



## PEER-REVIEW REPORT

**Name of journal:** *World Journal of Gastrointestinal Oncology*

**Manuscript NO:** 74252

**Title:** Glutamine deprivation impairs function of infiltrating CD8+ T cells in hepatocellular carcinoma by inducing mitochondrial damage and apoptosis

**Provenance and peer review:** Unsolicited manuscript; Externally peer reviewed

**Peer-review model:** Single blind

**Reviewer's code:** 03699912

**Position:** Peer Reviewer

**Academic degree:** PhD

**Professional title:** Full Professor

**Reviewer's Country/Territory:** Argentina

**Author's Country/Territory:** China

**Manuscript submission date:** 2021-12-18

**Reviewer chosen by:** Jin-Lei Wang

**Reviewer accepted review:** 2022-03-10 08:36

**Reviewer performed review:** 2022-03-21 09:46

**Review time:** 11 Days and 1 Hour

<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Re-review</b>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No



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<b>Peer-reviewer statements</b>	Peer-Review: [ <input checked="" type="checkbox"/> ] Anonymous [ <input type="checkbox"/> ] Onymous Conflicts-of-Interest: [ <input type="checkbox"/> ] Yes [ <input checked="" type="checkbox"/> ] No
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### **SPECIFIC COMMENTS TO AUTHORS**

Tex cells are characterized by loss of effector functions, elevated and sustained expression of inhibitory receptors, and a distinct metabolic profile[7-8]. Recently, the mechanisms of CD8+T cell exhaustion have become a research hotspot, which has increased interest in how changes in metabolomics correlate with changes in immune cell functions. Gln is the most abundant free amino acid in serum, it is not only involved in the occurrence, development, and metastasis of tumor cells but also regulates the growth and function of immune cells. Gln has been reported to regulate the phenotype of CD4 cells, and increasing Gln levels can skew regulatory CD4+T cells toward more inflammatory subtypes. However, whether Gln also regulates CD8+T cells and the mechanism of this regulation have not been reported. It has also been shown in the literature that after glucose deprivation, CD8+T cells in the tumor microenvironment produce ROS, which subsequently triggers mitochondrial damage. This study was designed to investigated whether Gln regulated CD8+T cell function through the mitochondrial damage and apoptotic pathways to clarify the relationship between Gln metabolism and CD8+T cell depletion, laying a foundation for new anti-tumor treatments. The study design is very well, the methods are described in detail. The results are very interesting. The manuscript is very well written. The reviewer recomends to accept this manuscript after a minor editing, such as minor language editing, update the figures with high resolution ratio images, etc.



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**Peer-review model:** Single blind

**Reviewer's code:** 05821393

**Position:** Peer Reviewer

**Academic degree:** PhD

**Professional title:** Assistant Professor, Senior Researcher

**Reviewer's Country/Territory:** Iran

**Author's Country/Territory:** China

**Manuscript submission date:** 2021-12-18

**Reviewer chosen by:** Jin-Lei Wang

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<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
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### **SPECIFIC COMMENTS TO AUTHORS**

This is an interesting study of glutamine metabolism affects the function of tissue infiltrating CD8+T cells. The study is very well designed and performed. Data in the results and the figures are very interesting. A minor revision is required: Please make a short discuss about the limit of the study.



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**Peer-review model:** Single blind

**Reviewer's code:** 03672082

**Position:** Peer Reviewer

**Academic degree:** MD

**Professional title:** Associate Professor

**Reviewer's Country/Territory:** Denmark

**Author's Country/Territory:** China

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### **SPECIFIC COMMENTS TO AUTHORS**

Congratulations to the authors, a very interesting study was performed. I read the study with great interest, and found that the study is suitable for publication. Thank you.