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PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology

Manuscript NO: 46963

Title: Prolonged High-Fat-Diet Feeding Promotes NAFLD and Alters Gut Microbiota In Mice

Reviewer's code: 00054303

Reviewer's country: Australia

Science editor: Li-Jun Cui

Reviewer accepted review: 2019-03-12 01:55

Reviewer performed review: 2019-03-25 03:51

Review time: 13 Days and 1 Hour

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection	[ ] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [Y] Major revision [ ] Rejection	Peer-Review: [Y] Anonymous [ ] Onymous Peer-reviewer's expertise on the topic of the manuscript: [ ] Advanced [Y] General [ ] No expertise Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

The manuscript by Velazquez et al describes a long term high fat diet model to generate NAFLD and aims to examine the effect of HFD on hepatic histology, metabolic parameters, ER stress, inflammatory pathways and alterations in microbiota

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composition. The manuscript is clearly written and figures clearly presented. While the authors show significant differences in the observed parameters there are queries (in questions below) in regards to the model and conclusions drawn. 1) Figure 1 graph labels include "Chow" – is this an error, should this read LFD? If chow is correct then how does composition of the low fat diet compare with a normal chow diet? Why is chow interchanged with LFD? Likewise what micro- and macronutrient composition differences are there between the LFD and HFD? 2) To what extent does differences in carbohydrates rather than fat content affect the liver and gut results observed? 3) What age were the mice at the start of the experiment? 4) A large section of the discussion is simply repeated text (ER stress discussion) – this needs to be corrected. Page 16 is repeated on page 17/18. 5) Can the authors comment on the mild fibrosis and inflammation seen in the young-LFD model? What causes mild hepatic injury in this model in such a small time frame? Are these animals age matched for the start or end of the experiment? Do the authors have measure of liver function such as transaminase levels? 6) In Figure 3, what magnification are the inserts and what is being shown in these inserts? 7) Can the authors further describe their NASH score, Figure 3J? Is this equivalent to the NAS score as described by Kleiner et al and referred to in reference 21 of the manuscript? Given the significant ballooning, inflammation and steatosis in the old HFD animals wouldn't a higher NAS score be expected? Indeed wouldn't the mild inflammation and steatosis in old LFD animals would generate a NAS score above 0? 8) Can the authors provide further explanation regarding the increased in p-EIF2a in the old LFD group? What other evidence is there that these older animals are in the early stage of chronic ER stress? 9) What evidence is there for cell death as described as an explanation for the reduced F4/80 expression?

INITIAL REVIEW OF THE MANUSCRIPT

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PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology

Manuscript NO: 46963

Title: Prolonged High-Fat-Diet Feeding Promotes NAFLD and Alters Gut Microbiota In Mice

Reviewer's code: 02444752

Reviewer's country: China

Science editor: Li-Jun Cui

Reviewer accepted review: 2019-03-21 01:30

Reviewer performed review: 2019-03-26 06:35

Review time: 5 Days and 5 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[Y] Grade A: Excellent [ ] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection	[Y] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [ ] Major revision [ ] Rejection	Peer-Review: [Y] Anonymous [ ] Onymous Peer-reviewer's expertise on the topic of the manuscript: [ ] Advanced [Y] General [ ] No expertise Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

The results of this study suggest that chronic HFD can mimic most of the pathophysiological events observed in NAFLD, such as obesity, steatosis, non-alcoholic stetohepatitis, insulin resistance, steatosis, liver ER stress, and gut dysbiosis. Therefore

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chronic HFD is suitable for the establishment of NAFLD model. The paper is well written and is recommended for publication.

INITIAL REVIEW OF THE MANUSCRIPT

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