

MPC-Dependent Lactate Oxidation and PGC-1alpha Biogenesis in CD8 T Cell Fate

Andrew Friedl

Precision Mito, Florida, USA

Correspondence: afriedl@precisionmito.com

Abstract

Background: Lactate, pyruvate oxidation, mitochondrial mass, memory markers, effector cytokines and antitumor function can move together in CD8 T cell studies, making it unclear whether immune fate is controlled by a lactate/pyruvate carbon-entry gate or by generic mitochondrial-biogenesis capacity.

Objective: This working paper retains the selected question: In activated and tumor-exposed CD8 T cells, does lactate/pyruvate control immune fate through MPC-dependent mitochondrial carbon entry separable from PGC-1alpha mitochondrial-biogenesis rescue?

Methods: Public primary literature and the reviewed private selection dossier were checked on 2026-10-10. Eight primary studies were source-coded, including six archived full texts and two current context papers. Endpoint classes were MPC perturbation, lactate uptake and oxidation, LDH-linked effector transcription, activation-linked mitochondrial biogenesis, PGC-1alpha rescue, memory phenotype, effector function and antitumor-function proxies. The analysis was a competing-model evidence synthesis and measurement-rule reanalysis; no pooled effect size, raw-sequencing reanalysis, causal validation, clinical benefit or treatment recommendation was inferred.

Results: The closest MPC study supported opposite context meanings: MPC restriction promoted memory programming during activation, whereas MPC loss reduced lactate oxidation and effector function in tumor-like nutrient stress [1]. PGC-1alpha sources supplied the strongest alternative because enforced PGC-1alpha improved CD8 mitochondrial fitness, persistence and antitumor outcomes without testing MPC or lactate tracing [2,3]. Lactate and LDH sources supported CD8 lactate use and effector-transcription boundaries but left LDH viability, tissue and compartment constraints unresolved [4,5,8]. Activation-linked mitochondrial biogenesis further showed that mitochondrial content is not a generic proxy for the same fate mechanism [6]. A 2024 MITO-66 CAR T paper strengthened the ex vivo manufacturing relevance of MPC inhibition while preserving the tumor-site warning [7].

Conclusions: Current evidence supports a bounded discriminability rule rather than a new biological validation. MPC inhibition can be discussed as an ex vivo memory-imprinting strategy only when tumor-site lactate oxidation is not generalized away; PGC-1alpha rescue remains the main competing account unless matched CD8 experiments measure MPC/MCT/LDH flux, PGC-1alpha state, mitochondrial outputs and immune fate endpoints in the same samples.

Keywords: CD8 T cells; mitochondrial pyruvate carrier; lactate; PGC-1alpha; adoptive cell therapy; immunometabolism

1 Introduction

CD8 T cell metabolic state is increasingly used to reason about adoptive cell therapy manufacturing, tumor-site persistence and effector function. The unresolved bottleneck is endpoint identity. Lactate uptake, pyruvate oxidation, mitochondrial mass, memory markers, cytokines and antitumor function can change in the same broad direction, but they do not automatically identify the same causal mechanism.

The selected research question asks whether activated and tumor-exposed CD8 T cell fate is controlled through MPC-dependent mitochondrial carbon entry in a way that is separable from PGC-1alpha mitochondrial-biogenesis rescue. The central relationship is intentionally narrow. Under nutrient-replete activation or manufacturing-like conditions, transient MPC restriction may promote memory programming. Under tumor-like lactate-reliant nutrient stress, MPC-dependent lactate or pyruvate oxidation may instead support effector function. The proposed relationship fails if PGC-1alpha-mediated mitochondrial biogenesis explains the same mitochondrial mass, respiration, persistence and antitumor endpoints without a distinct MPC/lactate dependency.

The strongest competing account is ordinary and credible: CD8 outcomes under lactate or pyruvate stress may be primarily explained by mitochondrial-biogenesis capacity. In that account, PGC-1alpha rescue is the actionable mechanism, and lactate or MPC status is a nutrient-context marker rather than a separate decision gate. Figure 1 summarizes the evidence workflow, and Figure 2 summarizes the discriminating model.

2 Methods

The reviewed candidate-selection dossier, archived public full texts, current primary-literature searches and prior Mito Map publication bundles were checked on 2026-10-10. Six complete public primary texts were retained from the selection phase: Wenes 2022, Scharping 2016, Klein Geltink 2020, Peng 2016, Quinn 2023 and Ron-Harel 2016 [1-6]. Two additional primary papers were added as current context rather than as selection-changing evidence: a 2024 MITO-66 CAR T manufacturing study and a CD8 carbon-source tracing study [7,8].

