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PEER-REVIEW REPORT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 84973

Title: Antagonizing adipose tissue-derived exosome miR-103-hepatocyte phosphatase and tensin homolog pathway alleviates autophagy in non-alcoholic steatohepatitis: A trans-cellular crosstalk

Provenance and peer review: Unsolicited manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 03259512
Position: Peer Reviewer
Academic degree: MSc, PhD
Professional title: Assistant Professor, Senior Researcher
Reviewer's Country/Territory: Australia
Author's Country/Territory: China

Manuscript submission date: 2023-04-05

Reviewer chosen by: Geng-Long Liu

Reviewer accepted review: 2023-05-18 07:17

Reviewer performed review: 2023-05-19 00:25

Review time: 17 Hours

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Novelty of this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No novelty

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Creativity or innovation of this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No creativity or innovation
Scientific significance of the conclusion in this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No scientific significance
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous
	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

The study demonstrated that miR-103 expression was increased in NASH mice. Moreover, inhibition of miR-103 alleviated NASH via inhibition of autophagy/PTEN pathway. miR-103 is an adipose-tissue derived exosomal miR. Authors concluded that miR-103 can inhibit autophagy in hepatocytes and thus, regulates the development of NASH (at least in mouse model in vivo). The study is interesting and addressed an important pathology. However, there are several issues which require amendments. 1. Abstract does not reflect the findings properly. Results section of the Abstract does not report which main indicators of autophagy were assessed. How did authors confirm the role of autophagy? Which markers were used? I suggest re-writing the Abstract/Results section to reflect clearly how authors confirmed the role of miR-103 in autophagy. For instance, Western blotting results with LC3 may be mentioned. 2. Abstract: the last sentence is confusing ("More importantly, the elevation of miR-103 in the liver of NASH

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mice is partly due to adipose tissue exosome secretion and integration, which also partially explains the mechanism of obesity leading to NAFLD"). This conclusion is confusing. I do not think that it is possible to claim this link. This should be re-phrased and/or more experimental data is required to support this statement. 3. miR-103 was found linked to G protein-coupled estrogen receptor 1 (GPER1) (see this paper Fang T, Li J, Wu X. Shenmai injection improves the postoperative immune function of papillary thyroid carcinoma patients by inhibiting differentiation into Treg cells via miR-103/GPER1 axis. Drug Dev Res. 2018 Nov;79(7):324-331. doi: 10.1002/ddr.21459.). This is a very promising and interesting findings which can be mentioned next to the problem of insulin sensitivity demonstrated in NAFLD patients. Fatty lever problem was recently linked to menopause (see this paper DiStefano JK. NAFLD and NASH in Postmenopausal Women: Implications for Diagnosis and Treatment. Endocrinology. 2020 Oct 1;161(10):bqaa134. doi: 10.1210/endocr/bqaa134.), and thus, potentially, with estrogen signaling pathway. Authors may need to mention this in the Introduction and Discussion section. 4. All abbreviations should be deciphered. 5. Methods: very few citations in this section. Please cite more relevant papers to direct readers towards the published papers which used similar techniques and described them properly (full description). 6. Figure 1: IHC images should be enlarged. It is hard to see the cellular composition with this magnification. 7. Fig.2D, 3A, 5c,d, 6c– should be enlarged; it is hard to see the cells and what is going on there. Good job with fig.4 – very clear presentation of data. Authors should do the same with Figure 1,2 , 3 , 5 and 6 IHC images. 8. Figure 7 should be improved. The conclusion is not shown. Inhibition of autophagy by miR-103 somehow influences the autophagosome formation (inhibits or stimulates? It is not shown on your diagram). Suggestively, the number of autophagosomes should be decreased – however, it is not clearly shown – there is a green arrow – what does it mean? Clarify. 9. Conclusions should be linked to the

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NAFLD and insulin resistance more clearly.

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Professional title: Assistant Professor
Reviewer's Country/Territory: Spain
Author's Country/Territory: China

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Reviewer performed review: 2023-05-19 07:56

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Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [Y] Major revision [ ] Rejection

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Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous
	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

Authors used an animal model to generate the NASH using a high fat diet, but authors do not show any data validating this model: in other words, NASH analysis must be shown in the animals submitted to the model diet. The design of the animal model is unclear: When miR_NC and mir-103-ANTA were injected (13 weeks according to the methods section), were the animals still on diet? The experimental groups are not clearly defined: control and model, and then these splitted in 2 groups?: Control diet + miR_NC; Control diet+miR103 ANTA; model diet + miR-NC and model diet + mir103ANTA, is that correct? If so, graphs should be labeled correctly to allow a proper reading of the manuscript. Otherwise, authors should carefully explain the experimental groups. I am looking forward to the explanations that will allow me to continue the peer review process.