

Dear editor:

Enclosed please find the revised manuscript No. 85445 "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 #1:

1. Make a figure depicting cuproptosis as cancer therapy - how it works

**A:** Thank you for your valuable comments. We have now added a figure (Figure 3) to illustrate the mechanisms of cuproptosis as a potential cancer therapy.

2. In discussion section, add limitations of therapy and future scope & recommendations

**A:** Thank you for your valuable comments. We have now added limitations of therapy, future scope & recommendations in the discussion section.

3. add a seperate conclusion paragraph

**A:** Thank you for your valuable comments. We have now added a separate conclusion paragraph.

Reviewer #2:

1. Please include a section on future directions to emphasize the constraints and future intentions for applications.

**A:** Thank you for your valuable comments. We have taken this into consideration and have added relevant limitations and future considerations in the discussion section.

2. The authors mentioned that "Using immunotherapy as an example. With copper ions' anti-angiogenic properties, immunotherapy drugs combined with copper chelators will become a new treatment for cancer" could the authors deeply discuss

the complex interactions of immune cells in the tumor microenvironment of cancer as well as cancer cells? reference: SnapShot: TP53 status and macrophages infiltration in TCGA-analyzed tumors. *Int Immunopharmacol.* 2020 Sep;86:106758. doi: 10.1016/j.intimp.2020.106758.

**A:** Thank you for your valuable comments. Based on the literature you suggested (PMID: 32663767) and other relevant studies (PMID: 32499786), we have now added the interactions between immune cells in the tumor microenvironment (TME) and different cancer types.

Reviewer #3:

1. This manuscript seems to be prematurely rushed into publication and is not acceptable in its current format. Despite the fact that it might have a scientific value, the lack of careful attention and awkwardness of many sections make it very hard to follow.

**A:** Thank you very much for your meticulous review and all the questions. We have modified the contents and we believe the current manuscript provides a better and more comprehensive summary of the latest research progress on copper death and its related aspects. We believe our review lays a theoretical foundation for further studies on copper death in cancer and can serve as a valuable scientific reference.

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 Oncology**. Thank you very much for your consideration.

Sincerely yours

Author name been removed