Eligibility required public primary evidence relevant to at least one endpoint class: MPC perturbation, MCT/LDH/lactate handling, lactate or pyruvate flux, PGC-1alpha abundance or activity, mitochondrial mass or respiration, CD8 memory programming, effector cytokines, antitumor-function proxies or activation-linked mitochondrial remodeling. Review articles, commentary, abstract-only records and clinical claims without matching mechanistic endpoints were excluded from central evidence.

A machine-readable evidence and assumption ledger is provided in Supplementary File S1, with a readable companion in Supplementary File S2. The ledger records exact manuscript anchors, source identifiers, exact excerpts, source-version hashes, actual quotation-check outcomes and unresolved assumptions; it does not establish biological or clinical validity.

Each source was coded for biological system, perturbation, endpoint class, observed evidence, interpretation limit and role in the competing-model analysis. The primary endpoint was not a pooled effect estimate. It was the ability of the source set to separate two explanations under matched CD8 conditions: an MPC-dependent carbon-entry gate versus PGC-1alpha-mediated mitochondrial-capacity rescue.

The prespecified contrast required same-condition measurement. A result would support the carbon-entry concept if transient MPC restriction improved ex vivo memory programming in nutrient-replete activation while MPC loss impaired lactate oxidation and effector function under tumor-like nutrient stress, even after PGC-1alpha state and mitochondrial mass were

measured. A result would support the alternative if enforced or restored PGC-1alpha explained mitochondrial mass, respiration, persistence and antitumor-function endpoints despite MPC/MCT/LDH disruption. Shared improvement in memory markers or respiration alone was treated as insufficient.

Sensitivity analyses were labeled by role before interpretation: decision-changing when removal could change the research decision, robustness when removal tested stability of the same decision, and exploratory when a current source expanded context without changing the selected question.

3 Results

3.1 Evidence synthesis

The source set contains eight primary studies and eight endpoint classes. Six archived full texts define the core evidence. The two added context papers are useful for currentness but are not allowed to turn the synthesis into a clinical or therapeutic claim.

Wenes 2022 is the closest direct source because it contains both sides of the proposed split. MPC inhibition or deletion promoted a memory-like CD8 program during activation, but MPC loss reduced lactate oxidation and effector function in a tumor-like nutrient-deprived context [1]. This supports a compartment and context rule rather than a global statement that MPC blockade is always beneficial. The same source also reports the critical limitation: in vivo TIL lactate oxidation is technically difficult to demonstrate, so the tumor-site lactate-dependence claim remains bounded.

Scharping 2016 and Klein Geltink 2020 define the strongest alternative. Tumor-infiltrating T cells showed loss of PGC-1alpha and mitochondrial sufficiency, and enforced PGC-1alpha improved intratumoral metabolic and effector function [2]. Separately, PGC-1alpha overexpression promoted CD8 central-memory features, persistence and antitumor immunity [3]. These findings can explain several desired endpoints without invoking MPC as a distinct decision gate. They also show why mitochondrial mass or respiration cannot be used alone to assign a lactate/pyruvate mechanism.

