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WORD COUNT 1319
TIME SUBMITTED 31-JUL-2022 09:30PM
PAPER ID 89018979

Name of Journal: *World Journal of Gastrointestinal Oncology*

Manuscript NO: 78296

Manuscript Type: LETTER TO THE EDITOR

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

Nutrition affects T cell function

Chunye Zhang, Shuai Liu, Ming Yang

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 (NAFLD) mainly contribute to HCC initiation and progression. Immunotherapy is one of the most powerful tools for unresectable HCC treatment in patients. $CD8^+$ T cells are a major immune component in the tumor microenvironment with cytotoxic effect against cancer cells. However, these $CD8^+$ 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 (TIM-3), and/or lymphocyte-activation gene 3 (LAG3), producing low levels of perforin (PRF1) and granzyme B (GZMB), as well as anti-tumor cytokines, such as interferon gamma (IFN-γ) and tumor necrosis factor alpha (TNF-α). In the referenced study, the authors also showed that deprivation of glutamine decreased the antitumor function of $CD8^+$ 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

Zhang C, Liu S, Yang M. Nutrition deprivation affects the cytotoxic effect of CD8 T cells in hepatocellular carcinoma. *World J Gastrointest Oncol* 2022; In press

Core Tip: Immunotherapy is one of the most powerful tools for patients with unresectable hepatocellular carcinoma (HCC). $CD8^+$ T cells are a major immune component in the tumor microenvironment with cytotoxic effect against tumor cells.

However, these CD8⁺ T cells commonly display an exhaustion phenotype with high expression of immune checkpoints such as programmed cell death protein 1 (PD-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.

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⁺ 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 (NAFLD) mainly contribute to HCC initiation and progression[3].

Immunotherapy is one of the most powerful tools for unresectable HCC treatment in patients[4]. CD8⁺ T cells are a major immune component in the tumor microenvironment with cytotoxic effect against tumor cells. However, these CD8⁺ 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 (TIM-3), and/or lymphocyte-activation gene 3 (LAG3), which produce low levels of anti-tumor cytokines, such as interferon gamma (IFN-γ) and tumor necrosis factor alpha (TNF-α) [5, 6]. In the referenced study, the authors also showed that deprivation of glutamine decreased the secretion of perforin (PRF1) and granzyme B (GZMB) in CD8⁺ T cells in HCC[1]. Treatment of immune checkpoint inhibitors (ICIs) 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 (FDA) 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 (CAR)-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 (TME), especially for cytotoxic effective $CD8^+$ 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 $CD8^+$ T cells[15]. In contrast, increased asparagine (Asn) levels enhance $CD8^+$ 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 (eg., 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 $CD8^+$ 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 $CD8^+$ 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 $CD8^+$ T cell cytotoxicity[20]. Another study also showed that accumulation of long-chain fatty acids (LCFAs) due to downregulation of regulating enzymes can impair $CD8^+$ T cell function by causing their mitochondrial dysfunction and reducing fatty acid catabolism[21]. Tumor cells can reprogram their metabolic pathways to compete with $CD8^+$ 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 $CD8^+$ T cell activation induced by anti-PD-1 immunotherapy[23].

Different nutrients show diverse functions in $CD8^+$ T cells. Regulation of tryptophan metabolism impacts the cytotoxic effect of $CD8^+$ T cells. For example, inhibiting tryptophan catabolism using indoleamine 2,3-dioxygenase (IDO) inhibitors can activate $CD8^+$ T cells and suppress their expression of PD-1 by elevating intracellular tryptophan levels[24]. Meanwhile, tryptophan supplementation also promoted the cytotoxic function of $CD8^+$ T cells against co-cultured B16F10 tumor cells *in vitro* and increased tumor-infiltration of $CD8^+$ 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 (AhR) activity in tumor-associated macrophages and increased tumor infiltration of tumor necrosis factor alpha $(TNF\alpha)^+IFN\gamma^+CD8^+$ T cells in pancreatic ductal adenocarcinoma (PDAC), while supplement of dietary indoles inhibited this effect[25].

In the reviewed study, the authors showed that mitochondrial damage and apoptosis caused $CD8^+$ 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 (Th17) cell differentiation but restrict Th1 and $CD8^+$ T cell differentiation through glutaminolysis (GLS) by regulating the production of reactive oxygen species (ROS) and expression of phosphoinositide-3-kinase interacting protein 1 (PIK3IP1) (**Figure 1**), respectively. Solute carrier family 1 member 5 (SLC1A5, also known as ASCT2) 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 (OXPHOS)[27]. In addition, hepatocyte mitochondrial pyruvate carrier (MPC) disruption redirected glutamine from glutathione synthesis into the tricarboxylic acid (TCA) 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 $CD8^+$ T cells against mouse lymphoma[29]. Overall, the function of

glutamine on $CD8^+$ T cells is dependent on tumor microenvironment and tumor type. Meanwhile, regulation of nutrient metabolism could be a synergetic strategy for cancer treatment.

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1	Wei Wang, Meng-Nan Guo, Ning Li, De-Quan Pang, Jing-Hua Wu. " Glutamine deprivation impairs function of infiltrating CD8 T cells in hepatocellular carcinoma by inducing mitochondrial damage and apoptosis ", World Journal of Gastrointestinal Oncology, 2022 Crossref	29 words — 2%
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