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**1887** Nutrition deprivation affects the cytotoxic effect of CD8 T cells in hepatocellular carcinoma

*Zhang CY, Liu S, Yang M*

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Editorial Board Member of *World Journal of Gastrointestinal Oncology*, Luigi Marano, MD, PhD, Associate Professor, Department of Medicine, Surgery, and Neurosciences, University of Siena, Siena 53100, Italy. [luigi.marano@unisi.it](mailto:luigi.marano@unisi.it)

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## Nutrition deprivation affects the cytotoxic effect of CD8 T cells in hepatocellular carcinoma

Chun-Ye Zhang, Shuai Liu, Ming Yang

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**Chun-Ye Zhang**, Department of Veterinary Pathobiology, University of Missouri, Columbia, MO 65211, United States

**Shuai Liu**, The First Affiliated Hospital, Zhejiang University, Hangzhou 310006, Zhejiang Province, China

**Ming Yang**, Department of Surgery, University of Missouri, Columbia, MO 65211, United States

**Corresponding author:** Ming Yang, DVM, PhD, Postdoctoral Fellow, Department of Surgery, University of Missouri, Room 2203, NexGen Precision Building, 1030 Hitt Street, Columbia, MO 65211, United States. [yangmin@health.missouri.edu](mailto:yangmin@health.missouri.edu)

### Abstract

Hepatocellular carcinoma (HCC) is the most common type of liver cancer and the third leading cause of cancer-related death worldwide. Factors including carcinogens, infection of hepatitis viruses, alcohol abuse, and metabolic disorders such as non-alcoholic fatty liver disease mainly contribute to HCC initiation and progression. Immunotherapy is one of the most powerful tools for unresectable HCC treatment in patients. CD8<sup>+</sup> T cells are a major immune component in the tumor microenvironment with cytotoxic effects against cancer cells. However, these CD8<sup>+</sup> T cells commonly display an exhaustion phenotype with high expression of programmed cell death protein 1, T-cell immunoglobulin and mucin-domain containing-3, and/or lymphocyte-activation gene 3, producing low levels of perforin (PRF1) and granzyme B (GZMB), as well as anti-tumor cytokines, such as interferon gamma and tumor necrosis factor alpha. In the referenced study, the authors also showed that deprivation of glutamine decreased the antitumor function of CD8<sup>+</sup> T cells, as well as the production of PRF1 and GZMB. However, the role of each amino acid in T cell function and exhaustion may depend on tumor type and tumor microenvironment, including the source of other nutrients. Overall, amino acids or other nutrient metabolites in the tumor microenvironment play a pivotal role in both tumor growth and immune response.

**Key Words:** Hepatocellular carcinoma; Metabolism; Amino acids; Tumor microenvironment; T cell function

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**Core Tip:** Immunotherapy is one of the most powerful tools for patients with unresectable hepatocellular carcinoma. CD8<sup>+</sup> T cells are a major immune component in the tumor microenvironment with cytotoxic effects against tumor cells. However, these CD8<sup>+</sup> T cells commonly display an exhaustion phenotype with high expression of immune checkpoints such as programmed cell death protein 1, producing less anti-tumor proteins and cytokines, such as perforin and granzyme B. Here, we show that the roles of amino acids such as glutamine in T cell activation and function are dependent on tumor types and nutrients in the tumor microenvironment. Overall, nutrient metabolism reprogramming in the tumor microenvironment plays a pivotal role in both tumor growth and immune response.

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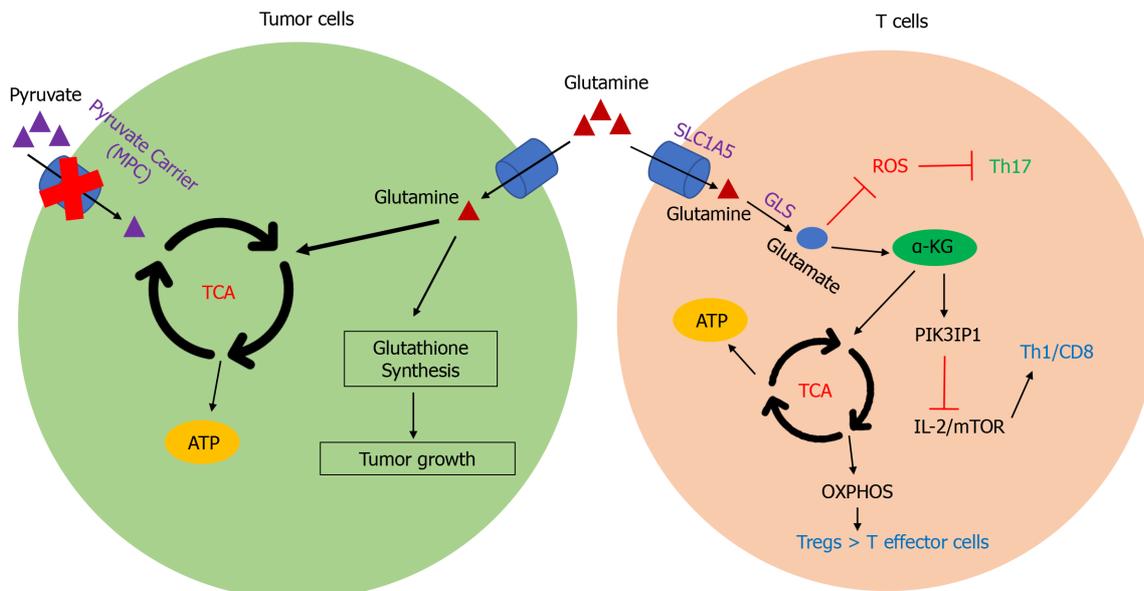
## TO THE EDITOR

