



## PEER-REVIEW REPORT

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

**Manuscript NO:** 55606

**Title:** Hepatic TNF receptor signaling is not protective in non-alcoholic steatohepatitis, but attenuates insulin resistance

**Reviewer's code:** 03465463

**Position:** Peer Reviewer

**Academic degree:** FCPS, PhD

**Professional title:** Adjunct Professor, Professor

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

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

**Manuscript submission date:** 2020-03-28

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

**Reviewer accepted review:** 2020-05-10 06:58

**Reviewer performed review:** 2020-05-10 07:52

**Review time:** 1 Hour

<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 Grade E: Do not publish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 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**

This submission demonstrated the negative role of TNFR1 signaling in hepatocytes for steatohepatitis development using a mouse model lacking hepatic TNFR1 to induce the diet-induced NASH. I like to give the following comments. 1. Results from mice lacking hepatic TNFR1 are not the same as that constitutional activation of TNFR1 promoted the progression of NASH. The suitable explains are not discussed in clear. 2. Role of TNFR2 did not conduct in introduction section. 3. In biochemical assay, tissue was homogenized in 6N HCl. Please give the reference(s) to support. 4. Plasma levels of cytokines in these mice seem helpful. 5. In Figure 2, legends need to check. Additionally, the significant variation for percentage of liver/body weight must show in correct. 6. In Figure 3, sample size in each group needs to show in clear. Variations also must indicate in correct. 7. Hepatic TNFR1 deficiency showed a role in glucose metabolism. Please add more data to support this new finding. 8. From the knockout mice, loss of TNFR1 in hepatocytes seems changed in glucose metabolism but not the lipid profiles. However, suitable speculation(s) were not discussed in clear. 9. Limitation(s) may assist the unclear points in this truth.



## PEER-REVIEW REPORT

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

**Manuscript NO:** 55606

**Title:** Hepatic TNF receptor signaling is not protective in non-alcoholic steatohepatitis, but attenuates insulin resistance

**Reviewer's code:** 02926997

**Position:** Peer Reviewer

**Academic degree:** MD

**Professional title:** Associate Professor

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

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

**Manuscript submission date:** 2020-03-28

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

**Reviewer accepted review:** 2020-05-11 10:05

**Reviewer performed review:** 2020-05-11 10:10

**Review time:** 1 Hour

<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 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**

This is a narrative review about role of TNFR1 in NASH. The result showed that obesity, liver injury, steatosis and fibrosis was not different between TNFR1 $\Delta$ HEP and TNFR1fl/fl mice. However, Tnfr1 deficiency in hepatocytes protected against glucose intolerance and insulin resistance. It concluded that Hepatic TNF receptor signaling is not protective in non-alcoholic steatohepatitis, but attenuates insulin resistance. The manuscript is well written and contains important data regarding the main focus of review. It could be accepted after minor English editing.



## PEER-REVIEW REPORT

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

**Manuscript NO:** 55606

**Title:** Hepatic TNF receptor signaling is not protective in non-alcoholic steatohepatitis, but attenuates insulin resistance

**Reviewer's code:** 03664938

**Position:** Peer Reviewer

**Academic degree:** PhD

**Professional title:** Associate Professor

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

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

**Manuscript submission date:** 2020-03-28

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

**Reviewer accepted review:** 2020-05-11 08:24

**Reviewer performed review:** 2020-05-14 09:17

**Review time:** 3 Days

<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input checked="" 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 proposed an interesting topic, exploring the role of TNF receptor in the development of non-alcoholic steatohepatitis (NASH). Through applied conditional TNFR1 knock out in hepatocytes, the authors concluded that Both NASH and HCC development were dependent on TNF produced by inflammatory macrophages that inhibition of TNFR1 signaling in hepatocytes can protect from diet-induced NASH, but improved insulin resistance. Although the conclusions are quite objective based on the data, the whole study seems to be incomplete. Major concerns 1. The title, according to the study design, the authors mainly explored the TNFR1 function in hepatocytes, whereas the liver contains heterogenous cells, it is not proper to use “hepatic”; 2. The phenotypic data of TNFR1 deficiency should be provided; 3. The authors get evidence that TNFR1 knockout in hepatocytes improved insulin resistance, at least to try to provide some data to explain such phenotype. 4. The authors mentioned that “In this study, Tnfr1 knock-out resulted in increased numbers of both resident (i.e., Kupffer cells) and recruited macrophages into the liver, as well as up-regulation of IL-1 $\beta$  and IL-6 in the liver along with increased release into the plasma. “, but I can not find these data in the present version; 5. Typos need to be carefully checked.



## PEER-REVIEW REPORT

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

**Manuscript NO:** 55606

**Title:** Hepatic TNF receptor signaling is not protective in non-alcoholic steatohepatitis, but attenuates insulin resistance

**Reviewer's code:** 02445646

**Position:** Peer Reviewer

**Academic degree:** FRCP (Hon), FRCS (Ed), MD

**Professional title:** Director, Professor

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

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

**Manuscript submission date:** 2020-03-28

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

**Reviewer accepted review:** 2020-05-12 15:35

**Reviewer performed review:** 2020-05-18 13:31

**Review time:** 5 Days and 21 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 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**

No comments to the authors.



**RE-REVIEW REPORT OF REVISED MANUSCRIPT**

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

**Manuscript NO:** 55606

**Title:** Hepatic TNF receptor signaling is not protective in non-alcoholic steatohepatitis, but attenuates insulin resistance

**Reviewer’s code:** 02926997

**Position:** Peer Reviewer

**Academic degree:** MD

**Professional title:** Associate Professor

**Reviewer’s Country/Territory:** Iran

**Author’s Country/Territory:** United States

**Manuscript submission date:** 2020-03-28

**Reviewer chosen by:** Ze-Mao Gong

**Reviewer accepted review:** 2020-07-24 19:33

**Reviewer performed review:** 2020-07-24 19:36

**Review time:** 1 Hour

<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 checked="" type="checkbox"/> Accept (General priority) <input 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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No comments



**RE-REVIEW REPORT OF REVISED MANUSCRIPT**

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

**Manuscript NO:** 55606

**Title:** Hepatic TNF receptor signaling is not protective in non-alcoholic steatohepatitis, but attenuates insulin resistance

**Reviewer’s code:** 03465463

**Position:** Peer Reviewer

**Academic degree:** FCPS, PhD

**Professional title:** Adjunct Professor, Professor

**Reviewer’s Country/Territory:** Taiwan

**Author’s Country/Territory:** United States

**Manuscript submission date:** 2020-03-28

**Reviewer chosen by:** Ze-Mao Gong

**Reviewer accepted review:** 2020-07-23 08:14

**Reviewer performed review:** 2020-07-25 08:02

**Review time:** 1 Day and 23 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 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
<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>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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It has been revised in a good way. Please take care of the language in context.