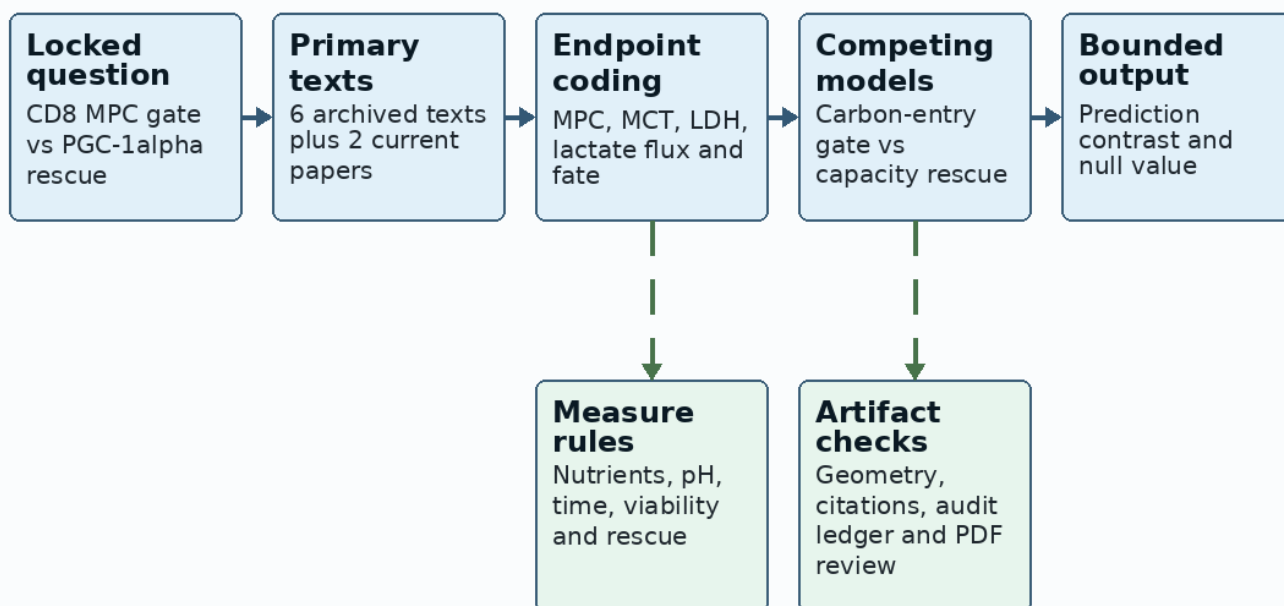
Peng 2016, Quinn 2023 and Ma 2019 define the lactate and LDH boundary. LDHA supported acetyl-CoA-linked histone acetylation and Ifng transcription in T cells, but the system was mainly CD4/Th1 rather than CD8 tumor or ACT context [4]. Quinn 2023 showed that pH-neutral exogenous lactate can be taken up and oxidized by activated CD8 T cells, but LDH inhibition caused viability problems that prevented direct attribution to LDH-mediated lactate-to-pyruvate conversion [5]. Ma 2019 supports lactate as a CD8 carbon source under physiologic activation, but it does not isolate MPC or compare PGC-1alpha rescue [8].

Ron-Harel 2016 prevents a generic mitochondrial-content interpretation. T cell activation induced mitochondrial biogenesis and proteome remodeling that supported one-carbon metabolism [6]. This makes mitochondrial mass a context-dependent endpoint rather than an all-purpose marker of better mitochondrial fitness or PGC-1alpha rescue.

The 2024 MITO-66 study strengthens the ex vivo manufacturing side of the research decision. It reports that a novel MPC inhibitor promoted stem cell-like memory CAR T generation and improved antileukemic efficacy in mouse models [7]. That finding is compatible with the proposed manufacturing rule, but it does not remove the tumor-site warning from Wenes 2022. The interpretation remains that ex vivo MPC inhibition and in vivo lactate-reliant effector support must be separated.

Table 1. Primary-study evidence matrix for the CD8 MPC, lactate and PGC-1alpha comparison.

