Name of Journal: World Journal of Stem Cells

Manuscript NO: 64960

Dear Prof. Ma, Editors-in-Chief, and members of the Editorial Board,

RE: Reviewer commentary

Primarily, I would like to thank the editor and the reviewers for their positive feedback and the valuable comments. Please find enclosed the original copy of the revised manuscript.

The comments provided were found to be fair and incredibly useful. As recommended, the manuscript has been revised accordingly and believe we were able to satisfy the reviewers' proposed questions and suggestions.

We hope that you would find our revised manuscript acceptable for publication in the World Journal of Stem Cells.

Yours sincerely,

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Science editor:

1 Scientific quality: The manuscript describes a review of the epigenetic regulation of autophagy: a key modification in cancer cells and cancer stem cells. The topic is within the scope of the WJSC. (1) Classification: Grade A, Grade C, Grade B and Grade B; (2) Summary of the Peer-Review Report: The authors summarized the recent progress in the roles and mechanisms of authophagy in cancer stem cells, differentiated cancer cells, especially focusing on the epigenetic regulation of cancer stem cells and cancer cells. The review is adequate for its objective and is thoroughly written with several current/up-to-date references. However, the questions raised by the reviewers should be answered; and (3) Format: There is 1 table and 3 figures. (4) References: A total of 208 references are cited, including 45 references published in the last 3 years; (5) Self-cited references: There are 21 self-cited references. The self-referencing rates should be less than 10%. Please keep the reasonable self-citations that are closely related to the topic of the manuscript, and remove other improper self-citations. If the authors fail to address the critical issue of self-citation, the editing process of this manuscript will be terminated; and (6) References recommend: The authors have the right to refuse to cite improper references recommended by peer reviewer(s), especially the references published by the peer reviewer(s) themselves. If the authors found the peer reviewer(s) request the authors to cite improper references published by themselves, please send the peer reviewer's ID number to the editorialoffice@wjgnet.com. The Editorial Office will close and remove the peer reviewer from the F6Publishing system immediately. 2 Language evaluation: Classification: Grade A, Grade B, Grade B and Grade B. 3 Academic norms and rules: No academic misconduct was found in the Bing search. 4 Supplementary comments: This is an invited manuscript. No financial support was obtained for the study. The topic has not previously been published in the WJSC. 5 Issues raised: (1) The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor; and (2) Please obtain permission for the use of picture(s). If an author of a submission is re-using a figure or figures published elsewhere, or that is copyrighted, the author must provide documentation that the previous publisher or copyright holder has given permission for the figure to be re-published; and correctly indicating the reference source and copyrights. For example, "Figure 1 Histopathological examination by hematoxylin-eosin staining (200 ×). A: Control group; B: Model group; C: Pioglitazone hydrochloride group; D: Chinese herbal medicine group. Citation: Yang JM, Sun Y, Wang M, Zhang XL, Zhang SJ, Gao YS, Chen L, Wu MY, Zhou L, Zhou YM, Wang Y, Zheng FJ, Li YH. Regulatory effect of a Chinese herbal medicine formula on non-alcoholic fatty liver disease. World J Gastroenterol 2019; 25(34): 5105-5119. Copyright ©The Author(s) 2019. Published by Baishideng Publishing Group Inc[6]". And please cite the reference source in the references list. If the author fails to properly cite the published or copyrighted picture(s) or table(s) as described above, he/she will be subject to withdrawal of the article from BPG publications and may even be held liable. 6 Recommendation: Conditional acceptance.

Authors reply: We revised the manuscript according to the reviewers' proposed questions and suggestions. Recent and relevant references have been added. We have also removed few of the self-citations and ensured that we are less than 10% of the total references. In this revised version, we have a total of 218 references; with only 16 self-citations (7.3%).

The originality of the figures can be found in the attached PowerPoint file. In the legend for Figure 1, a short comment has been included: "Several autophagy related genes (ATGs) aid in the development, maturation and closure of the autophagosome (the ATG related signaling has been exhaustively discussed in our previous review; this figure has been adapted accordingly)[8, 12]." Figures 2-3 are original, therefore, there is no need for a citation.

Reviewer's comments:

Reviewer #1:
Scientific Quality: Grade B (Very good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Accept (General priority)

Specific Comments to Authors: This manuscript by Harpreet K Mandhair et al summarized the recent progress in the roles and mechanisms of authophagy in cancer stem cells, differentiated cancer cells, especially focusing on the epigenetic regulation of cancer stem cells and cancer cells, including DNA methylation, histone remodeling and modifications, non-coding RNAs. This will help people in the related area.

