

April 28th, 2019

**Title:** Hepatocellular Carcinoma: Mechanisms of Progression and Immunotherapy

**Author:** Yu Jiang, Qiu-Ju Han, Jian Zhang

**Name of Journal:** *World Journal of Gastroenterology*

**Manuscript NO:** 46670

Dear Editors,

Thank you for your comments and those of the reviewers which are highly insightful and have enabled us to greatly improve our manuscript. We have carefully read the comments on the manuscript and revised the manuscript based on these comments.

Please find attached point-by-point responses to the reviewers' comments.

Revisions in the text are shown using yellow highlighting for additions. The figures and table have been inserted at the specified location. We have provided language certificate by professional English language editing companies mentioned in 'The Revision Policies of BPG for Article' in the uploaded documents. And we have also uploaded other required accompanying documents *via* the F6Publishing system.

We appreciate Editors/Reviewers' hard work earnestly and hope that the revisions in the manuscript and our accompanying responses will be sufficient to make our manuscript suitable for publication in *World Journal of Gastroenterology*.

Sincerely yours,

Jian Zhang, M.D., Ph.D.

Professor

Institute of Immunopharmaceutical Sciences

School of Pharmaceutical Sciences

## Response to Reviewer reports:

### 1. Reviewer's code: 02822399

Jiang and colleagues investigated the mechanisms of progression and immunotherapy in hepatocellular carcinoma. They did a good job but I suggested: 1- Adding a table or a graph for each pathway summarising its role in hepatocellular carcinoma. 2- Adding a paragraph at the end of the manuscript before the conclusion summarising the future directions in this field.

**Response:** Thank you for your positive comments. We are in agreement with your suggestions, which have been of great help for improving our manuscript.

**1-**We have added a table or a graph for each pathway summarising its role in hepatocellular carcinoma and inserted them at the specified location (before the references) in the manuscript.

**2-**We have added the paragraph at the end of the manuscript before the conclusion to summarise the future directions in this field (on page 19). The additions are shown as the following paragraph:

*"Despite the immunotherapy for HCC have made a lot of progress, the clinical efficacy still needs to be further improved. Finding new targets for the treatment of HCC is still the direction of scientific researchers in the next few years. In recent years, studies about the roles of epigenetics and metabolomics on HCC progression have also become the hot spots. Related drug development is also ongoing. A single treatment may not bring satisfactory therapeutic effect. Individual differences need to be more considered. Combined therapy and individualized therapy may be a promising option in HCC treatment."*

## 2. Reviewer's code: 02734287

A good overall review of the current knowledge on immune mechanisms of oncogenesis in HCC and current status of immunotherapy of the disease. The role of liver transplantation should be mentioned when conventional therapies for HCC are listed (page 12).

**Response:** Special thanks to you for your review and your insightful suggestions. The role of liver transplantation have been mentioned in our revised paper (on page 14), The additions are shown as the following paragraph:

*'Liver transplantation is the only treatment option for HCC patients with unresectable tumors or cirrhosis. The 5-year survival rates can reach 60–70% in patients with HCC after liver transplantation. However, the number of patients need liver transplantation exceeds the number of available donor organs. So, patients with HCC must be selected very carefully in terms of the tumor size and the number of tumor nodules.'*