ID	Model and perturbation	Key finding	Interpretive limitation
[1]	Mouse CD8 T cells, OT1/CAR T cell models and tumor nutrient modeling; MPC1 deletion or MPC inhibitor during activation, plus tumor-like nutrient conditions	MPC inhibition or deletion promoted a memory-like CD8 program in nutrient-replete activation, whereas MPC loss in a nutrient-deprived tumor setting reduced lactate oxidation and effector function.	The paper itself states that in vivo TIL lactate oxidation is technically difficult to demonstrate, so tumor-site lactate dependence remains a bounded inference.
[2]	Tumor-infiltrating CD8 T cells in mouse melanoma and human tumor contexts; Tumor microenvironment exposure, Akt inhibition and enforced PGC-1alpha	TILs lost PGC-1alpha and mitochondrial sufficiency, and enforced PGC-1alpha improved intratumoral metabolic and effector function.	The source does not test MPC, lactate tracing or lactate/pyruvate carbon-entry dependence as a competing gate.
[3]	Retrovirally engineered mouse CD8 T cells in infection, vaccination and melanoma ACT models; Enforced PGC-1alpha expression	PGC-1alpha overexpression increased mitochondrial activity, central-memory features, persistence and antitumor activity.	The work does not perturb lactate, pyruvate, MCT or MPC status, so it is a capacity alternative rather than evidence for carbon-entry gating.
[4]	Activated mouse T cells with emphasis on CD4/Th1 differentiation; LDHA deletion or glycolytic pathway disruption	LDHA maintained acetyl-CoA for histone acetylation and Ifng transcription in T cells.	This is boundary evidence for lactate/LDH-linked effector transcription and is not a CD8 tumor lactate-oxidation study.
[5]	Primary murine and human CD8 T cells activated with pH-neutral sodium lactate; Exogenous pH-neutral lactate exposure with metabolic flux and transcriptomic assays	Exogenous lactate was taken up and oxidized by activated CD8 T cells and displaced glucose as carbon for the TCA cycle and amino acid synthesis.	LDH inhibition harmed viability, preventing direct attribution of lactate effects to LDH-mediated lactate-to-pyruvate conversion in that experiment.
[6]	Naive T cell activation with mitochondrial proteome and functional assays; T cell activation time course	T cell activation induced mitochondrial biogenesis and proteome remodeling that supported one-carbon metabolism.	Activation-linked mitochondrial mass is not equivalent to PGC-1alpha rescue or lactate/MPC carbon-entry dependence.
[7]	Human CD19-CAR T cell manufacturing from healthy donors and relapsed/refractory B cell malignancy samples, with mouse leukemia stress models; MITO-66 MPC inhibitor during CAR T cell manufacturing	MITO-66-conditioned CAR T cells showed stem cell-like memory features and superior antileukemic control in mouse models.	The study supports ex vivo MPC inhibition as manufacturing conditioning; it does not show that systemic in vivo MPC inhibition would support tumor-site effector lactate oxidation.
[8]	Physiologically activated CD8+ effector T cells with stable-isotope nutrient tracing; Physiologic carbon-source availability including lactate	CD8+ T cells used lactate as a mitochondrial and biosynthetic carbon source, including during functional responses in vivo.	The source supports lactate as a CD8 fuel but does not isolate MPC as the required inner-membrane gate or compare PGC-1alpha rescue.



Solid connectors indicate source-coded workflow; dashed connectors indicate required measurement and QA controls.

Figure 1. Analysis workflow for the CD8 lactate/pyruvate competing-model reanalysis. Solid connectors show the source-coded evidence workflow; dashed connectors show measurement and QA controls that prevent a generic mitochondrial-fitness interpretation.

3.2 Evidence-coded sensitivity analysis

The decision-changing sensitivity analysis removed Wenes 2022. Without that source, the paper no longer has same-axis evidence for both MPC-conditioned memory programming and tumor-like lactate oxidation failure. The concept would become an ordinary CD8 mitochondrial-fitness synthesis and would not be ready as a distinct Mito Map contribution.

The robustness sensitivity analysis removed one PGC-1alpha source at a time. Removing Scharping 2016 weakens the tumor-microenvironment PGC-1alpha alternative, but Klein Geltink 2020 still supports enforced PGC-1alpha as a CD8 memory and antitumor-fitness mechanism. Removing Klein Geltink 2020 weakens the memory side of the PGC-1alpha alternative, but Scharping 2016 still supports mitochondrial-biogenesis rescue in TIL dysfunction. The alternative therefore remains credible.

The exploratory sensitivity analysis added the 2024 MITO-66 CAR T paper. This increased the relevance of MPC inhibition to manufacturing but did not change the inference boundary. The added paper supports ex vivo conditioning and should not be used to infer that systemic MPC inhibition would improve tumor-site CD8 effector function.

The lactate-fuel-only robustness check treated Quinn 2023 and Ma 2019 strictly as carbon-use evidence. Under that conservative reading, lactate remains a real CD8 fuel, but fate assignment still requires matched MPC/MCT/LDH flux, PGC-1alpha state and immune endpoint measurement.

4 Discussion

The analysis supports one practical distinction. MPC inhibition can be useful as an ex vivo memory-imprinting strategy under nutrient-replete manufacturing conditions, while MPC-dependent lactate or pyruvate oxidation may be required for effector function in tumor-like nutrient stress. This distinction is not equivalent to a claim that lactate is universally beneficial or harmful, and it is not equivalent to a claim that PGC-1alpha rescue is irrelevant.

The competing PGC-1alpha account remains strong. Enforced PGC-1alpha can improve mitochondrial fitness, persistence, memory characteristics and antitumor outcomes in CD8 systems

[2,3]. Therefore, a study that measures only mitochondrial mass, oxygen consumption or memory markers cannot distinguish carbon-entry gating from mitochondrial-biogenesis rescue. The proposed test must measure flux and fate in the same samples.

