Jin-Lei Wang,
Science Editor,
World Journal of Gastrointestinal Oncology

August 5, 2018

Dear Jin-Lei Wang,

I am submitting our revised manuscript entitled, "*miR-122-5p* as a novel biomarker for alpha-fetoprotein-producing gastric cancer (No. 40517)" for your kind consideration of its suitability for publication in "World Journal of Gastrointestinal Oncology".

I found your comments most helpful, and have revised the manuscript as suggested by reviewers. I have underlined all changes made in the revised manuscript. Enclosed you find a point-by-point responses to critiques from you and the reviewers.

I believe that our revised manuscript has been improved by revisions, and satisfy the reviewer's concern. I hope that revised manuscript is now acceptable for publication in "World Journal of Gastrointestinal Oncology".

Sincerely yours,

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Comments to the Editor,

We have mostly accepted two reviewers' comment and revised out manuscript accordingly.

RESPONSE TO REVIEWER 1:

MAJOR CONCERNS

Comment 1: Is miR-122-5p expression truly a novel biomarker for liver metastasis? No statistical analysis supports the hypothesis in the manuscript. It is better to change the title of this manuscript.

Response: We thank the Reviewer for the constructive comment. We have changed the title from "miR-122-5p is a novel biomarker for liver metastasis in alpha-fetoprotein-producing gastric cancer" to "miR-122-5p as a novel biomarker for alpha-fetoprotein-producing gastric cancer".

Comment 2: Number of the patients should be mentioned in the abstract.

Response: We agree with your remark. We have added number of patients in the abstract.

Comment 3: The authors cannot state the relation between the miR-122-5p and prognostic prediction in conclusion. Same as comment 1, no statistically meaningful data supports the effect of onto the prognosis.

Response: We thank the Reviewer for the constructive comment. Figure 4 revealed miR-122-5p exhibited a stronger correlation with malignant potential than AFP. Therefore, we think miR-122-5p might be sufficient as a prognostic marker. However, as you mentioned, it was a small scale group. So, we have deleted sentences about prognostic prediction in abstract conclusion.

MINOR CONCERNS

Comment 1: In abstract, the authors mentioned the correlation of the miRNA and liver metastasis. Is it a correlation of a development of the liver metastasis?

Response: We thank the Reviewer for the constructive comment. As you indicated, we cannot reveal the correlation between miR-122-5p and the development of the liver metastasis directly in this study. We have deleted descriptions about the development of liver metastasis in result section according to your comment (p. 8).

Comment 2: In discussion, the authors said that two patients who developed liver metastases were diagnosed poorly differentiated and mucinous adenocarcinoma. It should be described in the result.

Response: We agree with your remarks. We have added histology information in the result.

Comment 3: In the legend of Fig 4, it is enough to state that black symbol indicate only “death”, not “death due to liver metastasis”. Did two deceased patients have only liver metastases?

Response: We thank the Reviewer for the constructive comment. Two deceased patients first developed only multiple liver metastasis, and finally they developed multiple metastasis (liver, bone, lymph node). We have changed the legend of Figure 4 according to your comments.

RESPONSE TO REVIEWER 2:

Comment 1: The number of cases in Figures 3 and 4 is too small, so it needs more additional case.

Response: We thank the Reviewer for the constructive comment. In figure 4, unfortunately, the five cases were the maximum number for the AFPGC tissue samples at our hospital because of its rareness. Instead, we have added data of more ten cases in Figure 3 according to your comments.

Comment 2: It looks to be associated with AFP and miR-122-5p, but it does not show any specific relevance between AFP and miR-122-5p. I am wondering how miR-122-5p expression changes when AFR is staged in stomach cancer cells.

Response: We thank the Reviewer for the constructive comment. We revealed the strong correlation between miR-122-5p and AFP in Figure 2 and 3. However, as you indicated, we cannot show any specific relevance between AFP and miR-122-5p. Some micro-RNA was reported that decreased in early cases and elevated again in staged-advanced cases. Therefore, miR-122-5p decreased in carcinogenesis might be elevated during tumor evolution to AFPGC. However, the exact mechanism is unknown at the present time. It is necessary to investigate the molecular research of miR-122-5p in the future. We have added some descriptions in discussion section (p. 9, 10).

Comment 3: In other studies, miR-122-5p has been reported to be inhibited rather in cancer, in contrast to this manuscript. It is necessary to discuss the results in detail.

Response: We thank the Reviewer for the constructive comment. As you mentioned, miR-122-5p has been reported to be suppressor gene. It's not known exactly why miR-122-5p, which is known as suppressor gene, is higher in AFPGC. We assume that AFPGC is completely different from non-AFPGC, and

the mechanism of liver metastasis between AFPGC and non-AFPGC is also distinct. We speculate AFPGC has specific ability of liver metastasis, and correlated with miR-122-5p. But it is necessary to investigate the further research in the future. We have added some descriptions in discussion section (p. 9, 10).