OPEN ACCESS

COMMENTARY

The Innovation Nutrition

Fueling the fight: β-hydroxybutyrate as a metabolic modulator of CAR T cell therapy

Xiaoxiao Zhou,[1] Jihan Liu,[1] Chen Chen,[1] and Xue-Yan He[1,*]

[1]Department of Cell Biology and Physiology, Washington University School of Medicine in St. Louis. St Louis MO, 63110, USA

*Correspondence: xueyanh@wustl.edu

Received: April 9, 2026; Accepted: June 11, 2026; Published Online: June 13, 2026; https://doi.org/10.59717/j.xinn-nutri.2026.100017

© 2026 The Author(s). This is an open access article under the CC BY license (https://creativecommons.org/licenses/by/4.0/).

Citation: Zhou X., Liu J., Chen C., et al. (2026). Fueling the fight: β-hydroxybutyrate as a metabolic modulator of CAR T cell therapy. *The Innovation Nutrition* **1**:100017.

Over the past decades, chimeric antigen receptor (CAR) T cells therapies have greatly reshaped the treatment of cancers. CAR T therapy against CD19 was effective in treating relapsed and refractory acute lymphoblastic leukemia (ALL). However, there are a great number of patients who don't respond to the CAR T cell therapy or eventually relapse, especially for patients with solid tumors.[1] The metabolic fragility of CAR T cells is a well-established barrier to durable therapeutic responses. In the nutrient-deprived, hypoxic tumor microenvironment, activated effector T cells undergo progressive dysfunction driven by mitochondrial stress, impaired OXPHOS, and reduced cytolytic capacity.[2] Efforts to overcome this problem have largely focused on cell-intrinsic engineering strategies, including rewiring transcriptional programs that promote memory formation and oxidative metabolism. These approaches have shown strong preclinical promise, but they add complexity to manufacturing and may complicate clinical implementation. In this context, the study by Liu et al.[3] demonstrates that a single circulating metabolite, β-hydroxybutyrate (BHB), can be as effective as a full ketogenic diet in rewiring CAR T cell metabolism, challenging the assumption that complex dietary interventions are necessary for metabolic reprogramming in adoptive immunotherapy.

