

Dear editor:

Enclosed please find the revised manuscript No. 85867 "Recent Progress in Understanding Mitokines as Diagnostic and Therapeutic Targets in Hepatocellular Carcinoma". We greatly appreciate the comments and have learned a lot from the reviewers. The critics have been addressed as following.

Reviewer Comments:

Reviewer 1:

1. The English need improvement since there are some grammatical and syntax errors in the manuscript. For example, the words "abnormal" may be as "an abnormal"; "the endoplasmic" as "endoplasmic"; "the "ER stress."" as ""ER stress.""; "Binding" as "The binding". The grammar mistakes which are not mentioned here are also to be checked and corrected properly.

A: We are grateful for your comments. According to your suggestion, we have a professional editor review the manuscript to improve the English language quality and avoid errors.

2. There are some typing mistakes as well, and authors are advised to carefully proof-read the text. For example, the words "school" may be as "School"; "ethic" as "ethics"; "Diagnosistic" as "Diagnostic"; "intertissue" as "inter tissue". The typos not mentioned here are also to be checked and corrected properly.

A: We appreciate your wonderful comments. According to your suggestion, we have carefully proofread the text, checking and correcting spelling errors.

3. Check the abbreviations throughout the manuscript and introduce the abbreviation when the full word appears the first time in the abstract and the remaining for the text and then use only the abbreviation (For example, reactive oxygen species (ROS), damage-associated molecular patterns (DAMPs), etc.,). Make a word abbreviated in the article that is repeated at least three times in the text, not all words to be abbreviated.

A: We appreciate your wonderful comments. We have cross-checked the abbreviations in the entire text and have abbreviated or presented the relevant words in full form according to the rules.

4. The introduction part appears less informative about the Hepatocellular Carcinoma, thus this section should be indicated as detailed to understand the manuscript in clear.

A: Thanks for your great comment, We appreciate your suggestion and have added relevant content about HCC in the introduction section.

5. The literature search should be described in detail. The authors are encouraged to include the database, search engines (like PubMed, ScienceDirect, Google scholar etc.), the keywords used etc., which may be included since it is a review article.

A: Thank you for your suggestion. We have added relevant content in the manuscript about the databases used for literature retrieval and the keywords.

6. The authors are encouraged to include one table for better outcome of the manuscript since it is a review article.

A: Thank you for your suggestion. According to your suggestion, we have added a table (Table 1) regarding the relationship between mitokines and HCC prognosis.

Reviewer 2:

1. As described, mitochondrial stress elicits the production of stress response molecules indicated as mitokines. However, the contents described that most mitokines are only expressed in the nucleus. The theoretical background and research that mitokines is secreted directly from mitochondria and related to HCC growth and differentiation is lacking. The factors are already known as biomarkers of HCC, even if not related to mitochondria stress. It is wondering whether all expression factors in the nucleus can be defined as mitokines.

A: Thank you very much for your careful review. According to the relevant definition, mitokines are a class of cellular factors and peptides produced by the cell nucleus or mitochondria as non-autonomous cellular effects in response to cellular stress.

2. There have been no investigations into clinical trials targeting mitokines (eg. NCT04725474). 3. It is strongly recommended that several mitokines presented by the authors be summarized in a separate table related to molecular biological features or as the role of prognostic factors.

A: Thank you for your suggestion. According to your suggestion, we have added a table (Table 1) regarding the association between mitokines and HCC prognosis.

We feel that these changes are more persuasive and strongly support our statement in the manuscript. We hope the reviewers agree with our answers and the new version of this manuscript meets the standard of the prestigious **World Journal of Clinical Cases**. Thank you very much for your consideration.

Sincerely yours

Author name been removed