



## PEER-REVIEW REPORT

**Name of journal:** World Journal of Gastroenterology

**Manuscript NO:** 59907

**Title:** Lipotoxic hepatocyte-derived exosomal miR-1297 promotes hepatic stellate cell activation through the PTEN signaling pathway in MAFLD

**Reviewer's code:** 03647305

**Position:** Editorial Board

**Academic degree:** MD

**Professional title:** Associate Professor, Director, Doctor

**Reviewer's Country/Territory:** Turkey

**Author's Country/Territory:** China

**Manuscript submission date:** 2020-10-14

**Reviewer chosen by:** Jia-Ping Yan

**Reviewer accepted review:** 2020-12-04 11:01

**Reviewer performed review:** 2020-12-04 12:26

**Review time:** 1 Hour

<b>Scientific quality</b>	<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 Grade E: Do not publish
<b>Language quality</b>	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<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
<b>Re-review</b>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<b>Peer-reviewer statements</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



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**SPECIFIC COMMENTS TO AUTHORS**

Congrats a quality work



## PEER-REVIEW REPORT

**Name of journal:** World Journal of Gastroenterology

**Manuscript NO:** 59907

**Title:** Lipotoxic hepatocyte-derived exosomal miR-1297 promotes hepatic stellate cell activation through the PTEN signaling pathway in MAFLD

**Reviewer's code:** 02444986

**Position:** Editorial Board

**Academic degree:** MD

**Professional title:** Academic Research, Doctor, Professor

**Reviewer's Country/Territory:** Turkey

**Author's Country/Territory:** China

**Manuscript submission date:** 2020-10-14

**Reviewer chosen by:** Jia-Ping Yan

**Reviewer accepted review:** 2020-11-28 05:35

**Reviewer performed review:** 2020-12-04 12:44

**Review time:** 6 Days and 7 Hours

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 Grade E: Do not publish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



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#### **SPECIFIC COMMENTS TO AUTHORS**

Authors used primary hepatocyte (HC) line (LO2) cultures to isolate exosomes by treating HC with palmitic acid, identified miR-1297 top upregulated microRNA among DE-miRs, showed activation of hepatic stellate cell (HSC) line (LX2) by mi-1297 and exosomes isolated from serum samples of patients with MAFLD, and associated HSC activation with PTEN/PI3K/AKT signalling pathway. I would like to congratulate all authors for conducting such complex study with a small team and also clearly expressing the data within the manuscript. My comments: • MAFLD is proposed as new terminology for NAFLD, but the consensus has not been developed to use it. Therefore, I suggest to use NAFLD or at least make a referral to this terminology change. • The histologic (NAS and fibrosis) spectrum of patients must be given. Why were so much (20) serum samples used? Why analysis were done according to level of hepatosteatosis, instead of fibrosis, since mi-1297 was found to be related to fibrosis pathways? Was there any correlation between level of fibrosis in the liver and experimental finding? • Fig2: Labels on X and Y axes cannot be read. • Fig3-4: It is not available. • Suppl.Table1: the abbreviation LSM should be explained, and CAP values must be added to table.



### PEER-REVIEW REPORT

**Name of journal:** World Journal of Gastroenterology

**Manuscript NO:** 59907

**Title:** Lipotoxic hepatocyte-derived exosomal miR-1297 promotes hepatic stellate cell activation through the PTEN signaling pathway in MAFLD

**Reviewer's code:** 05038583

**Position:** Peer Reviewer

**Academic degree:** MD

**Professional title:** Doctor

**Reviewer's Country/Territory:** United States

**Author's Country/Territory:** China

**Manuscript submission date:** 2020-10-14

**Reviewer chosen by:** Jia-Ping Yan

**Reviewer accepted review:** 2020-12-04 21:22

**Reviewer performed review:** 2020-12-04 21:46

**Review time:** 1 Hour

<b>Scientific quality</b>	<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
<b>Language quality</b>	<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
<b>Conclusion</b>	<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
<b>Re-review</b>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<b>Peer-reviewer statements</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



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#### **SPECIFIC COMMENTS TO AUTHORS**

General comments This study analyzed the role of lipotoxic exosomal miR-1297 in the pathogenesis of MAFLD. As author stated, MAFLD is becoming more prevalent, and there are many clinical trials to evaluate the efficacy of medications to prevent progression of MAFLD to cirrhosis. As such, elucidating the pathogenesis of MAFLD has clinical relevance for future drug development. Please note, I am not a basic scientist, so I cannot comments on the technical aspect of this study, however this is a well written manuscript with clinical importance, so this should be considered for possible publication after addressing minor comments as below. Specific comments For methodology section. It stated that fibroscan was used to classify mild vs sever fatty liver. Biopsy is usually regarded as the gold standard. Was there any biopsy result?