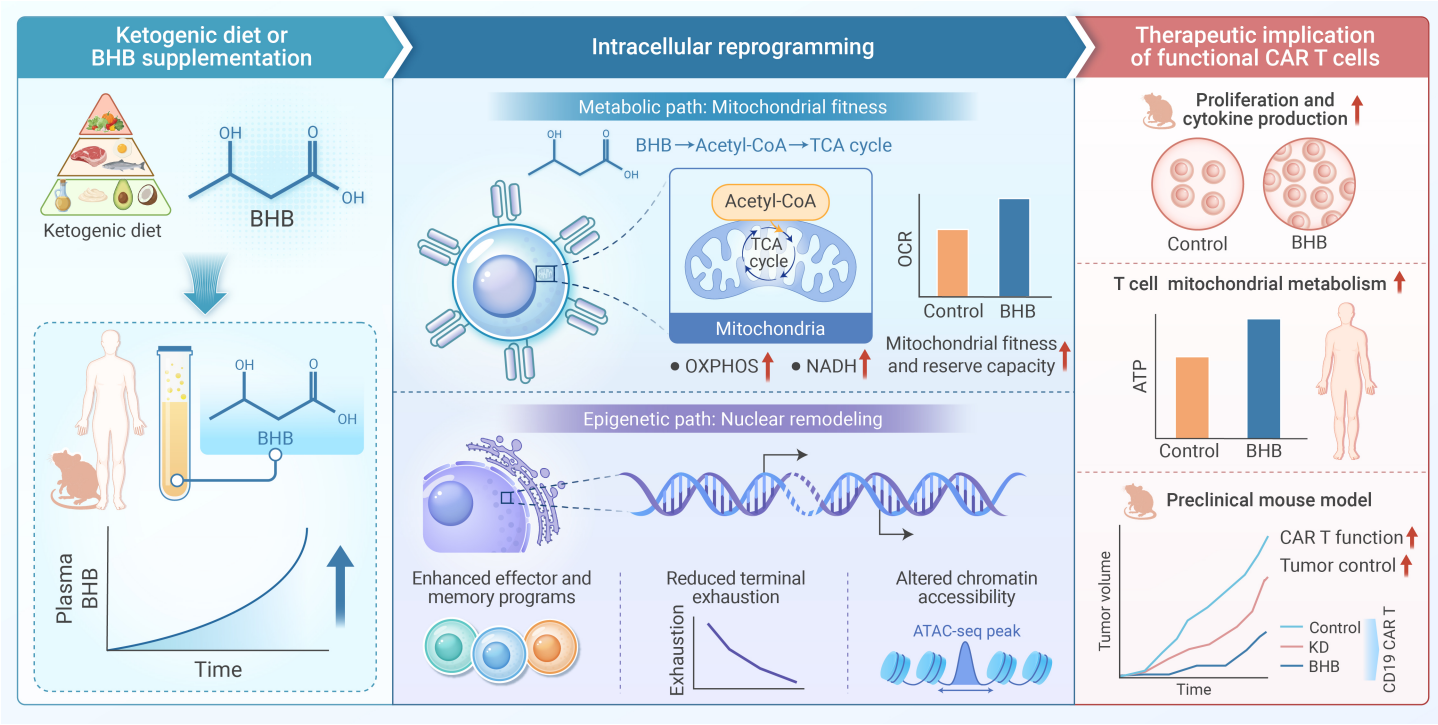

Figure 1. Ketogenic input enhances CAR T cell function via BHB-driven reprogramming.

DIETARY SCREENING: BHB-PRODUCING KETOGENIC DIET (KD) AS A FUNCTIONAL PRECONDITIONER

To establish whether diet alters CAR T efficacy, Liu et al. used a syngeneic CD19$^+$ A20 B cell lymphoma model in BALB/c mice and compared six defined diets reflecting common human patterns: high-fiber, high-protein, Western-type, high-fat, ketogenic, and a carbohydrate-based control. Across multiple cohorts, the ketogenic diet produced significantly better tumor control and improved survival compared with the control diet. Untargeted serum metabolomics identified BHB as the most prominently enriched metabolite in KD-fed mice, and follow-up *in vitro* screening showed that BHB alone was sufficient to enhance CAR T cell proliferation. Supplementation of drinking water with BHB recapitulated much of the antitumor benefit of the full KD, and this effect depended on CAR-antigen engagement.

One appealing aspect of this result is its relative translational simplicity. In contrast to genetic approaches that require additional engineering steps, BHB supplementation could in principle be implemented as a pharmacologic or nutritional adjunct.

BHB AS DIRECT METABOLIC FUEL FOR CAR T CELLS

BHB enters T cells via monocarboxylate transporters and undergoes ketolysis to acetoacetate and then acetyl-CoA, which feeds directly into the tricarboxylic acid cycle, supporting oxidative phosphorylation even when glucose availability is low. Using metabolic assays, they showed that BHB treatment increases oxygen consumption and spare respiratory capacity, indicating more robust mitochondrial oxidative metabolism and a higher bioenergetic reserve. Stable isotope approaches and genetic perturbation of ketolysis pathways, including CRISPR-based editing of the ketone-metabolizing enzyme BDH1 in primary mouse T cells, confirmed that ketone utilization is necessary for the full functional gain. When BDH1 was disrupted, BHB no longer enhanced CAR T antitumor activity, indicating that the benefit of BHB is largely dependent on intact ketolysis. Functionally, BHB-conditioned CAR T cells exhibited enhanced proliferation and cytokine production in vitro. During manufacturing, BHB supplementation increased the fold expansion of patient-derived CAR T cells. In vivo, antitumor efficacy was demonstrated across

multiple tumor models, including an OCI-Ly18 diffuse large B cell lymphoma xenograft model in NSG mice.

