Lian-Sheng Ma, Science Editor, Company Editor-in-Chief, Editorial Office
World Journal of Gastrointestinal Oncology

Re: **Manuscript NO: 64684** June 4, 2021

Dear Editor-in-Chief Ma,

We have attached a copy of our revised manuscript entitled " **PCLAF, a potential proto-oncogene with increased expression in malignant gastrointestinal tumors**". We want to thank you and the reviewers for carefully reading the manuscript and the helpful comments.

We have carefully addressed the reviewer's questions and the editorial office's comments point-by-point (please refer to the following pages for the details of change).

As suggested, we have completed the description of different gastrointestinal tumors and added a series of new literature regarding the role of PCLAF in various cancers. We have also added the references in the specific study and enriched the contents of Figure 2.

We believe that the revised manuscript has been substantially improved and hope it meets the standard for publication in the World Journal of Gastrointestinal Oncology. We look forward to hearing from you.

Sincerely yours,

Fan Zhu, Ph. D., Professor

State Key Laboratory of Virology

Department of Medical Microbiology

School of Medicine, Wuhan University

Wuhan 430071, Hubei, P. R. China

Tel: 86-27-68759906(O)

Fax: 86-27-68759906(O)

Cell phone: 86-18942900238

E-mail: fanzhu@whu.edu.cn; zhufan@hotmail.com

RESPONSES TO THE REFEREE'S COMMENTS (blue texts are the original comments)

Many thanks for the valuable comments on the manuscript. We have made a substantial revision to the manuscript. Please see below for details of our responses to your comments.

Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: PCLAF is a protein involved in many pathways that regulate embryonic and cancer cells. It is upregulated in many neoplasms and often associated with poor prognosis. Researches are ongoing to decipher some more details on its role in tumorigenesis and cancer treatment. The present review summarize data regarding PCLAF in cancer. The paper is well-written and authors gave a wide overview of the topic. However, I have some suggestions and in my opinion some minor revisions should be done.

(1) Since the main aim of the review is to describe PCLAF in malignant gastrointestinal tumors, authors should pinpoint it, reserving specific sentences/paragraphs to these neoplasms and distinguishing them from the other tumors.

Response: Thank you for reminding us of that. We have completed the description of different gastrointestinal tumors, including esophageal cancer (page 8, paragraph 2), gastric cancer (page 9, paragraph 1), colorectal cancer (page 10, paragraph 1), pancreatic cancer (page 11, paragraph 1), and liver cancer (page 11, paragraph 2).

(2) A more updated literature revision could enrich the review. In particular some new findings have been recently published regarding the role of PCLAF in lung tumorigenesis (doi: 10.1016/j.molcel.2021.02.001), chronic lymphocytic leukemia cells (doi: 10.21037/atm-21-626), nasopharyngeal carcinoma (doi: 10.1016/j.biopha.2020.109905), but also in gastrointestinal tumors (doi: 10.1007/s12032-014-0106-5; PMID: 33970778, DOI: 10.1186/s12885-021-07994-3).

Response: Many thanks for reminding us of that. These newly published papers help us comprehensively summarize the new progress of PCLAF in gastrointestinal tumors and other cancers. As a result, we have added a series of literature including the reviewer mentioned above (page 9, paragraph 1; page 12, paragraphs 1; page 13, paragraphs 1-2; page 14, paragraph 1; page 16, paragraph 2; page 17, paragraph 2).

(3) A new Fig/Table (or a enrichment of Fig2) summarizing all the pathways in which PCLAF is involved could be useful (if possibly, distinguishing PCLAF main roles in gastrointestinal cancer).

Response: We agree with Reviewer #1's comments. As suggested, we have enriched the contents of Figure 2. We believe that the revised figure can summarize all the pathways associated with PCLAF.

(4) With regard to gastrointestinal cancers, Yu P (ref 16, DOI: 10.1038/sj.onc.1204113) many years ago showed that PCLAF increased mRNA level is especially dramatic in esophageal tumor suggesting that it could be used to predict clinical prognosis for esophageal cancer patients. Authors should mention these results into specific "esophageal cancer" paragraph.

Response: Many thanks for your reminder. We agree that adding this information will make the content about PCLAF in esophageal cancer exhaustive. As a result, we have completed this result that PCLAF mRNA level increases dramatically in esophageal tumor from Yu's group to "esophageal cancer" paragraph (page 8, paragraph 2).