We read a basic study recently published by Wang *et al*[1] with great interest, which shows that glutamine deprivation impairs the cytotoxic function of tumor-infiltrating CD8<sup>+</sup> T cells in hepatocellular carcinoma (HCC) by inducing mitochondrial dysfunction and apoptosis. HCC is the primary liver cancer and the third leading cause of cancer-related death worldwide[2]. Factors including carcinogens, infection of hepatitis viruses, alcohol abuse, and metabolic disorders such as non-alcoholic fatty liver disease mainly contribute to HCC initiation and progression[3].

Immunotherapy is one of the most powerful tools for unresectable HCC treatment in patients[4]. CD8<sup>+</sup> T cells are a major immune component in the tumor microenvironment with cytotoxic effects against tumor cells. However, these CD8<sup>+</sup> T cells commonly display an exhaustion phenotype with high expression of programmed cell death protein 1 (PD-1), T-cell immunoglobulin and mucin-domain containing-3, and/or lymphocyte-activation gene 3, which produce low levels of anti-tumor cytokines, such as interferon gamma (IFN- $\gamma$ ) and tumor necrosis factor alpha (TNF- $\alpha$ )[5,6]. In the referenced study, the authors also showed that deprivation of glutamine decreased the secretion of perforin and granzyme B in CD8<sup>+</sup> T cells in HCC[1]. Treatment of immune checkpoint inhibitors by targeting PD-1, programmed death protein-ligand-1 (PD-L1), or cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) has shown clinical effects in HCC patients[7,8]. For example, the U.S. Food and Drug Administration approved the use of nivolumab (anti-PD1) or in combination with ipilimumab or ipilimumab (anti-CTLA-4) for the treatment of patients with HCC in certain conditions[9-11]. Furthermore, the state-art chimeric antigen receptor-engineered T-cell therapy has displayed the promise for HCC treatment[12, 13].

Accumulating data indicate that tumor cells can compete with immune cells for nutrition in a nutrient-poor tumor microenvironment, especially for cytotoxic effective CD8<sup>+</sup> T cells to suppress their anti-tumor immunity[14]. For example, restriction of dietary asparagine (Asn), asparaginase administration, or inhibition of the asparagine transporter solute carrier family 1 member 5 (SLC1A5) impaired the function of CD8<sup>+</sup> T cells[15]. In contrast, increased Asn levels enhance CD8<sup>+</sup> T-cell activation and function against tumor cells (*e.g.*, B16-OVA) *in vitro* and *in vivo*[15]. Supplementation of creatine significantly inhibited tumor growth in multiple mouse tumor models (*e.g.*, B16-OVA melanoma) by activating T cells, which had a synergistic with a PD-1/PD-L1 blockade treatment[16]. Some non-essential amino acids such as serine are required for T cell proliferation by promoting nucleotide biosynthesis[17]. Additionally, nutrients are also required for CD8<sup>+</sup> T cell differentiation into effector and memory subsets, such as glucose, lactate, glutamine, methionine, and neutral amino acids[18]. Under a low-glucose tumor microenvironment, due to the consumption of glucose by tumor cells, the function of effector CD8<sup>+</sup> T cells was impaired and the expression of PD-1 was enhanced in regulatory T cells, resulting in treatment failure of PD-1 blockade[19]. In addition, tumor cell-derived metabolites such as lactate can also inhibit CD8<sup>+</sup> T cell cytotoxicity[20]. Another study also showed that accumulation of long-chain fatty acids (LCFAs) due to downregulation of regulating enzymes can impair CD8<sup>+</sup> T cell function by causing their mitochondrial dysfunction and reducing fatty acid catabolism[21]. Tumor cells can reprogram their metabolic pathways to compete with CD8<sup>+</sup> T cells for nutrients such as fatty acids [22]. Therefore, regulation of nutrient metabolism can impact the function of T cells. Inhibiting glutaminase, an amidohydrolase enzyme that can generate glutamate from glutamine, can also suppress CD8<sup>+</sup> T cell activation induced by anti-PD-1 immunotherapy[23].