Authors reply: We thank the reviewer for the positive and supportive comments.

Reviewer #2:
Scientific Quality: Grade C (Good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Minor revision

Specific Comments to Authors: The manuscript 'Epigenetic regulation of autophagy: a key modification in cancer cells and cancer stem cells' discusses the role of epigenetic alterations as a major player within the autophagy of cancer stem cells and also in cancer cells. In detail, the authors provide comprehensive presentations and backgrounds of different epigenetic modifications like DNA methylation, histone modification or non-coding RNAs and outlined respective correlations to the autophagic signaling of cancer cells and cancer stem cells. Moreover, the link from the existing knowledge of cancer (stem) cell-based epigenetic regulation of autophagy to a clinical context with possible therapeutic approaches is well described. However, some minor issues should be addressed:

1. The authors should partially extent their manuscript part of 'DNA methylation' (page 9), concerning the shift from describing the generalized process, to highlighting some selected examples for DNA methylation in context with cancer and cancer (stem) cells. This brief extension will give a prior information on this type of epigenetic modification, as it is outlined for the directly following chapter of 'Histone remodeling and modifications'.

Authors reply: Since the main focus of our manuscript is epigenetic regulation of autophagy in cancer, we have therefore kept the general DNA methylation part brief, describing the generalized process (page 9). The comprehensive mechanism of epigenetic regulation of autophagy in cancer cells and cancer stem cells has been discussed in detail in their respective sections.

2. By explaining the 'Histone methylation' and by describing 'Short non-coding RNA and microRNA' as epigenetic mechanisms, the authors briefly mentioned two connections from autophagic signaling to NF-κB transcription factor activation (page 16 and 19). It would be very interesting to shortly recapitulate the common relation from autophagy to NF-κB in cancer (stem) cells, as the NF-κB transcription factor is one of the major regulators of cell survival.

Authors reply: To address this point, a detailed literature review has been added to the "TRANSCRIPTIONAL REGULATION OF AUTOPHAGY" section.

3. The following typos were found in the text and should be revised: "Table 1 DMA methylation or histone modification", "ER: endothelial reticulum" and the change from "CS" to "CC" as an explanation for 'cancer cell' within figure 1, are to be corrected.

Authors reply: We have addressed these errors and made amendments accordingly.

Reviewer #3:
Scientific Quality: Grade A (Excellent)
Language Quality: Grade A (Priority publishing)
Conclusion: Accept (General priority)

Specific Comments to Authors: The authors have reviewed the critical role of epigenetic modification in cancer stem cells (CSCs) and cancer cells through various mechanisms including regulation of tumor suppressor genes and modulation of key signaling pathways. They specifically pointed the role of autophagy in cancer development and how epigenetic modulation mechanism could be used to circumvent the effect of autophagy thereby providing novel cancer therapeutics. The authors pinpointed specific epigenetic mechanisms including DNA methylation, histone modifications and non-coding RNAs, how they mediate genomic instabilities and cause cancer development. However, they also provided a hope through epigenetic therapeutics targeting of autophagy and reactivation of tumor suppressor genes. They highlighted several epigenetic elements including lncRNAs and miRNAs from various studies that are associated with different tumor types. The authors proposed 3 models which is promising and educative, providing a new direction for targeted cancer therapy/treatment. This review is adequate for its objective and is thoroughly written with several current/up-to-date references. Main concerns: My question is that the authors should confirm if figures 1-3 belong to them or not. These figures were not referenced, and I am assuming their proposed model/pathway. It will be nice if your readers know this. Please tell the readers. It is also not a crime if you got it from somewhere else but must reference them.

Authors reply: We thank the reviewer for the positive and supportive comments. Concerning Figures 1-3, the legend for Figure 1 is corrected as "Several autophagy related genes (ATGs) aid in the development, maturation and closure of the autophagosome (the ATG related signaling has been exhaustively discussed in our previous review; this figure has been adapted accordingly)[8, 12]." Figures 2-3 are original, therefore, no need for citation.

Reviewer #4:
Scientific Quality: Grade B (Very good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Accept (General priority)

Specific Comments to Authors: We appreciate the manuscript and agree to accept its publication

Authors reply: We thank the reviewer for the positive and supportive comments.