

Dear Editor and Reviewers:

Thank you for your letter and for the reviewers' comments concerning our manuscript entitled "**KMT2D deficiency enhances the anti-cancer activity of L48H37 in pancreatic ductal adenocarcinoma.**" (ID: 42785) Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied comments carefully and have made correction which we hope meet with approval. The main corrections in the paper and the responses to the reviewer's comments are as follows:

Responses to the reviewer's comments:

Reviewer #1:

1 Abstract: The aim of the study: The statement "Its therapy-related factors" are these possible underlying mechanisms? Is the study in vivo or in vitro or a combination of both?

Response: The parts of study design and method have been modified. Our experiments are taken both in vivo and in vitro.

2 Abstract: Methods: It is not clear which component is in vitro or In vivo studies. Also whether you have used human cell line. The English language needs to be improved. For example, "we examined cells growth inhibition by using CCK8", could be changed to "we examined the effect of CCK8 on cell growth inhibition and.". Also change to "using flow cytometry" instead of "by flow cytometry". Similar problems noted throughout the manuscript.

Response: The words and expressions in this article have been refined by native English speakers.

3 Abstract: The last 6 lines under methods are not clearly written and confusing. What are your aims? You may need to limit the study to what you stated in the title.

Response: Research purpose and title have been modified to be more accurate.

4 Abstract and results again state (clarify) which component was the in vitro and which part was in vivo study results.

Response: The component of in vitro and in vivo parts has been reclassified in this research.

5 Conclusion could be strengthened.

Response: Upon request, we further strengthened our conclusions.

6 Key words: Did you study drug resistance and epigenesis in this study? I cannot see this.

Response: KMT2D as an epigenetic regulator involved in tumor occurrence and progression, and we have modified the over-extended part in this article.

7 Introduction: you need to add appropriate references. For example, third line, fifth line, and after the statement ending with "a trifle"

Response: Thanks for your suggestion, appropriate references reference have been added.

8 The authors are stating "inter-individual differences in drug reaction and thus precision medicine or personalised medicine has been proposed...." as a limitation for current therapy of pancreatic cancer, but you have not studied or tested this component in the current study. These statements should be omitted.

Response: Thanks for your suggestion, these inappropriate statements have been omitted.

9 Again we need references after epigenetic abnormalities and after "and so on".

Response: Thanks for your suggestion, appropriate references reference have been added.

10 The authors should amend the introduction and make it more focused to justify the needs for this study. It could also be shortened. Again, several statements are made on page.

Response: Thanks for your suggestion, the introduction has been streamlined and more focused on our research.

11 Introduction: The statement of in clinical practice (last 4-5 lines) should be omitted. I cannot see clinical work here.

Response: Perhaps our statement is too vague. In fact, in addition to analyzing the characteristics of cases from the TCGA database, we have also obtained clinical specimens of patients with pancreatic ductal adenocarcinoma and tested the target molecules. To this end, we have rewritten this part.

12 Material and methods: start with a sub title, "Study Design" to outline the experimental plan and how you designed these experiments to answer your research questions.

Response: Thanks for your suggestion. The "study design" has been arranged under the section of methods.

13 All subtitles under methods need appropriate references. I cannot see. Any references under methods. How can the readers know from where you came with these methods, and if other researchers would like to check on your work and follow these studies, they need to examine the references you have used. We need references from the broad literature.

Response: The appropriate references have been added to the part of method.

14 The SIX links on page 15 could be changed to references. In these references add the link and state when was last accessed. Follow the journal guidelines.

Response: Thanks for your suggestion. The SIX links on page 15 have been changed to references.

15 Results: could be reduced and made more focused. Indicate which component is in vivo and in vitro.

Response: This issue has been mentioned again, and we have clearly explained the in vivo and in vitro parts of the experiment.

16 Discussion: The authors are repeating the results again. This should not be the case. The authors need to rewrite the discussion and conclusion, and they should discuss their findings against other studies in the literature, identify the limitation of the study. The discussion should be reduced and focused. Rewrite the conclusion and strengthen it.

Response: Thanks for your suggestion. The discussion has been rewritten.

17 The English writing should be carefully reviewed. An agent in academic scientific writing could be asked to review the English.

Response: Thanks for your help. The words and expressions in this article have been refined by native English speakers.

18. The references are poorly selected. Please check PubMed, Scopus, and Web of Science, and include appropriate references.

Response: According to your suggestion, the reference has been re-selected.

Reviewer #2:

In the present work the cytotoxic effect of curcumine analog on different pancreatic cancer cells and its mechanism was investigated. The study use different methods with standard design to prove the hypothesis. However, some point should be clarified.

1 The full name of PDAC should be mention in the abstract.

Response: Thanks for your suggestion. The full name of PDAC has been mentioned in the abstract.

2 epigenetic, genetic and drug resistance were not key words. KM2D should be added as keywords.

Response: According to your suggestion, we removed the sections that were not covered and over-extended in the text.

3 In the introduction section the authors must describe the background and present the status and importance of the work, but in the last 2 paragraphs the result of the study was present in detail. In this study we identified the role of L48H37 in anti-human pancreatic tumors. L48H37 promoted the apoptosis of tumor cells by activating..... we found no relationship between the level of KMT2D lowering and clinical features as well as prognosis. The last 2 paragraph must change.

Response: We have highlighted status and importance of research in the introduction.

4 In the cell viability assay section, why the authors use different concentrations of DMSO? What was the final concentration of DMSO in media?

Response: L48H37 reconstituted in DMSO were diluted with media gradient when using and the final concentration of DMSO in the media was 0.001%, along with the same final concentration of DMSO as the negative control.

5 Which equation was used for IC50 calculation?

Response: The IC50 values were calculated with the help of a sigmoidal dose-response variable slope model using GraphPad PRISM6 (GraphPad Software, La Jolla, CA)

Reviewer #3:

Each figure is busy. All figures involve a lot of images, and it is so difficult to see these data. All figures should be remade.

Response: Thanks for your suggestion, we have remade the figures and some of the images have been placed in supplementary figures.