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PEER-REVIEW REPORT

Name of journal: World Journal of Stem Cells

Manuscript NO: 54971

Title: Photodynamic therapy regulates fate of cancer stem cells through reactive oxygen species

Reviewer's code: 00693245
Position: Peer Reviewer
Academic degree: PhD
Professional title: Assistant Professor
Reviewer's Country/Territory: United States
Author's Country/Territory: China

Manuscript submission date: 2020-02-26
Reviewer chosen by: Ruo-Yu Ma
Reviewer accepted review: 2020-04-14 13:26
Reviewer performed review: 2020-04-19 15:15
Review time: 5 Days and 1 Hour

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish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	[ ] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

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SPECIFIC COMMENTS TO AUTHORS

Given that photodynamic therapy (PDT) kills tumor cells primarily through generating reactive oxygen species (ROS), and CSCs have dysregulated ROS system, it is believed that PDT can efficiently kill CSCs by generating ROS. In this manuscript, the authors attempt to provide a comprehensive review on the related studies to draw a complete picture describing how PDT regulates CSCs through generating ROS. Besides reviewing how ROS are generated by PDT, the authors mainly focused on the impact of ROS from PDT on CSCs in terms of mitochondria, endoplasmic reticulum, lysosomes, cell membranes, immunogenicity, noncoding RNA, and EMT. To determine how ROS affects CSCs, the authors used tons of genes and proteins that may regulate CSCs and have relationship with ROS to support their opinion. However, although these genes and proteins may be related to ROS, their functions in CSC maintenance maybe not due to the ROS-related functions. For examples, in the discussion of ROS-related noncoding RNA in CSCs, some of these noncoding RNA may be ROS related, but their role in CSC maintenance may not be related to ROS. In addition, some genes and protein may be involved in the maintenance of CSC, no evidence showing that they are regulated by ROS. For examples, when authors are talking about NEAT1 and MALAT1, no direct relationship between these two genes and ROS was shown. There is no evidence showing that the PDT-induced immunogenicity is mediated by ROS in CSCs. Taken together, the authors provide abundant information attempting to decipher how PDT kill CSCs via ROS, but the evidence are not closely relevant, and are not organized logically. Thus, it is very hard for readers to gain a clear picture after reading this review. Other concerns: • The authors used lots of genes and proteins to support their opinion, but did not give a clear explanation on what these genes are. • It is unclear what MMP stands for? Mitochondria membrane potential? Or mitochondria membrane

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permeability? • Many mechanisms are not specific for CSCs. • It is unclear whether PDT can specifically eliminate CSCs.

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Position: Editorial Board
Academic degree: PhD
Professional title: Postdoctoral Fellow, Senior Researcher
Reviewer's Country/Territory: Spain
Author's Country/Territory: China

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SPECIFIC COMMENTS TO AUTHORS

The manuscript entitled ¨PDT regulates the fate of cancer stem cells through ROS¨, by Zhang et al. constitutes a very extensive review on the generation of ROS by photodynamic therapy and the various actions of these molecules on cellular organelles and the survival/apoptosis of CSCs. It is indeed a very considerable effort that the authors have made to cover as many studies as possible on the subject, as reflected by the vast number of references cited in the Ms. There are a series of typos and wrong expressions (e.g. end of paragraph 2 in Pg. 2: ¨The endoplasmic reticulum, nucleus….¨, should be written as ¨The effects on the endoplasmic….¨ / first sentence in ¨ROS and mitochondria in CSCs: Mitochondria are among the research focuses…¨) throughout the text whose removal will not present a major problem upon a careful revision of the Ms; in addition, it is well written. Moreover, the text is very well structured. Despite all these very positive aspects, it is actually quite hard to read this review, and this is mainly due to several reasons: - The text is plagued with initials and, although a good number of these initials have been explained, there are others that have not been explained at all (5-ALA (explained only in Table 1), PERK, FCL, CRT, ISGs, EGCG). This assumes that the reader will be wholly familiar with all the aspects discussed; this should not be taken for granted, since there will be readers who approach the Ms who come from different fields of expertise (e.g. CSCs, ROS generation, Autophagy, Apoptosis). In addition, the names of some genes/proteins are explained, while others are not (PACS2, XCT, XBP1, NOX, etc.). - As a main objection, although the great effort made by the authors to encompass as many issues as possible is highly commendable, there are sections throughout the text when the authors bring in a vast amount of information but, rather than presenting these data in an elaborate line of thought, they introduce this information in a very schematic way, merely mentioning some ideas in a disconnected

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way. Thus it is not clear what the intention of the authors is when bringing in some of the data. A few examples of this are (although this is a recurrent problem): - The last sentences in section ROS and the endoplasmic reticulum in CSCs: ¨…..Mfn2 can regulate the autophagy……In summary¨ - End of the second paragraph in section ROS and lysosomes in CSCs: ¨…..The lysosomal-mitochondrial cross talk pathway involved in RAB5/7……..apoptosis¨. - Last paragraph in section ROS and lysosomes in CSCs: ¨…..In addition, in the study of the antitumour effect of bafilomycin combined with….¨. While the authors indicate that Pc4 is a PS, they do not mention that bafilomycin is an autophagy inhibitor, its mode of action... These sections where a lot of data are briefly introduced, sometimes in a disorderly fashion (e.g. The Wnt pathway is mentioned at the beginning of Pg. 6, while discussing Bcl-2; then, Wnt is again discussed at the end of the next paragraph, and it is first discussed with regard to PDK1, and then the effect of PDT on Wnt is mentioned. It would probably be better to discuss first what PDT does to the Wnt pathway and then discuss this pathway in one paragraph, not through various sentences in various paragraphs). On the other hand, these sections are intercalated with others where the issue at hand is well and clearly discussed, posing the problem, the studies, the results obtained. In contrast to the point mentioned above, the Conclusion section is very clearly written and it underlines how some of the points discussed in it have been, either not clearly addressed in the main body of the Ms, or not addressed at all. Some other comments: - In the abstract, one would miss some indication that the authors are also going to discuss problems faced by PDT; there are promising aspects of this therapy, but PDT may also favour increased survival, migration and metastasis of CSCs. This should be already clearly stated in the abstract, rather than suddenly mentioning ¨intermittent PDT treatment to reduce side effects¨, in Pg. 2. - When discussing tumor immunity, should it not be stated as immunogenicity? Pg. 2-3: ¨…its immune activation has the

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potential…..; in a counterintuitive outcome, some low-dose PDT promotes tumor recurrence and metastasis¨: Is it really such an obvious conclusion? In my opinion, this point should be better introduced and argumented. - Although the authors refer the reader to Ref. 111, given the importance of PS localization, one misses a brief explanation on how a differential distribution of PSs is achieved. - First paragraph in section ROS and the endoplasmic reticulum in CSCs: Is ¨upregulation of various ER molecular chaperones¨ equivalent to their ¨loss of function¨? - Pg 8: Salva should be changed to Salva and colleagues, Salva et al.,…. In summary, this is a great effort to present the many complexities and the vast amount of work that is being done on PDT as a therapy to treat tumors and specifically target CSCs. However, changes should be introduced to its present form. Either: - Reduce the amount of information, integrate different studies into a series of main messages, clearly presented and discussed, so that the reader can follow the argumentations of the authors. - Keep all the information, but lengthen the extension of the Ms, introducing more thorough discussions on the many particular pathways, routes, studies that the authors desire to discuss. As it is now, the authors assume that the reader already knows the great majority of the studies that they are discussing. A review should help a reader get a good grasp of the work carried out in the field, not constitute a whole number of sentences that the reader should immediately interpret.