

Editorial Office of World Journal of Gastroenterology

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Ms. Ref. No.: 6759

December 12th, 2013

Dear Editor,

Enclosed please find our revised manuscript in word format (WJG#6759.docx) entitled: **“Embryonic Stem Cell Factors and Pancreatic Cancer”** authored by Marta Herreros-Villanueva, Luis Bujanda, and Jin-San Zhang, which we would like to publish in ***World Journal of Gastroenterology***.

We thank you for giving us the opportunity to write on this very exciting topic. We particularly would like to acknowledge the two expert reviewers for their remarkably insightful suggestions/comments, which we have fully embraced in revising the manuscript. Besides language editing, we also extend to include an introduction paragraph on pancreatic cancer incidence, a therapeutic perspective based on targeting cancer stem cells as well as provided more detailed information in response to the reviewers' suggestions/comments. We feel the quality and the scope of the paper are much improved. Below is our point-by-point response to the editor and reviewer's comments.

Editor:

According to editor suggestions, we have formatted the manuscript and add additional contact information such as Telephone, Fax, Zip code and author's contributions. We have reformatted the references including PMID numbers. We have highlighted the major changes, but not the numerous language polishing/diting.

Reviewer #1:

Q1.- The review contains some word mistakes. The English needs be more carefully revised.

Response:

We appreciate your pointing this out. The manuscript has now been edited by Dr. Krawczak and Andrew Harrison, two Colleagues at Mayo Clinic, who are native English speakers and highly proficient in English.

Q2.- In the introduction section the incidence of PDAC worldwide should be added.

Response:

Thanks for this great comment. We have added an introduction section with incidence, basic epidemiology data, and significance of pancreatic cancer stem cell research at the beginning of the manuscript.

Q3.- Figure 2 is too simple and redundant with figure 1. In my opinion it can be deleted. On the contrary, a table with the biological behaviors of OCT4, SOX2 and NANOG and their implication in PDAC will be much more helpful.

Response:

Following your recommendation we have replaced Figure 2 with a new Table to summarize the biological role and clinical implications of OCT4, NANOG and SOX2 in PDAC from published work, which should be much more informative for the reader.

Q4.- In the section “ESC factors and pancreatic cancer” or in “Stem cell definition and types” one, it might be included the last evidence on side-population of cells (SP) expressing cancer stem cell-associated genes. SP could be potentially stemness and contribute to CSCs, as well as their CSC-associated expressed genes could have potential prognostic and therapeutic values in PDAC (Van den Broek A.et al., 2013 PLOS ONE, vol 8, issue9, e73968).

Response:

We appreciate your suggestion and information about this reference. Data about evidence of SP and its association with CSCs described by Van den Broek et al. as well as information from several new publications have been included in this revised manuscript.

Q5.- At page 9 the correlation between OCT4, SOX2 and NANOG expression in human pancreatic cancer tissues and early diagnosis or prognosis requires a more extended description (i.e. detection of the protein or mRNA in the tissues, levels of expression and their correlation with the prognosis, etc.).

Importantly, a table with a data summary of the “in cell culture” and “in tissue” evidences about the implication of OCT4, SOX2 and NANOG in pancreatic cancer and on the potentially targeted therapies will be very helpful.

Response:

Thanks for pointing this out. We have provided the additional information including the new Table as suggested (see Q3).

Q6.- Please specify in the text the type of pancreatic cell lines you cited

Response:

Thanks for your note. Now, in the revised manuscript we have indicated whether cell lines are human or mouse and named them specifically.

Q7.- In the “Summary and perspective” section, a comment on the recent evidence that of u-PAR controlled oncolytic adenoviruses can eliminate CSCs in human pancreatic tumors (Sobrevals L et al. Stem Cell Res 2013, 12:1-10) is necessary (as u-PAR can down-regulated SOX2). Again, for the same reason, it is interesting to cite the connection between OCT4, SOX2, NANOG, KLF4 factors and DCLK1 based on the new evidence (Sureban SM et al. PLOS ONE 2013, volume 8, issue 9, e73940; Bailey JM et al. Gastroenterology 2013, DOI 10.1053/j.gastro.2013.09.0

Response:

Thanks again for pointing out these relevant references. Both have been cited now in the revised manuscript.

Reviewer #2:

Q1.- Specifically, more details are required with respect to the prognostic importance of ESC factors in pancreatic cancer (in vitro and in vivo). Further, a paragraph outlining other strategies under investigation targeting cancer stem cells in pancreatic would be of interest to the reader (i.e. STAT3, etc).

Response:

We appreciate your suggestion. In this revised version, we have extended the information along this line. For instance: “in agreement with several publications in breast cancer [42], patients with OCT4 positive PDAC have a shorter survival suggesting this ESCs factor as a marker of poor prognosis” Additionally and in agreement with Reviewer#1 Q3, a Table has been added to the review with clinical implications of ESCs factors in pancreatic cancer (Table I in the revised manuscript).

Moreover, we wrote a paragraph to emphasize new strategies to target CSCs in pancreatic cancer. It can be read: “ In addition, other strategies to target CSC have been proposed and are under investigation. For instance, metformin as directed against pancreatic CSC....”

Q2.- Minor issues: The entire manuscript should be reviewed by the authors for spelling mistakes : For example, in the Abstract – “Interstingly”; also in the same sentence should “of” be removed.

Response:

Thanks for your comment and apologize for the language errors made in the previous version. The manuscript has been reviewed and edited for spelling and language mistakes.

We appreciate that you have given us invaluable comments to improve our manuscript and sincerely hope that our revised manuscript is suitable for publication in **World Journal of Gastroenterology** after revision based on your helpful comments. Please, do not hesitate to ask for further information, we would be happy to respond you.

Sincerely,

A handwritten signature in black ink, appearing to read 'Jin-San Zhang' followed by a stylized monogram.

Jin-San Zhang, MD, Ph.D