigen specificity (Fig. 3), rather than systemic effects. While this approach may also impact stromal cells within the TME, this could still be beneficial by helping to restrict cancer cell growth. However, this concept has not been well studied. A key area for future research is to determine the extent of nutrient-competency-based therapy's effects on normal cells within the TME, and whether it induces increased inflammation or other compensatory mechanisms that could influence cancer progression and normal function.

Interestingly, recent studies have shown that either GLUT1 or GLUT3 overexpression alone can confer a better competitive advantage than the other transporter for improving CAR T-cell function in glucose-deprived TME [31, 35]. It's possible that optimal glucose-binding cleft opening may not be achieved through enforced GLUT1 or GLUT3 overexpression in different CAR T-cells [102]. Indeed, one study demonstrated combining GLUT3 and phosphofructokinase overexpression had enhanced antitumor efficacy [34], suggesting combining GLUT overexpression with other relevant metabolic protein overexpression could be beneficial. Instead of solely focusing on GLUT comparison, we observed that rapid glucose influx, when unbalanced, can disrupt T-cell metabolic homeostasis and adversely affect the mitochondrial respiratory chain (unpublished manuscript), which is critical for the persistence and clinical efficacy of CAR T-cell therapy [136]. To address this challenge, we implemented a complementary strategy: in addition to GLUT1 overexpression, we engineered T cells with TFAM (a transcription factor critical for regulating mitochondrial biogenesis) to achieve balanced genetic reprogramming of T-cell metabolism and maximize competitive advantage through alternative angles besides just GLUT and glycolysis overexpression like other studies have investigated [29].

Altogether, GLUT1-based nutrient-competency-enhanced T-cell immunotherapies [29–32] not only redirects glucose utilization in favor of T cells but also provides a possible backup strategy to treat cancers in cases where pre-designed CAR T-cell therapies fail due to refractory subclones with antigen variants (Fig. 3). Moreover, this nutrient-competency-based strategy lays the foundation for exploring other candidates of receptors or transporters of metabolites to further reprogram and empower T cells in combating cancers (Fig. 5). In addition to T cells, different cell vehicles, such as healthy hematopoietic stem cells (HSCs), can be equipped with

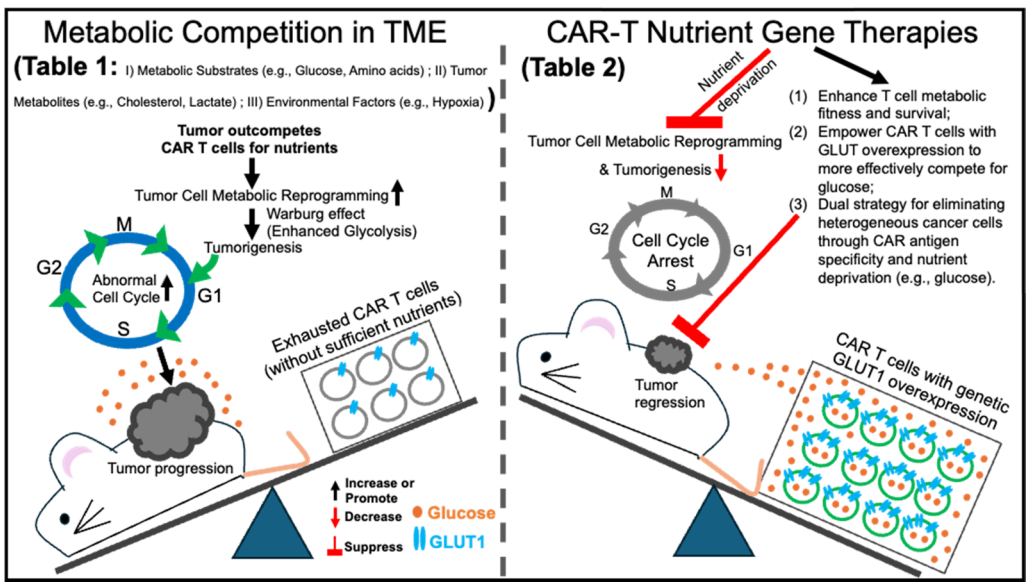



**Fig. 5** A graphical summary of the tables and key findings from this review

the nutrient-competency-based strategy. This would enhance the integration and durable survival of HSCs in blasts-occupied bone marrow, allowing for the regeneration of functional blood and immune systems to support the quality of life in cancer survivors [137].

