

Dear professor,

We are submitting the revised version of our **manuscript NO.: 67321, “Solute carrier family 2 members 1 and 2 as prognostic biomarkers in hepatocellular carcinoma associated with immune infiltration”** to *World Journal of Clinical Cases*. We really appreciate the valuable and detailed comments provided by the reviewers. We tried our best to make substantial changes and improve the manuscript accordingly in the manuscript. All of the changes did not influence the contents and framework of the paper. In addition, we have provided point-to-point responses to the reviewers' comments on the following pages. We have also consulted native English speakers for language editing and revision. We hope you will find the revised version of our manuscript suitable for publication with *World Journal of Clinical Cases*. Please do not hesitate to contact us if you have any additional questions and suggestions on improving the paper.

Thank you for your attention and consideration of our manuscript.

Yours Sincerely,

Xinli Shi,

Pathobiology and Immunology, Hebei University of Chinese Medicine, No. 3 Xingyuan Road, Luquan District, Shijiazhuang 050200, Hebei Province, China
Tel: +86-0311-89926262; E-mail: sxlsunshine@sina.com.

Response to the reviewer's comments:

Response to Reviewer #1:

Based on the detailed comments, we have made careful modifications to our paper as follows:

1) The innovative point for this manuscript is the correlation of the metabolic shifting with the immune cells. In this way, the authors should provide more experiments that support this idea.

Response: Thank you very much for your valuable advice. We believe that the detection of immune cell status after liver tumor induction by SLC2A1 and SLC2A2 gene knockout or overexpressed mice, or the correlation of SLC2A1 and SLC2A1 with immune cells demonstrated by clinical sample protein can be a good solution to this problem. However, due to the long period of the experiment, I cannot supplement the experiment within 14 days. But I think it's certainly an interesting question to explore in the future.

In addition, other studies have found that High expression of SLC2A1 in gastric cancer cells was associated with suppressing CD8⁺ T cells and B cells^[1]. And an inverse correlation between SLC2A1 expression and the number of CD8⁺ T cells in renal cell carcinoma^[2]. Other studies reported that T cells, CD8⁺ T cells, and B cells reduced in the SLC2A1 expressive group of human papillomavirus type 16-positive cervical cancer^[3]. This part has been added to the manuscript, and placed in the discussion section on lines 80 through 84.

2) Does the abstract follow the guidelines?

Response: Thank you very much for your valuable advice. We have revised

the abstract according to the guidelines. Guidelines for the following:

1.8 Abstract. An informative, structured abstract of no less than 350 words should accompany each manuscript. Abbreviations should be avoided, but if used should be spelled out at first mention. The 5 sections of the structured abstract are: Background, Aims, Methods, Results, and Conclusion. Each section should adhere to the word count thresholds (indicated in parentheses) and the content guidelines below:

BACKGROUND (no more than 100 words)

This section should clearly describe the rationale for the study. It should end with a statement of the specific study hypothesis.

AIM (no more than 20 words)

The purpose of the study should be stated clearly, with no or minimal background information, following the format of: "To investigate/ study/ determine..."

METHODS (no less than 80 words)

This section should describe the materials and methods used for all of the data presented in the proceeding Results section of the abstract. This information should include the following details, as applicable: basic study design (*e.g.*, randomized controlled trial, cross sectional study, cohort study, case series, *etc.*); setting, please specify study location (*e.g.*, primary or tertiary care setting, hospital, general community, *etc.*); number of participants and how they were selected; intervention, the method of administration and the duration; major statistical methods used.

RESULTS (no less than 120 words)

This section should describe the key findings of the study, including absolute values and risk differences. *P* values should be presented where appropriate, and not for data that did not reach the threshold of statistical significance. You must provide relevant data to illustrate how the statistical values were obtained (*e.g.*, 6.92 ± 3.86 vs 3.61 ± 1.67 , $P < 0.001$).

CONCLUSION (no more than 30 words)

This section should succinctly and cogently present the findings and implications that are within the scope of the data you have presented in the preceding Results section of the abstract. You should state only conclusions that are directly supported by the evidence presented and the implications of the findings presented. This section should be written in the present tense.

3) Is there any other data in another cell line, since HepG2 is a hepatoma cell line and

the authors are working with HCC?

Response: Thank you very much for your valuable advice. In figure 1C, SLC2A1 was also high and SLC2A2 was low in HepG2215 cells by RNA sequencing.

In addition, other studies have found that SLC2A1 was highly expressed in HepG2, Hep3B, and SK-HEP1 cells compared with normal hepatocytes^[4]. This part has been added to the manuscript, and placed in the discussion section on lines 20 through 22.

Reference

1. **Min KW**, Kim DH, Son BK, Moon KM, Kim SM, Intazur Rahaman M, Kim SW, Kim EK, Kwon MJ, Koh YW, Oh IH. High SLC2A1 expression associated with suppressing CD8 T cells and B cells promoted cancer survival in gastric cancer. *PLoS One* 2021; **16**: e0245075 [PMID: 33735188 DOI:10.1371/journal.pone.0245075]
2. **Singer K**, Kastenberger M, Gottfried E, Hammerschmied CG, Büttner M, Aigner M, Seliger B, Walter B, Schlösser H, Hartmann A, Andreesen R, Mackensen A, Kreutz M. Warburg phenotype in renal cell carcinoma: high expression of glucose-transporter 1 (GLUT-1) correlates with low CD8(+) T-cell infiltration in the tumor. *Int J Cancer* 2011; **128**: 2085-2095 [PMID: 20607826 DOI:10.1002/ijc.25543]
3. **Kim BH**, Chang JH. Differential effect of GLUT1 overexpression on survival and tumor immune microenvironment of human papilloma virus type 16-positive and -negative cervical cancer. *Sci Rep* 2019; **9**: 13301 [PMID: 31527827 DOI:10.1038/s41598-019-49928-x]
4. **Zhao J**, Zhang Z, Nie D, Ma H, Yuan G, Su S, Liu S, Liu S, Tang G. PET Imaging of Hepatocellular Carcinomas: (18)F-Fluoropropionic Acid as a Complementary Radiotracer for (18)F-Fluorodeoxyglucose. *Mol Imaging* 2019; **18**: 1536012118821032 [PMID: 30799682 DOI:10.1177/1536012118821032]

Response to Reviewer #2:

Based on the detailed comments, we have made careful modifications to our paper as follows:

1) The most important comment is the rush of unexplained abbreviations that make it

hardly read, please spell out abbreviations when you first use.

Response: Thank you very much for your valuable advice. A large number of unexplained abbreviations do affect the readability of the article, and we have made modifications to these.

2) In addition few comments are to be corrected.

Response: Thank you very much for your valuable advice. We have made modifications according to your specific comments.