

Cover Letter

Dear Editors and Reviewers,

Authors first appreciate the great effort and comments from the editors and reviewers. The manuscript (Manuscript NO.: 74670) was made revisions according to each comment from the reviewers. The following steps outlined below were completed at re-submission.

Please check the responses to each point. All the revisions were tracked in the revised manuscript and were also pointed in the reply to the reviewers' comments in this letter.

Thank you so much. Please let us know if you have any concerns.

Sincerely,

Ming Yang, PhD

University of Missouri-Columbia

1 MANUSCRIPT REVISION DEADLINE

We request that you submit your revision in no more than **14 days**. **Please note that you have only two chances for revising the manuscript.**

Response: The revised manuscript was submitted on time.

2 PLEASE SELECT TO REVISE THIS MANUSCRIPT OR NOT

Please login to the F6Publishing system at <https://www.f6publishing.com> by entering your registered E-mail and password. After clicking on the "Author Login" button, please click on "Manuscripts Needing Revision" under the "Revisions" heading to find your manuscript that needs revision. Clicking on the "Handle" button allows you to choose to revise this manuscript or not. If you choose not to revise your manuscript, please click on the "Decline" button, and the manuscript will be WITHDRAWN.

Response: Author accepted to revise the manuscript according to all the reviewers' comments.

3 SCIENTIFIC QUALITY

Please resolve all issues in the manuscript based on the peer review report and make a point-by-point response to each of the issues raised in the peer review report. Note, authors must resolve all issues in the manuscript that are raised in the peer-review

report(s) and provide point-by-point responses to each of the issues raised in the peer-review report(s); these are listed below for your convenience:

Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: In this work, the authors demonstrated Ubiquitination plays an essential role in the biochemical processes of cells, tried to illustrate overexpression of UBE2C, UBE2T, and UBE2S was negatively associated with prognostic outcomes and overall survival times, indicating an association between UBE2 expression with p53 function, which could be a diagnostic and prognostic biomarkers for HCC. However, there are major specific points in this manuscript as shown in following comments: 1. The range of title is too large, the research of function for a gene should include proliferation, apoptosis, invasion and metastasis in HCC cells level. Please explain it. 2. It is recommended that immunofluorescence double-labeling experiments demonstrate subcellular localization of UBE2 protein. 3. Please highlight what are the major functions of UBE2 in HCC in the discussion of the manuscript.

Response: The authors appreciated the great comments from the reviewer. The title of the manuscript was changed to “The functions of three ubiquitin-conjugating enzyme 2 genes in hepatocellular carcinoma diagnosis and prognosis”, which more specifically to describe the context of the revised manuscript. 2. The histology data of expression of UBE2 genes were shown in the revised manuscript. 3. The major functions of UBE2 in HCC were discussed in the discussion of the revised manuscript. “It has been shown that the mRNA expression of UBE2A in liver cancer cell lines (e.g., HepG2 and Huh-7) was significantly higher compared that in normal liver cancer line HL-7702. Meanwhile, UBE2A mRNA and protein were highly expressed in HCC tumor tissues than those in the adjacent normal tissues[31]. In HCC, qPCR data showed that the expression of UBE2S was significantly increased in HCC samples compared to non-tumor liver tissues[32]. Another study showed that the expression UBE2T mRNA and protein was increased in HCC tissues compared to adjacent non-tumor tissues. Molecular mechanism study showed that UBE2T can suppress G2/M transition of hepatoma cells by regulating cyclin B1 and cyclin-dependent kinase 1 expression[33]. A recent study showed that the expression of UBE2T can be regulated by microRNA miR-212-5p, and overexpression of UBE2T can promote HCC cell proliferation and migration[34].”

Reviewer #2:

Scientific Quality: Grade D (Fair)

Language Quality: Grade B (Minor language polishing)

Conclusion: Rejection

Specific Comments to Authors: In this study, the authors analyzed TCGA database and found diagnostic and prognostic roles of UBE2C, UBE2T, UBE2S in HCC. My major concern is the study lack of novelty. Data digging in TCGA database is far from convincing. First, UBE2 is a large enzyme family contained many proteins. The authors did not show the reason to choose UBE2C, UBE2T, and UBE2S (ranked as top 4, top 8, and top 31) rather than the top3 proteins. Second, several previous studies have revealed the function and mechanism of UBE2 in HCC. This paper presented the same conclusions that upregulation of UBE2T, UBE2S, UBE2C, UBE2I in HCC predicted poor prognosis and promoted HCC progression. Third, the study should includes not only analysis from the databases but also data from clinical samples. In addition, relationship between p53 mutation and UBE2 overexpression was interesting, but not convincing.

