Dear Editor and Reviewers,

Thank you very much for editing our manuscript entitled "**Epithelial-mesenchymal transition in chemoresistance of pancreatic ductal adenocarcinoma**" (Manuscript NO: 63450). The editor and reviewers' comments are all valuable and very helpful for us to revise and improve the quality of our paper. Following the suggestions from you and the reviewers, we have revised our manuscript for your consideration again. Revised portion are marked in red in the revised manuscript. We also included herein a detailed point-by-point response to the reviewers' comments.

Many thanks again to you for considering our work and to the reviewers for their insightful comments that helped make our manuscript a greatly improved one.

Best Regards,

Sincerely yours,

Wei Chen.

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Point-by-point response to the editors' and reviewers' comments:

Editor' comments

We greatly appreciate the editorial office's comments on our manuscript.

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

Response: Thanks to the editor for pointing this out. We have added the "Author Contributions" section in revised version.

(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: Done. Thank you for pointing this out.

Reviewer' comments

We greatly appreciate the reviewer's comments on our manuscript. Following the reviewer's suggestion, we drew a figure to summarize key points, and revised manuscript.

(1) *Given the complexity and the great number of different pathways that you describe, in my opinion, you should consider adding one or more figures or tables in order to summarize key points.*

Response: Thank you for the suggestion. We drew a figure and presented in revised manuscript to summarize key points.

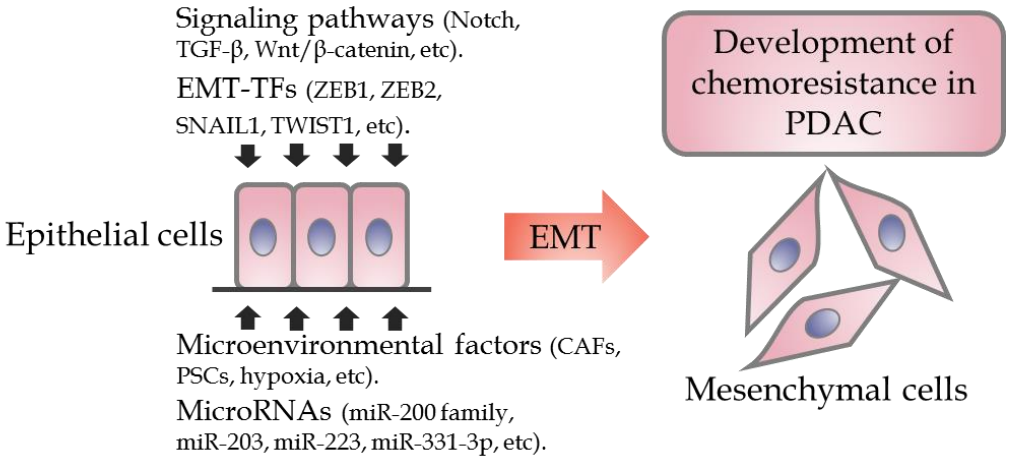

Figure 1 EMT involvement in PDAC therapy resistance. EMT is induced by various factors including signaling pathways, EMT-activating transcription factors (EMT-TFs), microRNAs, or microenvironment. Promotion of the EMT program enhances the chemoresistance of PDAC.

(2) *"In 1996, gemcitabine was approved by Food and Drug Administration (FDA) to treat all stages of advanced PC and has been the first-line treatment until now[25]" No, since 2011 first line therapy is FOLFIRINOX and in 2013-4 was approved for this use also gemcitabine plus nab-paclitaxel*

Response: We apologize for mistyping the information on gemcitabine has been the first-line treatment until now, which has been corrected in the revised manuscript by using red colored text, which is also copied below.

"In 1996, gemcitabine was approved by Food and Drug Administration (FDA) to treat all stages of advanced PC, and it is still an important drug for the treatment of PC until now."

(3) *"Numerous other studies revealed that the tumor microenvironment plays a pivotal role in EMT-driven drug resistance (reviewed in reference 21)[21]" You should consider summarize these studies (in my opinion even a couple of sentences are enough, or a table)*

Response: We appreciate this point. Following the reviewer's suggestions, we summarized these studies in the revised manuscript, as copied below:

"Tumor microenvironment such as cancer-associated fibroblasts (CAFs),

pancreatic stellate cells (PSCs) and hypoxia facilitate PC cells to undergo EMT and acquire chemoresistance."

(4) *Language needs further polishing* • *"Chemoresistance, defined as drugs showing no or less response to cancer cells at the effective inhibitory concentration" Cancer cells showing no or less ecc…* • *"Although some studies showed that EMT makes an limited"* • *"The expression pattern of hMENA isoforms, alternative splicing products of the actin regulator, regulated"*

Response: Thanks for your valuable comments and reminder. Following the reviewer's suggestions, we checked and corrected the language including the above sentence, as copied below.

Chemoresistance, defined as cancer cells showing no or less response to drugs at the effective inhibitory concentration, is classified as primary and acquired resistance.

The expression pattern of hMENA isoforms, which was regulated by TGF-β1, played a crucial role in TGF-β1-induced EMT, and might represent promising targets to develop new prognostic and therapeutic tools in PDAC.