

Cover Letter

Date: 2022-04-16

Dear Company Editor-in-Chief, Science Editor and Reviewers of *World Journal of Gastroenterology*:

Thank you for your e-mail dated 6 April 2022 enclosing the reviewers' reports on our manuscript titled "**RING finger and WD repeat domain 3 Regulates Proliferation and Metastasis through the Wnt/ β -catenin signalling pathways in Hepatocellular Carcinoma.**" Manuscript NO. 75609, Basic Study.

We appreciate the time and efforts you and the reviewer put in to review our manuscript. The insightful comments have aided the revision and improvement of our manuscript and offered important guidance to highlight the significance of our research. We have carefully reviewed the comments and have revised the manuscript accordingly.

Here, I am sending our revised manuscript on behalf of all the authors. In the attached document, we described the changes made in response to the editorial officers' and reviewers' comments point-by-point.

This manuscript has not been published and is not under consideration for publication elsewhere. All the authors have read the manuscript and have approved this submission version. I believe the manuscript has been improved satisfactorily and hope that the revised version is now suitable for publication in the *World Journal of Gastroenterology*.

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Editorial Officers' Comments

Response to Science editor:

Comment:

Dear authors! I read with interest your manuscript "RFWD3 Regulates Proliferation and Metastasis through the Wnt/ β -catenin signaling pathways in Hepatocellular Carcinoma", which is based on the data obtained in original study. I suppose that the subject of the manuscript is actual, the methods used in the study are adequate and allowed obtaining the described results. The conclusions are based on the results. Although the manuscript is generally well-written, there are some language and format issues. Please, check the for correct spelling, for example, "signaling", "ations", etc. Please, consider correction of the title to avoid abbreviations. Please, follow the guidelines for manuscript preparation, including Journal's requirements for the title page. I should repeat that these minor flaws in any way diminish the scientific quality of the paper.

Answer:

Thank you for your valuable suggestion. We sincerely agree with your decision. We checked the article carefully again and modified the article title, author contributions, financial support, and acknowledgements part according to the specified format of guidelines. We also modified some incorrect spelling and inappropriate punctuation marks. The revisions were further polished for language by Editage. We hope the revised version is now suitable for publication in the World Journal of Gastroenterology. Thank you!

Response to Company editor-in-chief:

Comment:

I have reviewed the Peer-Review Report, the full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Gastroenterology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. Before final acceptance, uniform presentation should be used for figures showing the same or similar contents; for example, "Figure 1 Pathological changes of atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ...". Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file. Please authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content. In order to respect and protect the author's intellectual property rights and prevent others from misappropriating figures without the author's authorization or abusing figures without indicating the source, we will indicate the author's copyright for figures originally generated by the author, and if the author has used a figure published elsewhere or that is copyrighted, the author needs to be authorized by the previous publisher or the copyright holder and/or indicate the reference source and copyrights. Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is 'original', the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2022.

Answer:

Thank you for your suggestions. We have edited the article and ensured that the revised version conforms to the journal formatting. We believe the revised version is now suitable for publication in the World Journal of Gastroenterology. Thank you!

Reviewers' Comments

Response to Reviewer #1:

Comment:

Authors have demonstrated that RFWD3 expression is important in cell replication for DNA damage repair process. In HCC cell lines due to its increased function cells gain viability and it is directly related to TNM staging of tumor cells. By showing shRNAi cells which downregulated RFWD3 expression, they also showed decreased migration and metastasis of tumor cells in mice. Further on microarray analysis, they could demonstrate that by inhibiting RFWD3 expression through shRNAi cells, they could regulate Wnt/ β -catenin signaling pathways by either downregulation/upregulation of certain genes. In HCC we moving forward to molecular targeted therapies not only for cure but also for containment of malignant cells and preventing migration and metastasis. The results open a research area for exploration of RFWD3 expression in HCC cells. The results should be taken with caution as these molecular targets can also affect replication and DNA damage repair process in normal hepatocytes as well as other cells of body.

Answer:

Thank you for your efforts and time to review our manuscript. We highly appreciate your comments. At the beginning of our research, we found that some previous articles have reported that the essential role of RFWD3 in homologous recombination makes it important for cell survival, promotes the repair of DNA damage, as we wrote this sentence in the article:" In other words, this condition may be explained by a common theory: there are more firefighters in the fire scene than ordinary people." We also found that some articles proposed that RFWD3 was involved in tumorigenesis. Therefore, it was intriguing to explore the precise roles of RFWD3. In particular, we were interested to know whether it mediates a compensatory mechanism to deal with increased genomic instability or acts as a Janus-faced regulator that plays

other roles in HCC.

Some molecules are multifaceted. As proposed in Anderson Richard's article, even p53 may promote or inhibit tumorigenesis, and the key lies in its mechanism (Choi Suyong, Chen Mo, Cryns Vincent L., Anderson Richard A. (2019). A nuclear phosphoinositide kinase complex regulates p53. *Nat Cell Biol*, 21(4), 462-475. doi:10.1038/s41556-019-0297-2). Therefore, we explored the underlying mechanism and demonstrated that RFWD3 might influence the progression of HCC via the Wnt/ β -catenin signalling pathway.

Based on the findings, we inferred that RFWD3 acts as a Janus-faced regulator that plays other roles in HCC. However, its underlying mechanism remains to be explored. We plan to continue to explore the deep link between RFWD3 and HCC in the follow-up research. We hope our reply can get your approval. Thank you again for your critical review.

Response to Reviewer #2:**Comment:**

The title reflects the main subject/hypothesis of the manuscript The abstract summarizes and reflects the work described in the manuscript The key words reflect the focus of the manuscript The manuscript adequately describes the background, present status and significance of the study The manuscript describes methods in adequate detail The manuscript interprets the findings adequately and appropriately, highlighting the key points concisely, clearly and logically The manuscript cites appropriately the latest, important and authoritative references in the introduction and discussion sections.

Answer:

We are honored to receive your appreciation. Thank you for your time and efforts to review our manuscript thoroughly.