## PEER-REVIEW REPORT

**Name of journal:** World Journal of Gastroenterology

**Manuscript NO:** 59907

**Title:** Lipotoxic hepatocyte-derived exosomal miR-1297 promotes hepatic stellate cell activation through the PTEN signaling pathway in MAFLD

**Reviewer's code:** 00069262

**Position:** Editorial Board

**Academic degree:** DSc, MD, PhD

**Professional title:** Academic Research, Doctor, Professor

**Reviewer's Country/Territory:** Mexico

**Author's Country/Territory:** China

**Manuscript submission date:** 2020-10-14

**Reviewer chosen by:** Jia-Ping Yan

**Reviewer accepted review:** 2020-12-05 00:40

**Reviewer performed review:** 2020-12-12 04:00

**Review time:** 7 Days and 3 Hours

<b>Scientific quality</b>	<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
<b>Language quality</b>	<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
<b>Conclusion</b>	<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
<b>Re-review</b>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<b>Peer-reviewer statements</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



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#### **SPECIFIC COMMENTS TO AUTHORS**

the manuscript by Xin Luo et al, is a good work, well presented and describes its methodological development and results very well. Congratulations



## PEER-REVIEW REPORT

**Name of journal:** World Journal of Gastroenterology

**Manuscript NO:** 59907

**Title:** Lipotoxic hepatocyte-derived exosomal miR-1297 promotes hepatic stellate cell activation through the PTEN signaling pathway in MAFLD

**Reviewer's code:** 00053419

**Position:** Editorial Board

**Academic degree:** PhD

**Professional title:** Professor

**Reviewer's Country/Territory:** Spain

**Author's Country/Territory:** China

**Manuscript submission date:** 2020-10-14

**Reviewer chosen by:** Jia-Ping Yan

**Reviewer accepted review:** 2020-12-09 08:58

**Reviewer performed review:** 2020-12-18 12:49

**Review time:** 9 Days and 3 Hours

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



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#### **SPECIFIC COMMENTS TO AUTHORS**

The study reports the vehiculization of mir1297 in exosomes communicating hepatocytes with HSC. The study is comprehensive and results are presented supporting the hypothesis. PTEN and downstream PI3, AKT have been involved. There are several open questions to be addressed as follows: 1. Is FIBROSCAN an efficient method to assess fatty liver disease and its degree of severity? This issue might be mentioned and a reference (such as Lancet 2020 Newsome PM et al) could be provided. 2. Data analysis of micro RNAseq experiments must be described. 3. Figures 3 and 4 are missing. 4. Are there differences between cells-derived and serum exosomes? 5. 1400 fold over expression of mir1297 in LX2 cells is far from physiological conditions. This might lead to artifactual effects and misleading interpretations. Please, discuss. 6. Please describe PTEN mutant.



## RE-REVIEW REPORT OF REVISED MANUSCRIPT

**Name of journal:** World Journal of Gastroenterology

**Manuscript NO:** 59907

**Title:** Lipotoxic hepatocyte-derived exosomal miR-1297 promotes hepatic stellate cell activation through the PTEN signaling pathway in MAFLD

**Reviewer's code:** 00053419

**Position:** Editorial Board

**Academic degree:** PhD

**Professional title:** Professor

**Reviewer's Country/Territory:** Spain

**Author's Country/Territory:** China

**Manuscript submission date:** 2020-10-14

**Reviewer chosen by:** Han Zhang (Part-Time Editor)

**Reviewer accepted review:** 2021-02-08 09:45

**Reviewer performed review:** 2021-02-10 15:49

**Review time:** 2 Days and 6 Hours

<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<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
<b>Peer-reviewer statements</b>	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



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The authors have addressed some of the issues raised by this reviewer. However, several aspects require further consideration: 1. Similarities and differences of cellular and serum exosomes should be further discussed and comments should be included in the manuscript. 2. Even though the authors provide previous studies reporting very large over expression of particular genes, it doesn't really respond the question of whether this unphysiological effect might lead to artifactual biological responses leading to misleading interpretations