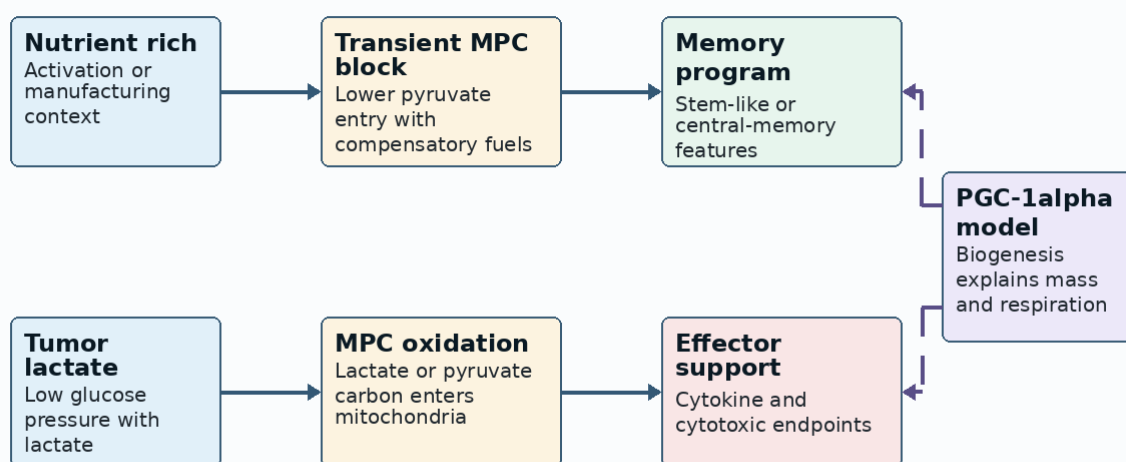
The research decision is specific. Mito Map should discuss immune-cell lactate as a context-specific CD8 carbon-entry rule for ACT manufacturing versus tumor-site effector support, not as a generic lactate-to-PGC-1alpha biogenesis pathway. Confirmation would change the design of follow-on work: ex vivo MPC inhibition should be evaluated separately from tumor-site MPC dependence, and PGC-1alpha rescue should be included as an active comparator rather than background biology.

Several follow-on investigations are supported. Publicly accessible Wenes 2022 ATAC resources could be reanalyzed against PGC-1alpha and mitochondrial-biogenesis modules to test whether MPC-conditioned memory chromatin separates from generic biogenesis. A matched perturbation matrix could combine lactate, glucose, MPC inhibition, MCT1 inhibition, LDH perturbation, PGC-1alpha gain/loss and rescue endpoints. Tumor-like lactate-rich nutrient stress could then be compared with ACT manufacturing media to identify when an MPC inhibitor is predicted to be beneficial, neutral or harmful.

5 Limitations

This working paper is a source-coded evidence synthesis and measurement-rule analysis. It does not include new wet-lab experiments, raw ATAC or metabolomics reanalysis, patient data, pooled effect sizes, clinical efficacy, safety evaluation or treatment advice. The included studies differ by species, cell state, tumor model, activation protocol, lactate concentration, nutrient composition, perturbation and time window.

Full public texts were available for the six selected core sources. The two added context sources were checked through public primary records and full-text availability, but their complete texts were not copied into the public bundle. The biological audit checks manuscript anchors and quoted source spans where the repository corpus can retrieve them; it does not certify biological truth. UNKNOWN or NOT_RUN audit results remain unresolved assumptions, not failures hidden by prose.



Discriminator: match MPC/MCT/LDH state, lactate/pyruvate flux, PGC-1alpha state, mitochondrial output and fate.

Figure 2. Concept summary distinguishing MPC restriction during nutrient-replete activation from MPC-dependent oxidation in tumor-like lactate stress, with PGC-1alpha biogenesis shown as the strongest competing account.

The main contrary evidence is not a single paper disproving the concept. It is the credible PGC-1alpha rescue literature, the viability limitation in LDH inhibition, and the Wenes 2022 limitation on in vivo TIL lactate oxidation. A null future result would be informative: if PGC-1alpha rescue explains matched endpoints after MPC/MCT/LDH disruption, the concept should be demoted to mitochondrial-capacity synthesis. If MPC perturbation has no endpoint-specific effect once PGC-1alpha is controlled, lactate/pyruvate carbon entry should not be framed as a distinct CD8 fate gate.

