

Dear Editor,

Thank you for your considering the publication of our manuscript entitled "Exosome-mediated transfer of circRNA563 promoting hepatocellular carcinoma by targeting the microRNA148a-3p/metal-regulatory transcription factor-1 pathway" (No. 88575). Please find below our responses to the reviewers' comments. We have also updated our manuscript according to the responses. The revised/added contents have been highlighted in yellow in the revised manuscript.

Response to reviewers

Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: Very well written paper A schematic diagram of microRNA148a-3p/metal-regulatory transcription factor-1 pathway is mandatory for the readers to understand the depth of the subject Language polishing is necessary

Response:

Thank you for your valuable suggestions.

We have created a schematic diagram in accordance with your suggestion.

The manuscript has been reviewed and approved by Editage as recommended by *World Journal of Gastroenterology*.

Reviewer #2:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: BACKGROUND Mesenchymal stem cells (MSCs) exert anti-oncogenic effects via exosomes containing non-coding RNA (ncRNA), which play important roles in tumor biology. Our preliminary study identified the interaction of the ncRNA hsa\_circ\_0000563 (circ563) and the circ563-associated miR-148a-3p in exosomes, as miR-148a-3p and its target metal-regulatory transcription factor-1 (MTF-1) are implicated in hepatocellular carcinoma (HCC) progression. AIM To identify the clinical significance, functional implications, and mechanisms of circ563 in HCC. METHODS Compared the expression levels of miR-148a-3p and MTF-1 in exosomes derived from MSC and HCC cells and assessed their tumor-suppressive effects on HCC cells. Using a dual-luciferase reporter assay, miR-148a-3p was identified as a circ563-associated miRNA, whose role

in HCC regulation was assessed in vitro and in vivo. RESULTS Silencing of circ563 blocked HCC cell proliferation and invasion and induced apoptosis. Co-culturing HCC cells with MSC-derived exosomes following circ563 overexpression promoted cell proliferation and metastasis and elicited changes in miR-148a-3p and MTF-1 expression. Tumor-promoting effects of circ563 were partially suppressed by miR-148a-3p overexpression or MTF-1 depletion. Xenograft experiments in nude mice confirmed that circ563-enriched exosomes facilitated tumor growth by upregulating MTF-1. In HCC tissue, circ563 expression was negatively correlated with miR-148a-3p expression but positively correlated with MTF-1 levels. CONCLUSION MSCs may exhibit anti-HCC activity through exosomal circ563/miR-148a-3p/MTF-1 pathway, while exosomes can transmit circ563 to HCC cells and promote oncogenic behavior by competitively binding to miR-148a-3p to activate MTF-1. In General: it's a good paper and the subject of the manuscript is applicable and useful. Title: the title properly explains the purpose and objective of the article Abstract: abstract contains an appropriate summary for the article, the language used in the abstract is easy to read and understand, and there are no suggestions for improvement. Introduction: authors do provide adequate background on the topic and reason for this article and describe what the authors hoped to achieve. MATERIALS AND METHODS: - The variables selected for the study are described clearly and are appropriate, given the nature of the question asked. - The research design is described in detail. - The research design is appropriate and does not contain particular weaknesses. - The measurement instrument, including its psychometric qualities, is described clearly. - The population of interest and the sampling procedure are defined clearly. - The data collection procedure is clearly described. - The setting in which the study took place is described. - The data analysis procedures are stated in precise terms. - The data analysis procedures are appropriate. Results: the results are presented clearly, the authors provide accurate research results, and there is sufficient

evidence for each result, Specific data accompany the result statement, and Tables and figures are used efficiently. Conclusion: in general: Good and the research provides sample data for the authors to make their conclusion. Grammar: There are a lot of grammatical errors. This must be taken care of and addressed. . (Check The Paper Comments). Finally, this was an attractive article. In its current state, it adds much new insightful information to the field.

Response:

Thank you for your insightful comments.

We have carefully reviewed the manuscript, and the revision has been reviewed and approved by Editage as recommended by *World Journal of Gastroenterology*.

Thank you for your valuable suggestions. We really appreciate your warm work, and hope that the revised manuscript could be considered for publication in *World Journal of Gastroenterology*.

Sincerely,

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Jinan, Shandong Province, 250021, China.