What distinguishes BHB from previously described T cell-supportive metabolites (e.g., acetate, butyrate, trans-vaccenic acid) is its direct entry into the TCA cycle distal to glycolysis, bypassing the rate-limiting step of pyruvate dehydrogenase. The paper does not simply associate BHB exposure with improved CAR T performance; rather, it shows that the benefit depends on an intact pathway for BHB utilization. In this respect, the work extends previous evidence that ketolysis can support $CD8^+$ T cell effector function through both metabolic and epigenetic mechanisms.[4]

TRANSCRIPTIONAL AND EPIGENETIC REPROGRAMMING

Liu et al. also investigated how BHB reshapes CAR T transcriptional and epigenetic programs. single-cell RNA sequencing, assay for transposase-accessible chromatin using sequencing (ATAC-seq), and cleavage under targets and release using nuclease (CUT&RUN) profiling converge on a coherent pro-effector, pro-metabolic epigenetic signature in BHB-treated CAR T cells, including increased chromatin accessibility at CCR7, EOMES, ICOS, and BCL2 loci and downregulation of exhaustion-associated transcripts. The multi-omics data also identify HPGD (15-hydroxyprostaglandin dehydrogenase) as a shared enriched gene across datasets. Because HPGD degrades prostaglandin E2 (PGE2), a known suppressor of T cell expansion, its induction raises the possibility that BHB may counteract prostaglandin-mediated immunosuppression.

The paper presents compelling evidence of chromatin remodeling, but it does not fully distinguish among these possibilities. Similarly, the proposed HPGD-PGE2 axis is intriguing, particularly given the immunosuppressive role of PGE2 in tumors, but the evidence presented is associative. The study identifies HPGD across several datasets and reports lower circulating PGE2 in the human cohort yet does not directly establish that this pathway drives the *in vivo* CAR T phenotype. These issues do not weaken the overall conclusion that BHB can reprogram CAR T cells, but they do define the current limits of mechanistic resolution. Direct evidence that HPGD upregulation mediates BHB's in vivo antitumor effects remains to be established.

HUMAN DATA: BHB ENHANCES MITOCHONDRIAL FUNCTION IN T CELLS

To evaluate relevance in humans, the authors conducted a study in healthy volunteers in which BHB was administered and T cell metabolism was assessed before and after supplementation. Using live-cell imaging and fluorescent probes to quantify mitochondrial membrane potential, they observed that peripheral T cells collected after BHB intake displayed increased mitochondrial polarization and higher NADH-related fluorescence, reflecting improved mitochondrial function. These findings extend the murine data by showing that human T cells can acutely increase mitochondrial activity in response to circulating BHB. Although cytokine output and clinical antitumor effects were not directly measured in this volunteer setting, the demonstration that a defined, orally delivered metabolite rapidly improves T cell mitochondrial parameters in people provides a mechanistic bridge to potential clinical application as a metabolic adjunct in patients receiving CAR T or other T cell-based therapies.

However, the human cohort is small, consists of healthy individuals rather than patients, and assesses short-term metabolic effects in peripheral blood T cells rather than functional outcomes of CAR T cells in tumor-bearing hosts. Moreover, R-1,3-butanediol, a BHB precursor used to elevate BHB levels, may exert biological effects independent of BHB itself. These experiments therefore provide evidence of biological plausibility in humans, but not clinical or functional validation. Similarly, any retrospective correlation between serum BHB and CAR T expansion in patients should be interpreted cautiously, as circulating BHB levels may be influenced by nutrition, disease burden, hepatic metabolism, or concomitant medications.

