## Contents

### REVIEW

**1604** Advances in postoperative adjuvant therapy for primary liver cancer  
Zeng ZM, Mo N, Zeng J, Ma FC, Jiang YF, Huang HS, Liao XW, Zhu GZ, Ma J, Peng T

**1622** Immunotherapy for nonalcoholic fatty liver disease-related hepatocellular carcinoma: Lights and shadows  
Costante F, Airola C, Santopao F, Gasbarrini A, Pompili M, Ponziani FR

**1637** Emerging role of caldesmon in cancer: A potential biomarker for colorectal cancer and other cancers  

### MINIREVIEWS

**1654** Liquid biopsy to detect resistance mutations against anti-epidermal growth factor receptor therapy in metastatic colorectal cancer  
Valenzuela G, Burotto M, Marcelain K, González-Montero J

**1665** Implication of gut microbiome in immunotherapy for colorectal cancer  

### ORIGINAL ARTICLE

**Basic Study**

**1675** Potential of six-transmembrane epithelial antigen of the prostate 4 as a prognostic marker for colorectal cancer  
Fang ZX, Li CL, Chen WJ, Wu HT, Liu J

**Case Control Study**

**1689** Inverse relations between *Helicobacter pylori* infection and risk of esophageal precancerous lesions in drinkers and peanut consumption  

**Retrospective Cohort Study**

**1699** Prognostic impact of tumor deposits on overall survival in colorectal cancer: Based on Surveillance, Epidemiology, and End Results database  
Wu WX, Zhang DK, Chen SX, Hou ZY, Sun BL, Yao L, Jie JZ

**1711** Consolidation chemotherapy with capecitabine after neoadjuvant chemoradiotherapy in high-risk patients with locally advanced rectal cancer: Propensity score study  
## Contents

### Retrospective Study

1727  
Efficacy and safety of computed tomography-guided microwave ablation with fine needle-assisted puncture positioning technique for hepatocellular carcinoma  
Hao MZ, Hu YB, Chen QZ, Chen ZX, Lin HL

1739  
Clinicopathological characterization of ten patients with primary malignant melanoma of the esophagus and literature review  

1758  
Endoscopic debulking resection with additive chemoradiotherapy: Optimal management of advanced inoperable esophageal squamous cell carcinoma  
Ren LH, Zhu Y, Chen R, Shrestha Sachin M, Lu Q, Xie WH, Lu T, Wei XY, Shi RH

1771  
Nomogram for predicting the prognosis of tumor patients with sepsis after gastrointestinal surgery  
Chen RX, Wu ZQ, Li ZY, Wang HZ, Ji JF

1785  
Efficacy and safety of laparoscopic radical resection following neoadjuvant therapy for pancreatic ductal adenocarcinoma: A retrospective study  
He YG, Huang XB, Li YM, Li J, Peng XH, Huang W, Tang YC, Zheng L

### Observational Study

1798  
To scope or not - the challenges of managing patients with positive fecal occult blood test after recent colonoscopy  

1808  
Clinical implications of interleukins-31, 32, and 33 in gastric cancer  
Liu QH, Zhang JW, Xia L, Wise SG, Hambly BD, Tao K, Bao SS

1823  
Construction and analysis of an ulcer risk prediction model after endoscopic submucosal dissection for early gastric cancer  
Gong SD, Li H, Xie YB, Wang XH

1833  
Percutaneous insertion of a novel dedicated metal stent to treat malignant hilar biliary obstruction  

### EVIDENCE-BASED MEDICINE

1844  
Prediction of gastric cancer risk by a polygenic risk score of *Helicobacter pylori*  

### META-ANALYSIS

1856  
Dissecting novel mechanisms of hepatitis B virus related hepatocellular carcinoma using meta-analysis of public data  

1874  
Prognostic and clinicopathological value of Twist expression in esophageal cancer: A meta-analysis  
Song WP, Wang SY, Zhou SC, Wu DS, Xie JY, Liu TT, Wu XZ, Che GW
LETTER TO THE EDITOR

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

Zhang CY, Liu S, Yang M
ABOUT COVER
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

AIMS AND SCOPE
The primary aim of World Journal of Gastrointestinal Oncology (WJGO, World J Gastrointest Oncol) is to provide scholars and readers from various fields of gastrointestinal oncology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.
WJGO mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal oncology and covering a wide range of topics including liver cell adenoma, gastric neoplasms, appendiceal neoplasms, biliary tract neoplasms, hepatocellular carcinoma, pancreatic carcinoma, cecal neoplasms, colonic neoplasms, colorectal neoplasms, duodenal neoplasms, oesophageal neoplasms, gallbladder neoplasms, etc.