Response: Thanks for the reviewer's comments. Three UBE2 genes were highly expressed in HCC tumor tissue compared to non-tumor tissue, listed from top 50 genes in TCGA database. Therefore, the author chose these three UBE2 genes to analyze their potential function in HCC as well as the potential as biomarkers for HCC diagnosis. The bioinformatic analysis is helpful to further illustrate the expression of the genes in single cell level as well as location in cells, and their expression in different cancers and different stage of liver cancer, valuably supporting the research studies. The data from the database were mainly from clinical samples. The relationship of p53 mutation with UBE2 expression will be studied in the future research.

4 LANGUAGE POLISHING REQUIREMENTS FOR REVISED MANUSCRIPTS SUBMITTED BY AUTHORS WHO ARE NON-NATIVE SPEAKERS OF ENGLISH

As the revision process results in changes to the content of the manuscript, language problems may exist in the revised manuscript. Thus, it is necessary to perform further language polishing that will ensure all grammatical, syntactical, formatting and other related errors be resolved, so that the revised manuscript will meet the publication requirement (Grade A).

Authors are requested to send their revised manuscript to a professional English language editing company or a native English-speaking expert to polish the manuscript further. When the authors submit the subsequent polished manuscript to us, they must provide a new language certificate along with the manuscript.

Once this step is completed, the manuscript will be quickly accepted and published online. Please visit the following website for the professional English language editing companies we recommend: <https://www.wjgnet.com/bpg/gerinfo/240>.

Response: The English grammar was checked by a native English speaker in academic study and was scored high from the reviewers.

5 ABBREVIATIONS

In general, do not use non-standard abbreviations, unless they appear at least two times in the text preceding the first usage/definition. Certain commonly used abbreviations, such as DNA, RNA, HIV, LD50, PCR, HBV, ECG, WBC, RBC, CT, ESR, CSF, IgG, ELISA, PBS, ATP, EDTA, and mAb, do not need to be defined and can be used directly.

The basic rules on abbreviations are provided here:

- (1) **Title:** Abbreviations are not permitted. Please spell out any abbreviation in the title.
- (2) **Running title:** Abbreviations are permitted. Also, please shorten the running title to no more than 6 words.
- (3) **Abstract:** Abbreviations must be defined upon first appearance in the Abstract.
Example 1: Hepatocellular carcinoma (HCC). Example 2: *Helicobacter pylori* (*H. pylori*).
- (4) **Key Words:** Abbreviations must be defined upon first appearance in the Key Words.
- (5) **Core Tip:** Abbreviations must be defined upon first appearance in the Core Tip.
Example 1: Hepatocellular carcinoma (HCC). Example 2: *Helicobacter pylori* (*H. pylori*)
- (6) **Main Text:** Abbreviations must be defined upon first appearance in the Main Text.
Example 1: Hepatocellular carcinoma (HCC). Example 2: *Helicobacter pylori* (*H. pylori*)
- (7) **Article Highlights:** Abbreviations must be defined upon first appearance in the Article Highlights. Example 1: Hepatocellular carcinoma (HCC).
Example 2: *Helicobacter pylori* (*H. pylori*)
- (8) **Figures:** Abbreviations are not allowed in the Figure title. For the Figure Legend text, abbreviations are allowed but must be defined upon first appearance in the text.
Example 1: A: Hepatocellular carcinoma (HCC) biopsy sample; B: HCC-adjacent tissue

sample. For any abbreviation that appears in the Figure itself but is not included in the Figure Legend textual description, it will be defined (separated by semicolons) at the end of the figure legend. Example 2: BMI: Body mass index; US: Ultrasound.

(9) Tables: Abbreviations are not allowed in the Table title. For the Table itself, please verify all abbreviations used in tables are defined (separated by semicolons) directly underneath the table. Example 1: BMI: Body mass index; US: Ultrasound.

Response: The manuscript was formatted according to the above rules.

6 EDITORIAL OFFICE'S COMMENTS

Authors must revise the manuscript according to the Editorial Office's comments and suggestions, which are listed below:

(1) Science editor:

This study analysis the tumor samples from HCC patients and non-tumor controls from the TCGA database. However, the corresponding clinical data analysis and basic experiments to verify the conclusions of the manuscript are needed.

Language Quality: Grade B (Minor language polishing)

Scientific Quality: Grade D (Fair)

(2) Company editor-in-chief:

I recommend the manuscript to be published in the World Journal of Meta-Analysis.

