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Manuscript NO.: 65488

Response to Reviewers

April 23, 2021

Dear Editors and Reviewers:

Hope everything goes well in your life and work! Particularly, we would like to thank you very much for sending us the Reviewers' reports on our manuscript (**Manuscript ID: 65488**). Our manuscript named "**USP15 contributes to gastric cancer progression via regulating the Wnt/ β -catenin signaling pathway**" could not be proceed without your help. And also we would like to thank the Reviewers for their valuable comments and criticisms which really improve our manuscript a lot.

Following your encouragement to resubmit our manuscript, we are now sending the revised version for resubmission.

According to the Reviewers and Editors' recommendations, we have revised carefully our manuscript. The revised version takes into account the reviewers' comments and suggestions, which we believe greatly improves the manuscript. The following is a detailed list of response to all comments and criticisms, and changes the authors have made. We hope our manuscript will be finally acceptable to be published in your journal. If you have any questions, please do not hesitate to contact us. We will try our best to fulfil it.

Thank you very much for your reconsideration.

Yours sincerely,

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Answers to Reviewer #1

Comments of Reviewer #1: The authors report the usefulness of USP15 as a prognostic marker for Gastric Cancer. Their research, presentation of findings, and report conforms with international standards. However, the manuscript needs substantive editing. I recommended that the manuscript be accepted subject to the editing of the English language.

1. The manuscript needs substantive editing. I recommended that the manuscript be accepted subject to the editing of the English language.

Answer: Thanks very much for your kind comments. We have already performed a language editing for our manuscript. We hope it would be better.

Answers to Reviewer #2

Comments of Reviewer #2: Major point I suggest that authors need to add some speculations and/or opinions in discussion not only repeated data. I think authors add the reasons that they chose the USP15 for gastric cancer progression, proliferation, and invasion, in this study. The relationship between Wnt/ β -catenin and USP15 is not clear.

1. Major point I suggest that authors need to add some speculations and/or opinions in discussion not only repeated data.

Answer: Thanks very much for your instructive comments. We have already modified discussion section of our manuscript. We hope it should be better.

2. I think authors add the reasons that they chose the USP15 for gastric cancer progression, proliferation, and invasion, in this study.

Answer: Thanks very much for your instructive comments. Increasing evidences showed that ubiquitin-specific proteases (USPs), the largest deubiquitinase subfamily, played an important role in gastric cancer. For example, USP14, USP42 and USP44 were up-regulated in gastric cancer, and could be used as independent prognostic markers in patients with gastric. USP15, as one of the most important members of the USPs, has been found to have some amplifications in many tumors. However, the function of USP15 in GC and its potential mechanism have not been identified. Bioinformatics databases (TIMER <https://cistrome.shinyapps.io/timer/>, UALCAN <http://ualcan.path.uab.edu/>, and Kaplan–Meier Plotter Database Analysis <http://kmplot.com/analysis/>), based on The Cancer Genome Atlas (TCGA) database, indicated that the mRNA levels of USP15 in GC tissues was higher than that in normal tissues and up-regulated of USP15 was related to poor prognosis in patients with GC. Therefore, we chose the USP15 for gastric cancer progression in this study. In response to your valuable comments, we have made appropriate revisions in the “Introduction” part section.

3. The relationship between Wnt/ β -catenin and USP15 is not clear.

Answer: Thanks very much for your instructive comments. According to the result of RNA-sequencing analysis, immunofluorescence and rescue experiments, we found that USP15 can activate the Wnt/ β -catenin to promote the progression of gastric cancer. We are so regret that we do not demonstrate USP15 and the relationship between Wnt/ β -catenin. Nevertheless, we used a protein interaction bioinformatics website, GeneMANIA, predicting that USP15 can interact with some upstream proteins (CTNNB1, NUSAP1) of the Wnt/ β -catenin pathway, and the specific molecular mechanism problems need to be resolved in our future research.

Thanks again for all your instructive suggestion and we are looking forward to your reply.

Answers to Comments of Science editor

Comments of Science editor: Issues raised: (1) Designation of co-first authors and co-corresponding authors is not permitted.; (2) The authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s); (3) The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor; (4) The “Article Highlights” section is missing. Please add the “Article Highlights” section at the end of the main text; (5) Institutional review board approval form or document. Please upload the primary version (PDF) of the Institutional Review Board’s official approval, prepared in the official language of the authors’ country to the system; for example, authors from China should upload the Chinese version of the document, authors from Italy should upload the Italian version of the document, authors from Germany should upload the Deutsch version of the document, and authors from the United States and the United Kingdom should upload the English version of the document, etc. Example: Download our sample of institutional review board approval, at <https://www.wjgnet.com/bpg/GerInfo/287>; and (6) Institutional animal care and use committee approval form or document. Please upload the primary version (PDF) of the Institutional Animal Care and Use Committee’s official approval in the official language of the authors’ country to the system, etc. Example: Download our sample of institutional animal care and use committee approval, at <https://www.wjgnet.com/bpg/GerInfo/287>.

1. Designation of co-first authors and co-corresponding authors is not permitted.

Answer: Thanks very much for your kind comments. We have revised it according to the requirements of the journal.

2. The authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s);

Answer: Thanks very much for your kind comments. We have revised it according to the requirements of the journal.

3. The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor;

Answer: Thanks very much for your kind comments. We have already

uploaded the original figure documents and arranged the figures using PowerPoint.

4. The “Article Highlights” section is missing. Please add the “Article Highlights” section at the end of the main text;

Answer: Thanks very much for your kind comments. We have added “Article Highlights” section in our revised manuscript.

5. Institutional review board approval form or document. Please upload the primary version (PDF) of the Institutional Review Board’s official approval, prepared in the official language of the authors’ country to the system; for example, authors from China should upload the Chinese version of the document, authors from Italy should upload the Italian version of the document, authors from Germany should upload the Deutsch version of the document, and authors from the United States and the United Kingdom should upload the English version of the document, etc. Example: Download our sample of institutional review board approval, at <https://www.wjgnet.com/bpg/GerInfo/287;>

Answer: Thanks very much for your kind comments. We have already uploaded primary version (PDF) of the Institutional Review Board’s official approval according to the requirements of the journal.

6. Institutional animal care and use committee approval form or document. Please upload the primary version (PDF) of the Institutional Animal Care and Use Committee’s official approval in the official language of the authors’ country to the system, etc. Example: Download our sample of institutional animal care and use committee approval, at [https://www.wjgnet.com/bpg/GerInfo/287.](https://www.wjgnet.com/bpg/GerInfo/287;)

Answer: Thanks very much for your kind comments. We have already uploaded primary version (PDF) of the Institutional Animal Care and Use Committee’s official approval according to the requirements of the journal.

Thanks again for all your instructive suggestion and we are looking forward to your reply.

Answers to Company editor-in-chief

Comments of Company editor-in-chief: 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 its final acceptance, please upload the primary version (PDF) of the Institutional Review Board's official approval in official language of the authors' country to the system; for example, authors from China should upload the Chinese version of the document, authors from Italy should upload the Italian version of the document, authors from Germany should upload the Deutsch version of the document, and authors from the United States and the United Kingdom should upload the English version of the document, etc.

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Answer: Thanks very much for your kind comments. We have already uploaded primary version (PDF) of the Institutional Review Board's official approval according to the requirements of the journal.

Thanks again for all your instructive suggestion and we are looking forward to your reply.