

ESPS Manuscript NO: 70923

Title: Circular RNAs in hepatocellular carcinoma: Recent advances

Author: Zhao-Shan Niu, Wen-Hong Wang

Name of Journal: World Journal of Gastrointestinal Oncology



Dear Editor and reviewers,

Thank you for carefully reviewing our manuscript entitled "Circular RNAs in hepatocellular carcinoma: Recent advances" for possible publication in the World Journal of Gastrointestinal Oncology as a review. We appreciate the comments and suggestions from the editor and reviewers. We have revised the manuscript, highlighting our revisions in red, and have attached point-by-point responses detailing how we have revised the manuscript according to the reviewers' comments below.

Yours Sincerely,

Zhao-Shan Niu (Corresponding Author)

Reviewer #1 Specific Comments to Authors:

The manuscript entitled "Circular RNAs in hepatocellular carcinoma: Recent advances" by Zhao-Shan Niu and Wen-Hong Wang submitted to the "World Journal of Gastroenterology" focuses on the discussion of recent advancements in the investigation of circRNAs and their roles in hepatocellular carcinoma (HCC). The manuscript is well-written and well-organized and can be of interest to the journal readers. However, there are some concerns and recommendations that can improve the quality of the manuscript.

Response: We appreciate the reviewer's positive comment. Our deepest gratitude goes to you for your excellent and thoughtful suggestions regarding better presentation of our manuscript.

1. The manuscript mechanistically lists the circRNAs involved in HCC regulation. Instead, it is recommended to discuss in more detail their biogenesis and mechanisms of their functioning (such as the involvement in circRNA-

miRNA-mRNA regulatory axes and interaction with RBPs).

Response: We appreciate the Reviewer's for this constructive comment. As suggested by the reviewer, we have added more details of their biogenesis and mechanisms of their functioning in the revised manuscript.

2. Consequently, it is recommended to include more (2-3) Figures to illustrate these mechanisms.

Response: Following the Reviewer suggestion, we have added 2 Figures to illustrate these mechanisms (including biogenesis of circRNAs and biological functions of circRNAs) in the revised manuscript.

3. In the "Role of circRNAs in HCC" section, it is recommended to discuss not only single circRNAs but regulatory axes in which they are involved. This helps to a more comprehensive discussion of their role in hepatocarcinogenesis and underlying mechanisms. For example, it is not clear from the manuscript, what are the mechanisms underlying the involvement of circRNAs in drug resistance, i.e., what genes are regulated.

Response: We have deleted the references that did not specify which genes are regulated by circRNA. For example, "In particular, a recent study found the importance of differentially expressed circRNAs such as hsa_circ_0006294, hsa_circ_0035944 and hsa_circ_0084663 in HCC resistance to sorafenib [100]." has been replaced by the following sentence, "In particular, circMEMO1 promotes the sensitivity of sorafenib to HCC through upregulating TCF21 expression by sponge miR-106b-5p [126]."

4. In Table 1, it is recommended to add gene names that are under the control of a circRNA where it is applicable.

Response: The names of genes controlled by circRNAs are listed in column 4 of Table 1 of the original manuscript.

5. Refs should be checked since some of them were not properly cited; for example, Ref. [3] does not discuss circRNA functions and Ref. [4] should be changed because it does not discuss genetic/epigenetic and posttranslational regulation of circRNAs. Instead of Ref [12] the following paper can be discussed:

Zhao X, Cai Y, Xu J. Circular RNAs: Biogenesis, Mechanism, and Function in Human Cancers. Int J Mol Sci. 2019 Aug 13;20(16):3926. doi: 10.3390/ijms20163926. So on.

Response: We are extremely grateful to reviewer for pointing out this problem. We apologize for incorrect citations of some references. We have made the following modification: Ref. [3] in the original manuscript has been replaced with a new reference in the revised manuscript. Ref. [4] in the original manuscript has been replaced with two new references in the revised manuscript. Ref. [13] in the original manuscript has been replaced by the reference recommended by the reviewer in the revised manuscript. In addition, references cited have been checked carefully for accuracy in the entire manuscript.

The revision-reviewer's comments

“The authors have properly addressed all my comments”.

Response: We appreciate the reviewer's positive comment.

Again, we greatly appreciate your consideration of our paper for publishing in the World Journal of Gastrointestinal Oncology.

Yours Sincerely,

Zhao-Shan Niu (Corresponding Author)