Dear Editor:

Thank you very much for your letter and for the reviewers' comments concerning our manuscript entitled "LncRNA TP73-AS1 promotes pancreatic cancer proliferation and metastasis through miRNA-128-3p/GOLM1 axis" (manuscript NO.61034). We appreciate the time and effort that you and the reviewers have dedicated to providing your valuable feedback on my manuscript. Those comments are all valuable and very helpful for revising and improving our paper. We have modified the manuscript in accordance with the comments. In this cover letter, the reviewers' comments are laid out below in *italicized font* and our response is given in normal font. Point by point responses to the reviewers' comments are listed below this letter.

Reviewers 1's comments: 05128663

1. *Several words throughout the manuscript appear to be merged. Please correct it.*

Our reply:

Thank you very much for your constructive comments. We have corrected the words which was merged before in our revised manuscript.

2. *Some minor grammatical errors occur. The manuscript contains significant language-related issues. Please correct these types of grammatical errors throughout the paper.*

Our reply:

Thank you for your comments. We sincerely apologize for such mistakes of grammatical errors. We have corrected the grammatical errors in our revised manuscript. Thank you very much for your reminding.

3. *Figure 2, 4 and 5. For the sake of the experiments, I recommend to check some EMT markers (Mesenchymal arkers and Epithelial Markers) such as vimentin, Laminin, N-cadherin and E-cadherine in order to further evaluate the effect of invasive properties of the cells.*

Our reply:

Thank you for your comments. We have conducted the western blot assay on the EMT-related markers in our manuscript.

4. *Figure 7. I strongly recommend checking some apoptotic markers (PARP-1,cl. Caspase-3) after protein extraction from tumors.*

Our reply:

Thank you for your suggestions. Western blot had been conducted on the apoptotic markers (Caspase-3 and Bcl-2) in our manuscript.

5. *Authors used several pancreatic cancer cells lines for the experiments. It is necessary to mention and further discussed some differences between these cell lines. For example, PANC-1 and BXPC3 harboring mutant and wild type KRAS mutation respectively. The Kras gene is mutated to an oncogenic form in most pancreatic tumors. However, early attempts to use this molecule as a specific biomarker of the disease, or inhibit its activity as a cancer therapy, failed. Thus, I recommend to add a paragraph in discussion where the authors expound the role of KRAS in their experiments.*

Our reply:

Thank you very much for your recommendations. We have added a paragraph about KRAS in our research to the discussion. The following is our added paragraph.

KRAS gene, the most common genetic driver in pancreatic cancer, is mutated in

about 93% of pancreatic cancers[1, 2]. The KRAS protein is a small GTPase, which is responsible for interacting with cell membrane growth factor receptors and controlling the switch of multiple signaling pathways and cellular processes. Oncogenic KRAS mutations have been found in 95% of PDAC tissues[3, 4]. Decades of research have discovered and clarified the complex picture of KRAS-regulated biological processes, including cell metabolism, tumor cell signaling, the tumor microenvironment, micropinocytosis, apoptosis, and redox homeostasis[5, 6]. In our research, ASPC-1 and Capan 1 cells were the two pancreatic cancer cell lines we selected, both of which contained mutations in the KRAS gene. As our results showed, the regulatory roles of TP73-AS1 in cell proliferation, migration and invasion ability were verified by Cell Counting Kit-8, wound-healing and transwell assays in ASPC-1 and Capan 1 cells. Due to the vital role that KRAS could play in pancreatic cancer, we are also curious about the role of TP73-AS1 in KRAS wild cells. Therefore, in our further research, we would select BXPC-3 cell line, which contains wild KRAS gene, for *in vitro* and *in vivo* functional assays of TP73-AS1 to detect whether KRAS gene could modulate the function of TP73-AS1 in pancreatic cancer.

Reference:

1. Haigis KM. KRAS Alleles: The Devil Is in the Detail. Trends in cancer. 2017; 3: 686-97.
2. di Magliano MP, Logsdon CD. Roles for KRAS in pancreatic tumor development and progression. Gastroenterology. 2013; 144: 1220-9.
3. Jones S, Zhang X, Parsons DW, Lin JC, Leary RJ, Angenendt P, et al. Core signaling pathways in human pancreatic cancers revealed by global genomic analyses. Science (New York, NY). 2008; 321: 1801-6.
4. Ryan DP, Hong TS, Bardeesy N. Pancreatic adenocarcinoma. N Engl J Med. 2014; 371: 2140-1.
5. Tape CJ, Ling S, Dimitriadi M, McMahon KM, Worboys JD, Leong HS, et al. Oncogenic KRAS Regulates Tumor Cell Signaling via Stromal Reciprocation. Cell. 2016; 165: 1818.
6. Liang C, Qin Y, Zhang B, Ji S, Shi S, Xu W, et al. Metabolic plasticity in heterogeneous pancreatic ductal adenocarcinoma. Biochim Biophys Acta. 2016; 1866: 177-88.

