

16-May-2021

Dear Editors,

We would like to thank the reviewers for their thoughtful and constructive comments regarding our manuscript. We have carefully read through the comments from reviewers. To fully address reviewers' questions and comments, we have revised our manuscript accordingly. Revised portions are highlighted in red in the manuscript. The point-by-point responses to the reviewers' comments are listed as follows.

Comments to the Author

The topic of the manuscript is very interesting and summarizes the current research interest of personalized nutrition/medicine. Although the importance of this topic, there are few comments.

Response: Thank you very much for your affirmation. The issues raised are addressed as follows.

Reviewer 1:

1. There are references missing, see point 3) Amino Acid metabolism- 3rd line, after maintenance. There are other places/gaps where references are missing.

Response: Thanks for your suggestion. We have modified the reference section.

2. grammatic - there are a lot of mistakes throughout the manuscript, e.g. this person "s".

Response: We have carefully checked the sentences and typos in our manuscript according to your suggestions. The manuscript has been revised by a native English speaker. The certificate document has been provided as well. We hope the revised manuscript could be up to the standard.

3. The classification/ division is not clear. In particular nucleotide metabolism is not mentioning ncRNAs, which might be regulated by nutrients. Folate and a-KG are mentioned in this section, whereas a-KG is referred to the earlier section. Folate is involved in nucleotide metabolism, but rather it is a micronutrient and should be placed within this section.

Response: Thanks for raising this constructive comment. We have carefully read through the articles about ncRNAs, discuss its Metabolic-Epigenetic Nexus effect in the nucleotide metabolism part. As for folate, it has been put into the micronutrient part as the suggestion of reviewer. When it comes to a-KG, a crucial substance participating in metabolism, especially in amino acid metabolism, it seems more reasonable to discuss this material in amino acid metabolism part.

4. Instead of microelement, I would call this section "micronutrients"

Response: Thanks for your suggestion. We have modified the "microelement" into "micronutrients" and highlighted in red accordingly.

5. The conclusion is too short, I expected a better outlook and further direction of the topic.

Response: We appreciate reviewer's concern to improve our manuscript. Thanks for raising this comment. The corresponding contents to describe current study limitations and potential improvement points for further study, which are highlighted in red in the manuscript.

Reviewer 3:

1. The problem of inadequate citation of references in some sentences needed to be improved.

Response: Thanks for raising this comment. We have carefully check through the manuscript, have been read and adding more reference articles according to the reviewer's suggestion.

2. "The potential preventive and therapeutic strategies via targeting metabolites were discussed as well." In terms of this subject, the authors had a insufficient discussion in the manuscript, further relevant contents should be added. "In summary, NAD⁺ plays a key role in a diverse array of biological processes." Please improved the content that focus of the main subject.

Response: Thanks for your suggestion. We have modified the manuscript and increased the contents relevant to "The potential preventive and therapeutic strategies" and "the function of NAD⁺ in a diverse biological processes", which are highlighted in red in the manuscript.

Editorial Office:

Comments to the Author

Scientific quality: The manuscript ID: 76486 with the following title, The Metabolic-Epigenetic Nexus in Regulation of Stem Cell Fate, is consistent with the journal's scope and instructions. (1) Classification: Three peer reviewers have given A, D, and C grades for scientific quality and A, C and B grades for Language quality. The final recommendation by these reviewers are 1) Accept, 2) Major revision and 3) Minor revision. (2) Summary of the Peer-Review Report: The topic of the manuscript is very interesting and summarizes the current research interest of personalized nutrition/medicine. Although the importance of this topic, However, some issues should be improved.

Response: Thank you very much for your affirmation. The issues raised are addressed as follows.

Language evaluation: The language quality is acceptable (Grade B). Some English polishing is necessary. The Non-Native Speakers of English Editing Certificate is not provided.

Response: Thanks for raising this comment. The manuscript has been revised by a native English speaker. The certificate document has been provided as well. We hope the revised manuscript could be up to the standard.

3. Academic norms and rules: The authors must provide the signed Conflict-of-Interest Disclosure Form and Copyright License Agreement, and the Institutional Review Board Approval Form. Written informed consent was waived. No academic misconduct was found by the Google/Bing search.

Response: As the request in the before email, we need to complete the Copyright License Agreement online. With your help, two of our authors who didn't receive the email the first time have checked email and signed the Copyright License Agreement. However, one of our author, Li-wei Zheng (liweizheng@scu.edu.cn), still haven't received the check email. Therefore, we failed to fill the Agreement online. To ensure the copyright license agreement, we will upload the scanned agreement with authors' signature in the system when submitting the revised manuscript. We feel sorry for this.

We have carefully read through and addressed the reviewer and Editorial Office's comments. We hope our responses could address reviewer and Editorial Office's concern and our revised manuscript now is appropriate for publication in *World Journal of Stem Cells*.

Sincerely,

Mian Wan D.D.S., Ph.D.

#14, 3rd section of Renmin South Road

Chengdu, Sichuan, P.R.China, 610041

Email: mianwan@scu.edu.cn