

Cover letter

Dear Editor,

We revised the manuscript (No. 78296) according to the comments. Please the following point-by-point revision. All the revised part in the manuscript was listed in the following section of reviewers' comments.

Thank you for these great suggestions.

Sincerely,

Ming Yang, PhD

Department of Surgery

University of Missouri

1 MANUSCRIPT REVISION DEADLINE

We request that you submit your revision in no more than **14 days**. **Please note that you have only two chances for revising the manuscript.**

Response: The revised manuscript will be submitted on time.

2 PLEASE SELECT TO REVISE THIS MANUSCRIPT OR NOT

Please login to the F6Publishing system at <https://www.f6publishing.com> by entering your registered E-mail and password. After clicking on the "Author Login" button, please click on "Manuscripts Needing Revision" under the "Revisions" heading to find your manuscript that needs revision. Clicking on the "Handle" button allows you to choose to revise this manuscript or not. If you choose not to revise your manuscript, please click on the "Decline" button, and the manuscript will be WITHDRAWN.

Response: Authors have accepted to revise the manuscript according to all the reviewers' comments.

3 SCIENTIFIC QUALITY

Please resolve all issues in the manuscript based on the peer review report and make a point-by-point response to each of the issues raised in the peer review report. Note, authors must resolve all issues in the manuscript that are raised in the peer-review report(s) and provide point-by-point responses to each of the issues raised in the peer-review report(s); these are listed below for your convenience:

Reviewer #1:

Scientific Quality: Grade A (Excellent)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (High priority)

Specific Comments to Authors: NO

Response: The authors appreciated that reviewer reviewed the manuscript and agreed with the letter context.

Reviewer #2:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Minor revision

Specific Comments to Authors: Comments Name of Journal: World Journal of Gastrointestinal Oncology Manuscript NO: 78296 Manuscript Type: Letter to Editor Title: Nutrition deprivation affects the cytotoxic effect of CD8 T cells in hepatocellular carcinoma The author of this manuscript read a basic study recently published by Wang et al. with great interest and showed 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, amino acid metabolism reprogramming in the tumor microenvironment plays a pivotal role in both tumor growth and immune response. This paper is very interesting, but there are a few of defects need to be modified. The title of this article is: Nutrition deprivation affects the cytotoxic effect of CD8 T cells in hepatocellular carcinoma (Key word: Nutrition). The title of Reference 1 is: Glutamine deprivation impairs function of infiltrating CD8⁺ T cells in hepatocellular carcinoma by inducing mitochondrial damage and apoptosis (Key word: Glutamine). Maybe the author of this manuscript mean that there are other Nutrition or amino acids with the similar effects of Glutamine (affects the cytotoxic effect of CD8 T cells), but they did not mentioned in the text. It is recommended that the author list some other Nutrition or amino acids, and briefly discuss the them, and provide related references.

Response: We thank the reviewer's time and effort on these great comments. Nutrition or amino acids except glutamine has or have further been discussed in the revised manuscript, which are referenced. The context is also listed below: "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].”

Reviewer #3:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: According to what have been mentioned in this letter, the nutrition such as (glutamine, asparagine, serine, glucose, lactate, glutamine, methionine, neutral amino acids and tryptophan) deficiency effect CD8⁺ T-cell activation and function against tumor cells, proliferation, and cytotoxic effect of CD8⁺ T cells. The findings were declared in previous studies. Glutamine deprivation has a different effect on the CD8⁺T cells, that depends on the tumor microenvironment and tumor type.

Response: We appreciated the reviewer’s agreement with the letter and bringing out the core idea for the letter.

4 LANGUAGE POLISHING REQUIREMENTS FOR REVISED MANUSCRIPTS SUBMITTED BY AUTHORS WHO ARE NON-NATIVE SPEAKERS OF ENGLISH

Response: The English grammar was checked by a native English speaker.

5 ABBREVIATIONS

Response: The abbreviations in the manuscript were explained.

6 EDITORIAL OFFICE’S COMMENTS

Authors must revise the manuscript according to the Editorial Office’s comments and suggestions, which are listed below:

(1) Science editor:

The manuscript has been peer-reviewed, and it's ready for the first decision.

Language Quality: Grade A (Priority publishing)

Scientific Quality: Grade B (Very good)

(2) *Company editor-in-chief:*

This is not an invited "letter to the editor".

Response: Thank you for the comments. The reader code for letter to editor: 05225141.

7 STEPS FOR SUBMITTING THE REVISED MANUSCRIPT

(1) 78296-Answering Reviewers

(2) 78296-Audio Core Tip

(3) 78296-Conflict-of-Interest Disclosure Form

(4) 78296-Copyright License Agreement

(5) 78296-Approved Grant Application Form(s) or Funding Agency Copy of any Approval Document(s)

(6) 78296-Non-Native Speakers of English Editing Certificate

(7) 78296-Video

(8) 78296-Image File

(9) 78296-Table File

(10) 78296-Supplementary Material

Response: Thank you for these steps. Five of 10 were submitted according to the Article type and context.

8 COPYRIGHT LICENSE AGREEMENT

Response: All authors accepted and signed the Copyright License Agreement (CLA).

9 CONFLICT-OF-INTEREST DISCLOSURE FORM

Response: The form was filled and submitted together with manuscript.

Thank you for consideration of the revised manuscript.

All the best,

Ming Yang