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PEER-REVIEW REPORT

Name of journal: World Journal of Stem Cells

Manuscript NO: 58085

Title: Glutathione metabolism is essential for self-renewal and chemoresistance of pancreatic cancer stem cells

Reviewer's code: 02543925
Position: Peer Reviewer
Academic degree: MD
Professional title: Doctor
Reviewer's Country/Territory: United States
Author's Country/Territory: Spain

Manuscript submission date: 2020-07-10
Reviewer chosen by: AI Technique
Reviewer accepted review: 2020-07-10 15:29
Reviewer performed review: 2020-07-13 19:19
Review time: 3 Days and 3 Hours

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [Y] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

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SPECIFIC COMMENTS TO AUTHORS

The manuscript hypothesized that pancreatic cancer stem cells (CSCs) depended on glutathione for Ros detoxification, and showed data with increased GSH content in pancreatic cancer CSCs and expression of several genes involved in the glutathione metabolism pathway. Importantly, some of the genes showed correlation with stemness and disease-free survival in pancreatic cancer patients. Depletion of GSH levels in CSC enriched cultures with pharmacological inhibitors induced cell cycle arrest and apoptosis, and inhibited self-renew and expression of CD133. GSH depletion by the inhibitors sensitized CSCs to gemcitabine. The research is not completely novel but is novel in pancreatic cancer, and has its value in providing mechanistic basis for developing pharmacological tools targeting pancreatic cancer stem cells. However, there are some flaws in the methodology that dampened the rigor of the study. 1) Many comparisons are made between attached culture and spheres, however it is not appropriate to compare spheres to adherent cultures and conclude on CSC functions, gene expression and treatment results. 2D and 3D cultures are different by nature in many aspects, not only about CSCs, and therefore differences detected are not necessarily attribute to or even related to CSC. A better comparison would be sorted CSC population versus non-CSC population from the same culture by flow cytometry. 2) The "CSC-enriched condition" is not confirmed, only assumed by suspension culturing. Surface markers such as CD133 used in this manuscript (or other means) could be used to confirm that the suspension culture is actually CSC-enriched. This is critical because many conclusions in the manuscript is based on the comparison between "CSC-enriched" culture versus attached culture. 3) The "Results" subsection 1 paragraph 2 is confusing about how the analysis was done. Did the authors use the 5 PDX samples for analysis of correlation between the up-regulated genes and "stemness"?

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Or did they use TCGA and GTEx data on normal vs pancreatic cancer tissues? 4) Materials and Methods: Please make it clear whether "the PDXs-derived tumor tissue fragments" were primary tumor tissues from patients, or PDX tumors passaged in mice/rodents? And what's the number of passages if passaged? PDX stands for "patient derived xenograft". Some other minor comments are: 1) Fig1B, what are the dotted lines? 2) Figure 2 has no label on y-axis, I assume its fold changes vs attached culture?