(5) Fig 2 need to be revised. Since the authors stated that PCLAF expression is negatively regulated by the Rb/E2F pathway, Fig 2 must be modify accordingly. The interaction with PCNA is not described in the Fig2.

Response: As suggested, we have revised the figure and enriched its contents. The detailed changes are shown in revised Figure 2.

(6) Authors should deeply revise the text, adding the right citation when some specific study is mentioned, since some of them are missing (eg "Esophageal Cancer" paragraph: "Further study has indicated that PCLAF is associated with higher stage, tumor recurrence, and poor survival" [?]; "Colorectal cancer" paragraph: " Immunostaining of colon cancer tissue microarray

confirms that PCLAF is strongly expressed in colon cancer tissues compared to the normal intestine "[?],…

Response: Many thanks for your reminder. Since the references are the same as the study in the following sentences, we have omitted some of them. We have deeply revised the manuscript by adding references in the specific research. And we believe there are no missed references.

(7) PCLAF seems to be involved also in the response to radiation: authors should add something about that in the paragraph of therapeutic strategies.

Response: We agree with Reviewer #1's comments. As a result, we have completed this part of the contents in the "POTENTIAL THERAPEUTIC STRATEGY BY TARGETING PCLAF" section (page 20, paragraph 2).

EDITORIAL OFFICE'S COMMENTS

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

Science editor:

1 Scientific quality: The manuscript describes a review of the PCLAF, a potential proto-oncogene with increased expression in malignant gastrointestinal tumors. The topic is within the scope of the WJGO. (1) Classification: Grade C; (2) Summary of the Peer-Review Report: The review summarized data regarding PCLAF in cancer. It is well-written and the authors gave a wide overview of the topic. However, the manuscript was based on a descriptive analysis. The questions raised by the reviewer should be answered;

Response: Thank you for your kind reminder. We have revised the manuscript according to the reviewer and given a point-by-point answer to all questions. We hope that the revised paper meets the standard for publication.

(3) Format: There are 2 figures. (4) References: A total of 82 references are cited, including 23 references published in the last 3 years; (5) Self-cited references: There are 4 self-cited references. The self-referencing rates should be less than 10%. Please keep the reasonable self-citations that are closely related to the topic of the manuscript, and remove other improper self-citations. If the authors fail to address the critical issue of self-citation, the editing process of this manuscript will be terminated;

Response: We have checked the self-cited references and found that only three references were self-citing: (1) Ref. 14: reporting the role of variant 1 of PCLAF in HCC; (2) Ref. 34: presenting the role of variant 2 of PCLAF in HCC; (3) Ref. 82: reviewing the aberrant regulation of wnt signaling in HCC. All these three references are closely related to the topic of the manuscript. The self-cited rate is less than 10% (3/89, 3.37%), which meets the magazine's standard.

Another reference (ref. 29. Jin C, Liu Z, Li Y, Bu H, Wang Y, Xu Y, Qiu C, Yan S, Yuan C, Li R, Diao N, Zhang Z, Wang X, Liu L, Kong B. PCNA-associated factor P15PAF, targeted by FOXM1, predicts poor prognosis in high-grade serous ovarian cancer patients.) showed the same name to our first author is not the same person. And this paper is not from our group.

(6) References recommend: The authors have the right to refuse to cite improper references recommended by peer reviewer(s), especially the references published by the peer reviewer(s) themselves. If the authors found the peer reviewer(s) request the authors to cite improper references published by themselves, please send the peer reviewer's ID number to the editorialoffice@wjgnet.com. The Editorial Office will close and remove the peer reviewer from the F6Publishing system immediately.

Response: Thank you very much for your help.

2 Language evaluation: Classification: Grade B. 3 Academic norms and rules: No academic misconduct was found in the Bing search. 4 Supplementary comments: This is an invited manuscript. The study was supported by 4 grants. The topic has not previously been published in the WJGO. 5 Issues raised: (1) The title is too long, and it should be no more than 18 words;

Response: Thank you for your suggestion. The title is 11 words, which is less than 18 words and meets the magazine's standards.

(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);

Response: We have uploaded the approved grant application forms attached to the revised manuscript.

(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;

Response: We have provided original pictures using PowerPoint to ensure all graphs or arrows or text portions can be reprocessed by the editor.

and (4) The column should be minireviews. 6 Recommendation: Conditional acceptance.

Response: We have changed the column to minireviews.

Company editor-in-chief: I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the

World Journal of Gastrointestinal Oncology, 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.

Response: Thank you very much for your help.