AMERICAN UNIVERSITY OF BEIRUT
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Tues, February 14, 2023

Re: Tissue-Specific Cancer Stem/Progenitor Cells: Therapeutic Implications

Dear Editors-in-Chief,

On behalf of my colleagues, I am returning to the World Journal of Stem Cells a revised version of a manuscript entitled: **"Tissue-Specific Cancer Stem/Progenitor Cells: Therapeutic Implications".**

The authors thank the editor and the reviewers for their constructive suggestions. Those comments are all valuable and very helpful for revising and improving our manuscript. We have carefully studied and evaluated the comments and have made the amended corrections. Accordingly, we have modified our manuscript to address all these comments. We believe that this version has addressed the editor's and reviewers' concerns. Please find below a point-by-point reply to all comments.

I sincerely hope that this manuscript will meet your requirements for publication.

Sincerely Yours,

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iewers' comments:

Reviewer #1:
Scientific Quality: Grade A (Excellent)
Language Quality: Grade A (Priority publishing)
Conclusion: Minor revision
Specific Comments to Authors: General comments The authors in this manuscript provide Therapeutic Implications of Tissue-Specific Cancer Stem/Progenitor Cells using patient-derived organoid models in 5 types of cancers. They also provide highlights on the advantage and relevance of the three-dimensional patient-derived organoids culture model as a platform for modeling cancer, evaluating CSC-based therapeutic efficacy, and predicting drug response in cancer patients. The manuscript to me is, in general, clearly written. The science and technical execution of the study are of good quality. The study is solid and the data, in general, support the conclusions. The theory, logic and, experimental design are easy to follow and in general make sense. However, some modifications are necessary to improve the quality of the manuscript.

Author's Response: We would like to express our sincere gratitude to reviewer #1 for his/her effort and time he/she put in the assessment of our manuscript. We really appreciate it.

Specific comments I recommend the authors to support the manuscript with figures related to:
1- PDO and their advantages other other preclinical models.

Author's Response: We thank the reviewer for his/her comment. Figure 2 has been added, showing the applications of PDOs in cancer.

2- Roles of CSC Markers in Cancer Tumorigenicity, cancer Progression, and resistance to therapy.

Author's Response: We thank the reviewer for his/her comment. Figure 1 has been added, showing the involvement of the CSC markers in cancer tumorigenicity, progression, and resistance to therapy.

3- Regulatory Pathways of CSCs for each cancer and another one for Potential Therapeutic Targets for CSCs in these cancers.

Author's Response: We thank the reviewer for his/her comment. We focused in our manuscript on TSCSC surface markers in five cancers (summarized in table 1). The common signaling pathways, not the tissue-specific ones, regulating CSCs were described briefly in the introduction. We aimed here to show the importance of these regulatory pathways without going deep into details (no figure was added). Regarding the potential therapeutic targets for CSCs in the cancers of interest, the same markers contributing to cancer tumorigenicity, progression, and resistance to therapy, are considered candidate targets for anti-CSC therapies (See Figure 1).

Line 67: support the sentence with this direct reference: https://doi.org/10.3390/ijms19041098 Line 228: support the sentence with this

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recent reference: https://doi.org/10.3390/cells9010235 Line 345: support the sentence with this recent reference: https://doi.org/10.1080/23808993.2020.1715794 Line 356: support the sentence with this recent reference: https://doi.org/10.1080/15384047.2021.1919004

Author's Response: We thank the reviewer for his/her comment. The mentioned references are now cited as requested, except for the second reference, https://doi.org/10.3390/, as the DOI was not found in the DOI System. Instead, the below reference was cited:

Ref 82: also MJ, Buchholz BA, White RW. Stem-like cells in bladder cancer cell lines with differential sensitivity to cisplatin. Anticancer Res 2012;32:733-8.

Overall, I believe the improved version of the manuscript will be of interest to the field of tumor biology and precision medicine using PDOs. Therefore, it should be recommended for publication in World Journal of Stem Cells after moderate revision.

Author's Response: We thank reviewer #1 for his/her constructive remarks. Thank you, Madam/Sir, for pushing us to improve the quality of our paper. We really appreciate it.

Reviewer #2:
Scientific Quality: Grade B (Very good)
Language Quality: Grade A (Priority publishing)
Conclusion: Accept (General priority)
Specific Comments to Authors: Complete review on CSCs features that could be promising anti-cancer targets in several tissue

Author's Response: We would like to express our sincere gratitude to reviewer #2 for his/her effort and time he/she put in the assessment of our manuscript. We really appreciate it.