

Responses to comments by reviewers

Ms. Ref. No.: 74912, Basic Study

Article title: Accumulation of poly (ADP-ribose) by sustained supply of calcium inducing mitochondrial stress in pancreatic cancer cells

We would like to thank the editor and the reviewers for the constructive comments on our manuscript. Reflecting on the comments, the manuscript has been revised as described in the following responses. We prepared a separate reference list to respond to the comments in this “Responses to Reviewers’ comments”. Modified sentences were written in ‘deep blue’ in the related paragraphs. Please see the revised manuscripts in accordance with our responses.

Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: This study reported that sustained calcium supply led to the increasement of mitochondrial ROS, excess accumulation of PAR, resulting in AIF-dependent cell death in pancreatic cancer cells. The potential role of PAR accumulation in pancreatic cancer therapy was highlighted in this article, but as the authors said, the effect and mechanism of antitumor in clinical application remains a huge challenge.

Authors’ response: We absolutely agree with the comments. Therefore, it will be planned further study to find a clear mode of action.

Reviewer #2:

Scientific Quality: Grade C (Good)

Language Quality: Grade A (Priority publishing)

Conclusion: Minor revision

Specific Comments to Authors: This study describes the potential anti-cancer effects of continuous calcium supplementation leading to excessive PAR accumulation on pancreatic cancer. It is well known that pancreatic cancer is highly refractory, and we need to investigate new anti-cancer mechanisms, so the study has potential scientific value. The study offers potential ideas for the clinical treatment of pancreatic cancer. Overall, the full text is quite well organized. However, several minor issues need to be addressed. 1. Insufficient photos of animals and tumors were provided for the animal experiments, and it is recommended that all photos of animals and tumors should be supplemented by subgroups. 2. Some of the references are outdated, and it is suggested that references from the last 3 years be cited.

Authors' response:

1. Insufficient photos of animals and tumors were provided for the animal experiments, and it is recommended that all photos of animals and tumors should be supplemented by subgroups.

: Thanks for the constructive comments. According to the reviewer's suggestion, all animal and tumor photos were submitted as supplementary material.

2. Some of the references are outdated, and it is suggested that references from the last 3 years be cited.

: Most of the outdated references have been changed. Thank you.

Reviewer #3:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Minor revision

Specific Comments to Authors: I would like to congratulate the authors for this manuscript. This study is interesting and can bring new perspective. The manuscript is well prepared. I have some comments about the manuscript: Materials and methods: please refer related previous study on the methods that you use. Statistical analysis: please provide the biostatistics review certificate signed by a biostatistician. Figure legends: Information about Figure 2 section F is missing. Figure 2 section E & F please address accordingly.

Authors' response:

1. Materials and methods: please refer related previous study on the methods that you use.

: Could you kindly point out where it should add the citation?

2. Statistical analysis: please provide the biostatistics review certificate signed by a biostatistician.

: All statistical analyses for basic research were performed by the corresponding author. If it is asked for clinical statistics, it is not relevant to the recent study.

3. Figure legends: Information about Figure 2 section F is missing. Figure 2 section E & F please address accordingly.

: Thank you for the constructive comments. All have been corrected according to the comments.