6 Conclusions

Current public primary evidence supports a bounded discriminability rule. In CD8 T cell work, MPC inhibition during ex vivo manufacturing should be interpreted separately from tumor-site lactate oxidation, and PGC-1alpha mitochondrial-biogenesis rescue should remain the strongest competing account. A distinct lactate/pyruvate carbon-entry concept becomes research-ready only when matched CD8 experiments or source-coded reanalysis measure MPC/MCT/LDH flux, PGC-1alpha state, mitochondrial outputs and fate endpoints together.

Declarations

Data and code availability. The repository deposit includes the manuscript source, evidence table, source data, analysis code, figures, measured figure geometry, biological-audit supplements, layout reports, QA record, Gemini review and checksums needed to replay the table, counts, figures and artifacts. Private replay inputs are retained locally and excluded from public manifests.

Source verification. The biological audit is a manuscript-integrity ledger, not proof of biological truth or clinical efficacy. Corpus anchors and archived normalized source files were replayed against recorded hashes; UNKNOWN or NOT_RUN biological interpretation statuses remain visible.

Ethics statement. This literature synthesis used no identifiable patient data and required no new human-participant or animal research.

Funding. No external funding was reported for this working paper.

Competing interests. The author reports no competing interests for this working paper.

Author contributions. Andrew Friedl conceived the project, directed the analysis, reviewed the evidence package, and approved the manuscript for repository review.

AI assistance. AI tools assisted literature synthesis, drafting, data visualization, formatting and QA preparation. Gemini independently reviewed the exact rendered PDF. Andrew Friedl remains solely responsible for the content and is the sole author.

References

- [1] Wenes M, Jaccard A, Wyss T, Maldonado-Perez N, Teoh ST, Lepez A, et al. The mitochondrial pyruvate carrier regulates memory T cell differentiation and antitumor function. *Cell Metab.* 2022;34:731-746.e9. doi:10.1016/j.cmet.2022.03.013. PMID:35452600.
- [2] Scharping NE, Menk AV, Moreci RS, Whetstone RD, Dadey RE, Watkins SC, et al. The tumor microenvironment represses T cell mitochondrial biogenesis to drive intratumoral T cell metabolic insufficiency and dysfunction. *Immunity.* 2016;45:374-388. doi:10.1016/j.immuni.2016.07.009. PMID:27496732.
- [3] Klein Geltink RI, O'Sullivan D, Corrado M, Bremser A, Buck MD, Buescher JM, et al. Enforced PGC-1alpha expression promotes CD8 T cell fitness, memory formation and antitumor immunity. *Cell Mol Immunol.* 2020;17:1761-1771. doi:10.1038/s41423-020-0371-9. PMID:32055005.
- [4] Peng M, Yin N, Chhangawala S, Xu K, Leslie CS, Li MO. Aerobic glycolysis promotes T helper 1 cell differentiation through an epigenetic mechanism. *Science.* 2016;354:481-484. doi:10.1126/science.aaf6284. PMID:27610503.

- [5] Quinn KM, Barbieri L, Velica P, Gameiro PA, Cunha PP, Foskolou IP, et al. Lactate exposure shapes the metabolic and transcriptomic profile of CD8+ T cells. *Front Immunol.* 2023;14:1101433. doi:10.3389/fimmu.2023.1101433. PMID:36923405.
- [6] Ron-Harel N, Santos D, Ghergurovich JM, Sage PT, Reddy A, Lovitch SB, et al. Mitochondrial biogenesis and proteome remodeling promote one-carbon metabolism for T cell activation. *Cell Metab.* 2016;24:104-117. doi:10.1016/j.cmet.2016.06.007. PMID:27411012.
- [7] Wenes M, Lepez A, Arinkin V, Maundrell K, Barabas O, Simonetta F, et al. A novel mitochondrial pyruvate carrier inhibitor drives stem cell-like memory CAR T cell generation and enhances antitumor efficacy. *Mol Ther Oncol.* 2024;32:200897. doi:10.1016/j.omton.2024.200897. PMID:39677155.
- [8] Ma EH, Verway MJ, Johnson RM, Roy DG, Steadman M, Hayes S, et al. Metabolic profiling using stable isotope tracing reveals distinct patterns of glucose utilization by physiologically activated CD8+ T cells. *Immunity.* 2019;51:856-870.e5. doi:10.1016/j.immuni.2019.09.003. PMID:31747582.