Reviewers 2's comments：03261315

1. *Very nice and original study. Well and clearly written. The results could have an impact in clinical practice regarding prognosis of pancreatic cancer or treatment strategy. Please provide informations regarding this abbreviations"Cells were cultured in DMEM .....supplemented with 10% FBS".*

Our reply:

Thank you very much for your suggestions. We have checked our manuscript and added information regarding DMEM (Dulbecco's modification of Eagle's medium) and FBS (Fatal Bovine Serum). We really appreciate your reminding.

Reviewers 3's comments：03104669

1. *In the manuscript entitled," LncRNA TP73-AS1 promotes pancreatic cancer proliferation and metastasis through miRNA-128-3p/GOLM1 axis.", the authors demonstrate that TP73-AS1 regulated Pancreatic Cancer progression by sponging the miR-128-3p/GOLM1 axis, which might provide a potential treatment strategy for patients with Pancreatic Cancer. The manuscript has an excellent summary but the explanation to a relation between LncRNA TP73-AS1 and miRNA-128-3p/GOLM1 is not enough in"Introduction".*

Our reply:

Thank you very much for your suggestions. We have redescribed the relation between LncRNA TP73-AS1 and miRNA-128-3p/GOLM1 in the introduction. Thank you for your reminding.

Reviewers 4's comments：02734287

1. *There is increasing evidence that lnc RNAs participate in tumorigenesis. The data on the role of lnc RNAs in pancreatic cancer is scarce. Therefore, this report is a valuable contribution to the field and I believe that the results of this research should be published.*

Our reply:

Thank you very much for your acknowledgement and your effort on our manuscript.

Science editor's comments:

1. *The "Author Contributions" section is missing. Please provide the author contributions;*

Our reply:

Thank you very much for your comments. The "Author Contributions" section had been put into our manuscript.

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);*

Our reply:

Thank you very much for your comments. We have re-uploaded the approved grant application form.

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;*

Our reply:

Thank you very much for your suggestions. We have re-uploaded the PowerPoint which contains all our original figures.

4. *PMID and DOI numbers are missing in the reference list. Please provide the*

PubMed numbers and DOI citation numbers to the reference list and list all authors of the references. Please revise throughout;

Our reply:

Thank you for your suggestions. We have corrected all the right citation format in our manuscript.

5. *The "Article Highlights" section is missing. Please add the "Article Highlights" section at the end of the main text;*

Our reply:

Thank you for your suggestions. The "Article Highlights" section had been put into our manuscript as following.

ARTICLE HIGHLIGHTS

Research background

Pancreatic cancer is the fourth most frequent cause of cancer-related deaths in the world. Emerging evidences have revealed that lncRNAs could play crucial roles in the progress of PC. However, the biological role and clinical significance of TP73-AS1 in Pancreatic Cancer remain unclear.

Research motivation

Treatments for pancreatic cancer are still limited and surgical resection is the only chance to obtain curative treatment. We hope to provide a novel therapeutic target for patients with pancreatic cancer.

Research objectives

The present study aimed to investigate the function of TP73-AS1 in proliferation and metastasis of Pancreatic cancer.

Research methods

QRT-PCR was used to detect the expression of lncRNA TP73-AS1, miR-128-3p and GOLM1 in Pancreatic Cancer tissues and cells. The regulatory roles of TP73-AS1 in cell proliferation and invasion ability were verified by Cell Counting Kit-8, wound-healing and transwell assays. The bioinformatics prediction software ENCORI was used to predict the putative binding sites of miR-128-3p. The interactions among TP73-AS1, miR-128-3p and GOLM1 were explored by bioinformatics prediction software, luciferase assay and Western blot.

Research results

Our data suggested that TP73-AS1 and miRNA-128-3p was dysregulated in Pancreatic Cancer tissues and cells. TP73-AS1 silencing inhibited Pancreatic Cancer cell proliferation, migration and invasion in vitro as well as suppressed tumor growth in vivo. Moreover, TP73-AS1 could promote growth and invasion through acting as a competing endogenous RNA (ceRNA) to promote GOLM1 expression by sponging miR-128-3p in PC.

Research conclusions

TP73-AS1 could promote Pancreatic Cancer cell proliferation and metastasis by modulating the miR-128-3p/GOLM1 axis.

Research perspectives

TP73-AS1 could promote Pancreatic Cancer progression, which might provide a potential treatment strategy for patients with Pancreatic Cancer.

6. *Authors should always cite references that are relevant to their study. Please check and remove any references that not relevant to this study;*

Our reply:

Thank you for your suggestions. We have carefully checked our manuscript and removed the references that relevant to our study weakly.

Company editor-in-chief's comments:

1. *The quality of the English language of the manuscript does not meet the requirements of the journal. Before final acceptance, the author(s) must provide the English Language Certificate issued by a professional English language editing company;*

Our reply:

Thank you very much for your comments. We have polished our manuscript again.

We sincerely thank the editor and all reviewers for their valuable feedback that we have used to improve the quality of our manuscript. We are looking forward to hearing from you in any time regarding our submission and to respond to any further questions and comments you may have.

Thank you and best regards.

Yours sincerely,

Zhengjun Qiu

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