

PEER-REVIEW REPORT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 86000

Title: Function and biomedical implications of exosomal microRNAs delivered by parenchymal and nonparenchymal cells in hepatocellular carcinoma

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 00028182

Position: Peer Reviewer

Academic degree: MD

Professional title: Associate Professor, Doctor

Reviewer's Country/Territory: Italy

Author's Country/Territory: China

Manuscript submission date: 2023-05-26

Reviewer chosen by: AI Technique

Reviewer accepted review: 2023-05-26 19:07

Reviewer performed review: 2023-05-26 19:33

Review time: 1 Hour

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Novelty of this manuscript	<input checked="" type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No novelty
Creativity or innovation of this manuscript	<input checked="" type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No creativity or innovation

Scientific significance of the conclusion in this manuscript	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No scientific significance
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous
	Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

This is an interesting review addressing the composition and function of exosomal miRNAs of different cell origins in hepatocellular carcinoma (HCC) and highlighting the association between exosomal miRNAs from stromal cells and immune cells in the TME and the progression of HCC. Of interest, the authors also described the potential applicability of exosomal miRNAs derived from mesenchymal stem cells in the treatment of HCC. The review is well presented and discussed. I have some comments to further improve the clinical impact of the manuscript. -the manuscript would benefit of a section discussing available data on the role of etiology of HCC and relationship with miRNAs, in particular whether there are differences according to etiology of underlying liver disease in patients with HCC.. - Intriguingly, the authors recall the major role of CD4⁺ CD25⁺ regulatory Tcells as they mentioend that tumor-derived exosomal miR-214 efficiently enhanced IL-10 expression by promoting CD4(+)CD25(high)Foxp3(+) regulatory T cell (Treg) expansion, thereby accelerating tumor growth. Since Tregs are now recognized as the most prominent immunosuppressive immune cell population in tumor microenvironemt of HCC, they

should further expand such a relevant issue also quoting their pathogenic role in HCC as well as in the development of immune-related adverse events under immune checkpoint inhibitors as well described and summarized in a comprehensive review (Hepatocellular carcinoma in viral and autoimmune liver diseases: Role of CD4+ CD25+ Foxp3+ regulatory T cells in the immune microenvironment. World J Gastroenterol. 2021 Jun 14;27(22):2994-3009. doi: 10.3748/wjg.v27.i22.2994).

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Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 03856292

Position: Peer Reviewer

Academic degree: PhD

Professional title: Associate Professor

Reviewer's Country/Territory: Egypt

Author's Country/Territory: China

Manuscript submission date: 2023-05-26

Reviewer chosen by: Geng-Long Liu

Reviewer accepted review: 2023-06-16 07:59

Reviewer performed review: 2023-07-10 01:29

Review time: 23 Days and 17 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

Peer-reviewer statements	Peer-Review: [<input checked="" type="checkbox"/>] Anonymous [<input type="checkbox"/>] Onymous
	Conflicts-of-Interest: [<input type="checkbox"/>] Yes [<input checked="" type="checkbox"/>] No

SPECIFIC COMMENTS TO AUTHORS

In the current review, the authors aimed to summarize the composition and function of exosomal miRNAs of different cell origins in HCC and highlighted the association between exosomal miRNAs from stromal cells and immune cells in the TME and the progression of HCC. Also, they described the potential applicability of exosomal miRNAs derived from mesenchymal stem cells in the treatment of HCC. However, there are some comments on this manuscript:

- Many facts in the introduction are mentioned without their references.
- The conclusion is very long.
- Some references are old (2011, 2005, 2012,etc).

Other comments are in the attached manuscript word file.

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Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 03948659

Position: Peer Reviewer

Academic degree: PhD

Professional title: Senior Lecturer, Senior Scientist

Reviewer's Country/Territory: Bangladesh

Author's Country/Territory: China

Manuscript submission date: 2023-05-26

Reviewer chosen by: Geng-Long Liu

Reviewer accepted review: 2023-07-03 09:02

Reviewer performed review: 2023-07-13 05:45

Review time: 9 Days and 20 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Novelty of this manuscript	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No novelty
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Language quality	<input type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input checked="" type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous
	Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

This manuscript has been written on an interesting topic. There are a few major issues that are needed to be resolved before further consideration of this manuscript. 1. The title does not reflect the conclusion of this study. Hence, it would be better to revise the title so that it aligns with the conclusion of the study. 2. This is highly narrative and lacking in critical review of the literature. 3. The conclusion does not summarize the role of particular miRNAs in the pathogenesis and reversion of the HCC. Hence, the conclusion requires major revision. 4. There are several typos and grammatical errors throughout this manuscript. This manuscript requires major English corrections.

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Peer-review model: Single blind

Reviewer's code: 03740782

Position: Peer Reviewer

Academic degree: MD

Professional title: Associate Professor

Reviewer's Country/Territory: Taiwan

Author's Country/Territory: China

Manuscript submission date: 2023-05-26

Reviewer chosen by: Geng-Long Liu

Reviewer accepted review: 2023-07-02 22:30

Reviewer performed review: 2023-07-14 08:15

Review time: 11 Days and 9 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Novelty of this manuscript	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No novelty
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Re-review	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous
	Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

The authors reviewed the exosomal microRNAs delivered by nonparenchymal cells in hepatocellular carcinoma. Overall, the manuscript is comprehensive and informative. There are some minor issues to improve: 1. In Figure 1, please add M1 and M2 associated MiRs in the Figure. 2. In Figure 1, please label or express the anti-tumor/tumor inhibition function or pro-tumor function of each MiR to make the functions more clearly. 3. miR-125a/b in Figure and Table is not described in the text of the manuscript. Please add the description in the text. 4. Please put the full names of the abbreviations in the Figure legend and under the Table 1.

RE-REVIEW REPORT OF REVISED MANUSCRIPT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 86000

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Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 00028182

Position: Peer Reviewer

Academic degree: MD

Professional title: Associate Professor, Doctor

Reviewer's Country/Territory: Italy

Author's Country/Territory: China

Manuscript submission date: 2023-05-26

Reviewer chosen by: Jia-Ping Yan

Reviewer accepted review: 2023-08-14 21:02

Reviewer performed review: 2023-08-14 21:07

Review time: 1 Hour

Scientific quality	<input checked="" type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input checked="" type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Peer-reviewer	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous



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statements

Conflicts-of-Interest: [] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

the authors addressed the raised points and the manuscript can be now accepted.