Response: We agree to be published in the World Journal of Meta-Analysis. Histology data were added in the revised manuscript.

7 STEPS FOR SUBMITTING THE REVISED MANUSCRIPT

Step 1: Author Information

Please click and download the [Format for authorship, institution, and corresponding author guidelines](#), and further check if the authors names and institutions meet the requirements of the journal.

Step 2: Manuscript Information

Please check if the manuscript information is correct.

Step 3: Abstract, Main Text, and Acknowledgements

(1) Guidelines for revising the content: Please download the guidelines for Original articles, Review articles, or Case Report articles for your specific manuscript type (Basic Study) at: <https://www.wjgnet.com/bpg/GerInfo/291>. Please further revise the content your manuscript according to the Guidelines and Requirements for Manuscript Revision.

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(3) Requirements for Article Highlights: If your manuscript is an Original Study (Basic Study or Clinical Study), Meta-Analysis, or Systemic Review, the “Article Highlights” section is required. Detailed writing requirements for the “Article Highlights” can be found in the Guidelines and Requirements for Manuscript Revision.

(4) Common issues in revised manuscript. Please click and download the [List of common issues in revised manuscripts by authors and comments](#) (PDF), and revise the manuscript accordingly.

Step 4: References

Please revise the references according to the [Format for References Guidelines](#), and be sure to edit the reference using the reference auto-analyser.

Reminder: It is unacceptable to have more than 3 references from the same journal. To resolve this issue and move forward in the peer-review/publication process, please revise your reference list accordingly.

Step 5: Footnotes and Figure Legends

(1) Requirements for Figures: Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file, and submit as “74670-Figures.pptx” on the system. The figures should be uploaded to the file destination of “Image File”. 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.
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(2) Requirements for Tables: Please provide decomposable Tables (in which all components are movable and editable), organize them into a single Word file, and submit as “74670-Tables.docx” on the system. The tables should be uploaded to the file destination of “Table File”.

Reminder: Please click and download the [Guidelines for preparation of bitmaps, vector graphics, and tables in revised manuscripts](#) (PDF), and prepare the figures and tables of your manuscript accordingly.

Step 6: Automatically Generate Full-Text Files

Authors cannot replace and upload the “Manuscript File” separately. Since we only accept a manuscript file that is automatically generated, please download the “Full Text File” or click “Preview” to ensure all the contents of the manuscript automatically generated by the system are correct and meet the requirements of the journal. If you find that there is content that needs to be modified in the Full-Text File, please return to the corresponding step(s), modify and update the content, and save. At this point, you then have to click the "Save & Continue" button in Step 5 and the F6Publishing system will automatically regenerate the Full-Text File, and it will be automatically stored.

Step 7: Upload the Revision Files

For all required accompanying documents (listed below), you can begin the uploading process *via* the F6Publishing system. Then, please download all the uploaded documents to ensure all of them are correct.

- (1) 74670-Answering Reviewers
- (2) 74670-Audio Core Tip
- (3) 74670-Biostatistics Review Certificate
- (4) 74670-Conflict-of-Interest Disclosure Form
- (5) 74670-Copyright License Agreement
- (6) 74670-Approved Grant Application Form(s) or Funding Agency Copy of any Approval Document(s)
- (7) 74670-Institutional Animal Care and Use Committee Approval Form or Document
- (8) 74670-Institutional Review Board Approval Form or Document
- (9) 74670-Non-Native Speakers of English Editing Certificate

- (10) 74670-Video
- (11) 74670-Image File
- (12) 74670-Table File
- (13) 74670-The ARRIVE Guidelines
- (14) 74670-Supplementary Material

If your manuscript has supportive foundations, the approved grant application form(s) or funding agency copy of any approval document(s) must be provided. Otherwise, we will delete the supportive foundations.

If your manuscript has no “Video” or “Supplementary Material”, you do not need to submit those two types of documents.

Response: The revised manuscript was submitted according to the 7 steps, with all the required documents.

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Response: Copyright was signed and uploaded.

9 CONFLICT-OF-INTEREST DISCLOSURE FORM

Please click and download the fillable [ICMJE Form for Disclosure of Potential Conflicts of Interest](#) (PDF), and fill it in. The Corresponding Author is responsible for filling out this form. Once filled out completely, the Conflict-of-Interest Disclosure Form should be uploaded to the file destination of ‘Conflict-of-Interest Disclosure Form’.

Response: The Conflict-of-Interest Disclosure Form was signed and uploaded.

All the best,
Ming Yang, PhD
University of Missouri