INDEXING/ABSTRACTING
The WJGO is now abstracted and indexed in PubMed, PubMed Central, Science Citation Index Expanded (SCIE, also known as SciSearch®), Journal Citation Reports/Science Edition, Scopus, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database. The 2022 edition of Journal Citation Reports® cites the 2021 impact factor (IF) for WJGO as 3.404; IF without journal self cites: 3.357; 5-year IF: 3.250; Journal Citation Indicator: 0.53; Ranking: 162 among 245 journals in oncology; Quartile category: Q3; Ranking: 59 among 93 journals in gastroenterology and hepatology; and Quartile category: Q3. The WJGO’s CiteScore for 2021 is 3.6 and Scopus CiteScore rank 2021: Gastroenterology is 72/149; Oncology is 203/360.

RESPONSIBLE EDITORS FOR THIS ISSUE
Production Editor: Ying-Yi Yuan; Production Department Director: Xiang Li; Editorial Office Director: Jia-Ru Fan.

NAME OF JOURNAL
World Journal of Gastrointestinal Oncology

ISSN
ISSN 1948-5204 (online)

LAUNCH DATE
February 15, 2009

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Monjur Ahmed, Florin Burada

EDITORIAL BOARD MEMBERS

PUBLICATION DATE
September 15, 2022

COPYRIGHT
© 2022 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.ffisite.com
LETTER TO THE EDITOR

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

Chun-Ye Zhang, Shuai Liu, Ming Yang

Specialty type: Oncology
Provenance and peer review: Invited article; Externally peer reviewed.
Peer-review model: Single blind

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+ T cells are a major immune component in the tumor microenvironment with cytotoxic effects against cancer cells. However, these CD8+ 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+ 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

©The Author(s) 2022. Published by Baishideng Publishing Group Inc. All rights reserved.
Core Tip: Immunotherapy is one of the most powerful tools for patients with unresectable hepatocellular carcinoma. CD8\(^+\) T cells are a major immune component in the tumor microenvironment with cytotoxic effects 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, 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.

Citation: Zhang CY, Liu S, Yang M. Nutrition deprivation affects the cytotoxic effect of CD8 T cells in hepatocellular carcinoma. World J Gastrointest Oncol 2022; 14(9): 1887-1891


DOI: https://dx.doi.org/10.4251/wjgo.v14.i9.1887

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 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 effects 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, 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\(^+\) T cells in HCC\(^{[4]}\). 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\(^+\) T cells to suppress their anti-tumor immunity\(^{[14]}\). For example, restriction of dietary asparagine (Asn), asparaginase administration, or inhibition of the asparaginase transporter solute carrier family 1 member 5 (SLC1A5) impaired the function of CD8\(^+\) T cells\(^{[15]}\). In contrast, increased Asn levels enhance CD8\(^+\) T-cell activation and function against tumor cells (e.g., B16-OVA) \textit{in vitro} and \textit{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\(^+\) 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 inhibitors can activate CD8\(^+\) T cells and suppress their expression of PD-1 by elevating intracellular tryptophan levels\(^{[24]}\). Meanwhile, tryptophan supplementation also

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 results in a slanted Treg differentiation through the inhibition of 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+ 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 activity in tumor-associated macrophages and increased tumor infiltration of tumor necrosis factor alpha (TNFα)+IFNγ+CD8+ 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+ 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+ 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 hepatocellular carcinoma 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.

FOOTNOTES

Author contributions: Zhang CY, Liu S, and Yang M designed, collected data, wrote, revised, and finalized the manuscript, contributed equally, and shared the first authorship.

Conflict-of-interest statement: All authors declare no conflicts of interest.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license
their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

Country/Territory of origin: United States

ORCID number: Chun-Ye Zhang 0000-0003-2567-029X; Shuai Liu 0000-0001-9695-2492; Ming Yang 0000-0002-4859-5864.

S-Editor: Wang LL
L-Editor: A
P-Editor: Wang LL

REFERENCES


Desdín-Micó G 2021; Wang W suppress anti-tumor immunity. Tryptophan-derived microbial metabolites activate the aryl hydrocarbon receptor in tumor-associated macrophages to


Joshi S, Yao CH, Yoon H, Sage PT, LaFleur MW, Trombley JD, Jacobson CA, Maliga Z, Gygi SP, Sorger PK, Rabinowitz


Kumagai S 2022 