However, a limitation of the current review is that it oversimplifies the complexity of the TME by focusing primarily on glucose metabolism, while minimizing the contribution of other critical immunosuppressive factors such as hypoxia and immune checkpoint inhibition. Therefore, our findings warrant further preclinical investigation to comprehensively evaluate their therapeutic potential.

## Conclusions

CAR T-cell therapies have been clinically evaluated for two decades, yielding promising yet not fully satisfactory therapeutic outcomes [138]. Several proof-of-principle preclinical studies have sought to enhance T-cell immunotherapy by targeting tumor metabolism across various cancers [29–35] (Table 2). Three significant breakthroughs have emerged as potential strategies to combat T-cell exhaustion and improve adoptive T-cell therapy via the genetic overexpression of GLUT transporters: (1) Reprogramming T-cell metabolism: Enhancing T-cell metabolic fitness and survival; (2) Enhancing glucose competition: Empowering T cells to more effectively compete for glucose, thereby starving leukemic blasts and inhibiting their Warburg effect (Fig. 2); and (3) Utilizing a nutrient deprivation approach targets a universal vulnerability of all cancer cells who rely on glucose as a primary source of energy in the tumor microenvironment, regardless of tumor antigen heterogeneity (Figs. 3, 4). Therefore, our nutrient-gene therapy has the potential to reshape the tumor microenvironment by simultaneously strengthening CAR T-cells and undermining both heterogeneous tumor cells and physical matrix barriers, offering a promising strategy for the treatment of both hematologic and solid cancers (Fig. 5).

CAR T-cell immunotherapy, as a cornerstone of the broader field of targeted cancer medicine, remains in its relative infancy and is currently prohibitively expensive for widespread application [139]. Further research and increased investment in original, innovative ideas are essential to develop and advance cost-effective adoptive cell therapies that integrate antigen specificity, metabolic modulation, and genetic engineering for the effective treatment of cancers and other diseases.

### Abbreviations

| | |
|---|---|
| C.I. | Cancer immunotherapy |
| AML | Acute myeloid leukemia |
| ACT | Adoptive cell transfer |
| TME | Tumor microenvironment |
| CAR | Chimeric antigen receptor |
| GLUT1 | Glucose transporter 1 |
| GLUT3 | Glucose transporter 3 |
| TIL | Tumor-infiltrating lymphocyte |
| TCR | T-cell receptor |
| NK | Natural killer |
| MDSCs | Myeloid-derived suppressor cells |
| NO | Nitric oxide |
| ROS | Reactive oxygen species |
| PGE2 | Prostaglandin E2 |
| IDO1 | Indoleamine 2,3-dioxygenase 1 |
| 5-HTTP | 5-Hydroxytryptophan |
| AhR | Aryl hydrocarbon receptor |
| Arg1 | Arginase-1 |
| CAT2B | Cationic amino acid transporter |
| $NF_KB$ | Nuclear factor-kappa B |
| ECM | Extracellular matrix |
| MMP | Matrix metalloproteinase |
| HSCs | Hematopoietic stem cells |

### Acknowledgements

We acknowledge the limited number of citations included in this review, as our focus on a narrow scope inherently restricted the breadth of literature examined. We thank Mark E Reeves, Bin (Amber) Zhang and Guido Marcucci for helpful discussion.

### Author contributions

Y.X. conceived the study and drafted the original manuscript. B.P., J.K., C.K., V.T. J.X. performed literature search, organized the table, and participated in writing the original manuscript. D.J.B., C.H., H.C., H.A.A., H.M., S.L., L.T., A.C., L.S., M.M., P.L.M., A.S.D. reviewed and edited the manuscript. All authors approved the final manuscript.

### Funding

This study was supported by Loma Linda University GRASP (Y.X.) and Loma Linda University Research Innovation Grant (H.C.). Funding support will be welcomed (Y.X.).

### Data availability

The original datasets are presented in the article. Further inquiries can be directed to the corresponding author.

## Declarations

### Ethics approval and consent to participate

Not applicable.

### Consent for publication

All authors agree to publish.

### Competing interests

The authors declare that they have no competing interests.

Received: 7 February 2025 Accepted: 12 May 2025
Published online: 06 June 2025

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