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PEER-REVIEW REPORT

Name of journal: *World Journal of Hepatology*

Manuscript NO: 76705

Title: Regulation of PPAR-γ activity in lipid-laden hepatocytes affects macrophage polarization and inflammation in nonalcoholic fatty liver disease

Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 00225294
Position: Editorial Board
Academic degree: PhD
Professional title: Full Professor
Reviewer's Country/Territory: Spain
Author's Country/Territory: China

Manuscript submission date: 2022-03-26

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-03-28 14:24

Reviewer performed review: 2022-04-05 19:49

Review time: 8 Days and 5 Hours

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [ ] Grade C: Good [Y] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [ ] Grade B: Minor language polishing [Y] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [Y] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No

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

SPECIFIC COMMENTS TO AUTHORS

The manuscript by Li et al is focused on the idea that lipid-laden hepatocytes promote a pro-inflammatory phenotype in macrophages (from a cell line) via soluble mediators. The idea is not new and the main strength is based on the use of hepatocytes genetically deficient on PPAR-γ. Authors should care the use of the words: M1 and M2 require definition, despite to be used in the past as indicators of pro-inflammatory and alternative activation of macrophages. Also, the wording in many parts of the text needs to be revised; for example, in the abstract, the authors use the construction 'manipulation of PPAR-γ'. This is not correct. Despite these minor errors, authors need to revise several points: Main points: Consider the use of an antagonist of PPAR-γ, in addition to the genetic models. It is known that targeting PPAR-γ alters the expression of other PPAR isoforms, in particular the delta. This needs to be assessed. One possibility is the use of antagonists. Regarding the genes, authors should consider the use of standard annotations: in italics and the first letter in capital. iNOS2 is not a gene! Use Nos2 in italics. For other genes, please refer to the gene annotation, not for the protein encoded. This is general in almost all figures of the manuscript. Why two activators of PPAR-γ are used? Which is the rationale? What about the viability of the cells after this strong load of FFAA? Lipotoxicity use to promote necrotic/apoptotic death in many cell types. The link between PPAR-γ and the inflammosome NLRP3 activation needs to be reinforced by pharmacological assays since it is the core of the work Use correct works regarding PPAR-γ activity: activation, deletion, inhibition (not considered, etc.).

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Reviewer's code: 05346681
Position: Peer Reviewer
Academic degree: PhD

Professional title: Lecturer

Reviewer's Country/Territory: Thailand

Author's Country/Territory: China

Manuscript submission date: 2022-03-26

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-04-06 05:10

Reviewer performed review: 2022-04-06 09:00

Review time: 3 Hours

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[Y] Grade A: Priority publishing [ ] 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
Re-review	[Y] Yes [ ] No

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

SPECIFIC COMMENTS TO AUTHORS

Summary of the study Lipid-accumulating murine hepatocytes polarized macrophage cell line to M1 phenotype in vitro cultures. Downregulation of PPAR-γ activity in the lipid-accumulated hepatocytes enhanced macrophage M1 polarization and reduced oxidative stress and NLRP3 inflammasome activation. Oral administration of Rosiglitazone, a PPAR-γ agonist, reduced oxidative stress and NLRP3 inflammasome in HF diet-induced NAFLD mice, paving a way to modulate PPAR-γ activity for treating NAFLD. Comments 1) In abstract, authors conclude that "Regulation of PPAR-γ alleviated NAFLD by modulating the crosstalk between hepatocytes and macrophages via the ROS-NLRP3-IL-1β signaling pathway". It would allow readers to understand if the term of downregulation and types of modulation are clearly written here. 2) In the introduction, research question or gap of knowledge is partially presented. It would be helpful to state what is unknown about PPAR-g regarding interaction between hepatocyte and macrophage in NAFLD. 3) NAFLD is a spectrum of conditions in which lipid-accumulated hepatocytes are resit to insulin, undergo chronic inflammation, and eventually lead to fibrosis in liver. The term of "NAFLD hepatocytes" need to be verified by examining lipotoxicity, including ER stress or pyroptosis or ROS as explained in the introduction. There are assays for assessing pyroptosis and ER stress. 4) For Fig. 1, it needs to explain what good condition in the cultures of primary hepatocytes was. Please provide higher magnified image if intend to show morphology of hepatocytes. Also insert scale bars. 5) Given key indicator of macrophage polarization, defining M1 and M2 must be accurate. In this study, M1 and M2 cells are characterized mainly based on mRNA level. Protein expression and functional assay would emphasize the existence of

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M1. This can be done using an immunocytochemistry or flow cytometry of iNOS, TNFa and IL-6 for M1 and Arg1, Mrc2 and IL-10 for M2. Moreover, release of pro-inflammatory cytokines directly indicates functioning M1, which can be examined using ELISA or WB analysis. 6) For data in Fig. 1, author wrote "Lipid-laden hepatocytes promoted M1 macrophage polarization and inflammation; however, the possible pathways of signal exchange between the two cell lines were unclear". Please ensure that primary hepatocyte and macrophage cells were used. 7) For Fig. 4, upregulation of PPAR-γ activity in hepatocyte need to be verified. The mRNA expression of PPAR-γ in primary hepatocytes from hepatocyte-specific PPAR-γ knockout mice was fully knocked out. However, protein level of PPAR-γ need to be examined to verify the down-regulation of PPAR-y in this study. 8) Fig. 6, gene expression of NLRP3, Caspase-1 and IL-1β was from hepatocyte or bulk of cells in the liver genes of high-fat diet-induced NAFLD mice (Fig. 6A)? Clearly explain in the result. 9) Fig. 6, given many cell types in a liver, protein expression of NLRP3, Caspase-1 or IL-1β in the albumin-expressing hepatocytes. Also, is there any difference in the M1 polarization in the liver of high-fat diet-induced NAFLD mice and wild type mouse in this study?

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RE-REVIEW REPORT OF REVISED MANUSCRIPT

Name of journal: *World Journal of Hepatology*

Manuscript NO: 76705

Title: Regulation of PPAR-γ activity in lipid-laden hepatocytes affects macrophage polarization and inflammation in nonalcoholic fatty liver disease

Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 00225294
Position: Editorial Board
Academic degree: PhD
Professional title: Full Professor
Reviewer's Country/Territory: Spain
Author's Country/Territory: China

Manuscript submission date: 2022-03-26

Reviewer chosen by: Li-Li Wang

Reviewer accepted review: 2022-06-06 16:33

Reviewer performed review: 2022-06-08 11:45

Review time: 1 Day and 19 Hours

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) [Y] Minor revision [ ] Major revision [ ] Rejection
Peer-reviewer	Peer-Review: [Y] Anonymous [ ] Onymous

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

SPECIFIC COMMENTS TO AUTHORS

The authors provided replies to the Reviewer's comments that are satisfactory, in general terms, However, some typos/specifications remain unsolved. Some genes are not correctly expressed and need revision to standardize this nomenclature (italic, first letter capital for rodents ,etc.). Please revise these data.