Different nutrients show diverse functions in CD8<sup>+</sup> T cells. Regulation of tryptophan metabolism impacts the cytotoxic effect of CD8<sup>+</sup> T cells. For example, inhibiting tryptophan catabolism using indoleamine 2,3-dioxygenase inhibitors can activate CD8<sup>+</sup> T cells and suppress their expression of PD-1 by elevating intracellular tryptophan levels[24]. Meanwhile, tryptophan supplementation also



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**Figure 1** Glutamine metabolism impacts T cell differentiation and tumor growth. Glutamine metabolism can be transferred into cells by solute carriers, such as Solute carrier family 1 member 5 (also known as alanine-serine-cysteine transporter 2). It can be metabolized into glutamate through glutaminolysis (GLS) to impact T helper 17 (Th17) cells, Th1, and CD8 T cell differentiation by regulating the production of reactive oxygen species and expression of phosphoinositide-3-Kinase Interacting Protein 1, respectively. Increasing GLS leads to a proinflammatory effector phenotype, while restriction of GLS causes a slanted Treg differentiation by inhibiting oxidative phosphorylation. In addition, hepatocyte mitochondrial pyruvate carrier disruption redirects glutamine from glutathione synthesis into the tricarboxylic acid cycle, which impaired hepatocellular carcinoma by limiting glutathione synthesis. MPC: Mitochondrial pyruvate carrier; TCA: Tricarboxylic acid; SLC1A5: Solute carrier family 1 member 5; GLS: Glutaminolysis; OXPHOS: Oxidative phosphorylation; TOR: Target of Rapamycin; Th1: T helper 1; PIK3IP1: Phosphoinositide-3-Kinase Interacting Protein 1; ROS: Reactive oxygen species.

promoted the cytotoxic function of CD8<sup>+</sup> T cells against co-cultured B16F10 tumor cells *in vitro* and increased tumor-infiltration of CD8<sup>+</sup> T cells and their functions in mouse lung cancer model[24]. In contrast, another study also showed that depletion of dietary tryptophan decreased aryl hydrocarbon receptor activity in tumor-associated macrophages and increased tumor infiltration of tumor necrosis factor alpha (TNF $\alpha$ )<sup>+</sup>IFN $\gamma$ <sup>+</sup>CD8<sup>+</sup> T cells in pancreatic ductal adenocarcinoma, while supplementation of dietary indoles inhibited this effect[25].

In the reviewed study, the authors showed that mitochondrial damage and apoptosis caused CD8<sup>+</sup> T cell dysfunction. These findings shed light on the need for further investigation into the molecular mechanisms of glutamine metabolism impacting T cell functions. Glutamine metabolism has been shown to regulate the T helper 17 cell differentiation but restrict Th1 and CD8<sup>+</sup> T cell differentiation through glutaminolysis (GLS) by regulating the production of reactive oxygen species and expression of phosphoinositide-3-kinase interacting protein 1 (Figure 1), respectively. SLC1A5, also known as alanine-serine-cysteine transporter 2, mediates glutamine transportation, as well as other solute carriers (SLCs) including SLC6A14, 19, and SLC38A1-5[26]. Increasing GLS leads to a proinflammatory effector phenotype, while restriction of GLS results in a slanted Treg differentiation through the inhibition of oxidative phosphorylation[27]. In addition, hepatocyte mitochondrial pyruvate carrier disruption redirected glutamine from glutathione synthesis into the tricarboxylic acid cycle, which impaired HCC by limiting glutathione synthesis[28]. Another study showed that inhibition of glutamine metabolism can reduce T-cell exhaustion and increase the antitumor activity of tumor-specific CD8<sup>+</sup> T cells against mouse lymphoma[29]. Overall, the function of glutamine on CD8<sup>+</sup> T cells is dependent on tumor microenvironment and tumor type. Meanwhile, regulation of nutrient metabolism could be a synergetic strategy for cancer treatment.

## FOOTNOTES

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**Country/Territory of origin:** United States

**ORCID number:** Chun-Ye Zhang 0000-0003-2567-029X; Shuai Liu 0000-0001-9695-2492; Ming Yang 0000-0002-4895-5864.

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