Detailed responses to reviewer comments:

Reviewer 2:

"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"

We have changed the title from "Hepatic TNF receptor signaling is not protective in non-alcoholic steatohepatitis, but attenuates insulin resistance" to "TNF receptor-1 deficiency in hepatocytes does not protect from non-alcoholic steatohepatitis, but attenuates insulin resistance in mice".

"2. The phenotypic data of TNFR1 deficiency should be provided"

We now show lower mRNA expression of *Tnfr1* in liver tissue, please refer to figure 1A.

"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."

Unfortunately, mice were not starved at the time of tissue harvesting and meaningful results for glucose metabolism cannot be obtained from non-fasted mice. However, we believe that our finding on glucose tolerance/insulin resistance in the TNFR1 knockout mice is valid, as the GTT and ITT tests were done in a large number of mice (up to 24 animals) and after mice were starved. We have added this information to the study limitations.

"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-1β and IL-6 in the liver along with increased release into the plasma. ", but I can not find these data in the present version."
This sentence referred to the reference mentioned in the preceding sentence. We have clarified this in the manuscript.

"5. Typos need to be carefully checked."

We have corrected all typos we noticed.

Reviewer 3:

"The manuscript is well written and contains important data regarding the main focus of review. It could be accepted after minor English editing."

We took care of the wording during revision.

Reviewer 4:

"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."

In published studies, constitutional activation of TNFR1 promoted NASH (PMID 22941955), while whole-body knock-out of TNFR1 was protective (PMID 20141834, 25132496). This was added to the discussion. In addition, we added some more details from the study that investigated the TNFR1 activation and discussed it in relation to our findings.

"2. Role of TNFR2 did not conduct in introduction section."

We have added information about TNFR2 in the introduction.

"3. In biochemical assay, tissue was homogenized in 6N HCl. Please give the reference(s) to support."

We have added references (Iwaisako et al. and Bluemel at al.) to the mentioned sentence in the reference section.

"4. Plasma levels of cytokines in these mice seem helpful."

Unfortunately, we did not have any plasma left. Instead, we did hepatic mRNA expressions of TNF, Ccl2 and IL1b (Figure 2G). Hepatic inflammation was not different between the genotypes following the western diet.

"5. In Figure 2, legends need to check. Additionally, the significant variation for percentage of liver/body weight must show in correct."

We have revised all legends: We corrected the labelling of sample sizes ("numbers of biological replicates") and added the significance criteria into the legends. In addition, we changed the graphs from columns to single symbols to more explicitly show variations within the data, and we added p-values in case of non-significant differences.

"6. In Figure 3, sample size in each group needs to show in clear. Variations also must indicate in correct."

This was corrected.

"7. Hepatic TNFR1 deficiency showed a role in glucose metabolism. Please add more data to support this new finding."

Unfortunately, mice were not starved at the time of tissue harvesting and meaningful results for glucose metabolism cannot be obtained from non-fasted mice. We have added this information to study limitations. We believe that our finding on glucose tolerance/insulin resistance in the TNFR1 knockout mice is valid, as the GTT and ITT tests were done in a large number of mice (up to 24 animals) and after mice were starved. In addition, we have added another, just recently published paper using anti-TNFR1-antibodies to attenuate NASH, to the discussion (Wandrer et al.). This new paper supports our findings.

“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.”

We have added a paragraph discussing the interrelation of hepatic steatosis and insulin resistance.

“9. Limitation(s) may assist the unclear points in this truth.”

We have added a paragraph with study limitations at the end of the discussion section.