CONCLUSION

Liu et al. identified BHB supplementation as a plausible strategy to enhance CAR T cell therapy (Figure 1). The major contribution of the paper is not merely that BHB improves CAR T cell activity in several preclinical models, but that it provides a mechanistically coherent approach linking nutrient availability, mitochondrial metabolism, and transcriptional state. The stepwise diet-to-metabolite discovery framework, the *Bdh1* knockout rescue experiment, and the multi-omics convergence on a pro-effector epigenetic signature collectively constitute a compelling preclinical case. The prospective human data provide an important proof-of-concept that BHB can acutely enhance T cell oxidative metabolism in people. However, the translational path remains long. The most important unresolved biological question concerns oxygen availability. The benefits of BHB described in this study depend heavily on mitochondrial oxidation, yet one of the defining features of many tumor microenvironments, especially in solid tumors, is hypoxia. Continuous antigen stimulation under hypoxic conditions is known to accelerate mitochondrial stress and T cell dysfunction.[1] Whether BHB can sustain a useful metabolic advantage when oxygen becomes limiting is therefore uncertain. This issue is particularly relevant to the pancreatic cancer experiments, as subcutaneous xenografts may not faithfully reproduce the metabolic constraints of native pancreatic tumors. A strategy that is highly effective in circulating or lymphoid compartments may not translate equivalently to deeply hypoxic tumor sites. A second unresolved issue is systemic specificity. Because BHB is a circulating metabolite, its effects are unlikely to be confined to CAR T cells. Other immune populations within the tumor microenvironment, including regulatory T cells and innate effectors, may also be metabolically reshaped by ketone exposure. Whether these parallel effects are favorable, neutral, or counterproductive remains unclear. For a clinically deployable adjunct, this broader immunologic context will be important.

The broader principle that diet-derived metabolites can shape the epigenetic and metabolic state of engineered T cells is an important and underexplored dimension of adoptive cell therapy. In that context, a recent Nature study showed that postprandial lipid metabolism can durably enhance T cell immunity by increasing metabolic fitness during early activation, with downstream benefits for persistence and effector function, including in CAR T settings[5]. Read alongside Liu et al., these findings support the idea that short-lived systemic metabolic states can leave durable imprints on T cell behavior.

Ketogenic diet or BHB supplementation elevates systemic β-hydroxybutyrate (BHB), which fuels acetyl-CoA production and the TCA cycle to enhance mitochondrial oxidative metabolism. BHB also promotes transcriptional and epigenetic remodeling, improving effector and memory programs while reducing exhaustion. These changes increase proliferation, cytokine production, and mitochondrial fitness, ultimately enhancing tumor control.

REFERENCES

1. Hou A. J., Chen L. C. and Chen Y. Y. (2021). Navigating CAR-T cells through the solid-tumour microenvironment. *Nat. Rev. Drug. Discov.* **20**:531–550. DOI:10.1038/s41573-021-00189-2
2. Scharping N. E., Rivadeneira D. B., Menk A. V., et al. (2021). Mitochondrial stress induced by continuous stimulation under hypoxia rapidly drives T cell exhaustion. *Nat. Immunol.* **22**:205–215. DOI:10.1038/s41590-020-00834-9
3. Liu S., Guruprasad P., Ramasubramanian R., et al. (2026). β-hydroxybutyrate enhances the metabolic fitness of CAR T cells in cancer. *Cell* **189**:1701–1716.e1724. DOI:10.1016/j.cell.2026.02.004
4. Luda K. M., Longo J., Kitchen-Goosen S. M., et al. (2023). Ketolysis drives CD8(+) T cell effector function through effects on histone acetylation. *Immunity* **56**:2021–2035.e2028. DOI:10.1016/j.immuni.2023.07.002
5. Kumar A., Rivadeneira D. B., Mehta I., et al. (2026). Postprandial lipid metabolism durably enhances T cell immunity. *Nature*. DOI:10.1038/s41586-026-10432-8

FUNDING AND ACKNOWLEDGMENTS

This work was supported by the Alvin J. Siteman Cancer Center through The Foundation for Barnes - Jewish Hospital (to X-Y. H.). The funder had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

AUTHOR CONTRIBUTIONS

All authors contributed to and approved the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.