**Scientific editor:** Yuan Qi

Dear Reviewers and Editors,

We thank the reviewers for their comments. Please find the revised manuscript modified as per the reviewer's comments.

***Reviewer # 1****'In this Editorial, the authors gave a brief background of nonalcoholic steatohepatitis (NASH) and summarized a recent JCI paper. It is recommended to publish with minor language polishing. Also, I feel too much emphases on describing the results, most of which could be found in the original paper. I suggest expending the discussion and providing more insights in the future research and clinical directions.'*

**Response:** We thank the reviewer for the comments and have now modified the manuscript accordingly.

1. We have added information on innate immune signaling.
2. We have shortened the results of the discussed JCI manuscript.
3. We have added information on current and future potential therapeutics of NAFLD/NASH.
4. We have made editorial modifications in the text of the manuscript, as suggested by reviewer.

***Reviewer # 2****' 'In this Editorial, the authors summarized a recent JCI paper about hepatocyte mitochondrial DNA serves as DAMP activating a hepatic PRR, TLR9, in mice and in the plasma of NASH patients leading to NASH. The description of the paper was clear, but the opinion of*

*the authors was few. It's better to provide more insights about the trend of NSAH or what's need to do in future work.'*

**Response:** We thank the reviewer for the comments and have now modified the manuscript accordingly.

1. We have now added information on innate immunity.
2. We have now added information on current and research therapeutics of NAFLD/NASH.

***Reviewer # 3***' *'The manuscript (ESPS NO: 26383) entitled "Mitochondrial DNA from hepatocytes as a ligand for TLR9: Drivers of NASH?" is an editorial by Priya Handa et al. The authors of this manuscript try to indicate that hepatocyte mitochondrial DNA activates hepatic PRR, TLR9 and acts as an inducer for NASH. They suggest that blocking TLR9 may be a potential therapy for NASH. Major comments 1. Some editing is needed. For example, in lines 14-15 on page 4, "…which contribute to the increased serum free fatty acids in the liver" probably means "..increase uptake or entry…". It should be revised. 2. The description of fatty acids sources in hepatocytes is not complete. The fatty acids in hepatocytes can be from de novo lipogenesis, adipocytes and lipoproteins. Please include this in the revision. 3. The manuscript talked about mtDNA and its effects on TLR9. Please try to elaborate more about how mtDNA is shipped out of the cells and is taken into the cells. 4. In the figure, it seems that authors only indicated that IRS954 works in Kupffer cells, but not hepatocytes and stellate cells. Please elaborate the reason. Minor comments 1. In line 8 on page 6, should be "TNFα mRNA".'*

**Response:** We thank the reviewer for the comments and have now modified the manuscript accordingly.

1. We have revised the lines 14-15 on page 3 and made the desired changes.
2. We have added description of fatty acid sources in hepatocytes.
3. It is thought that cell injury, apoptosis and necrosis results in release of mtDNA out of the cell leading to increased amount of extracellular mtDNA. *(ref: M Pinti, C Mussini and A Cossarizza. Mitochondrial DNA: a proinflammatory 'enemy from within' during HIV infection? Cell Death and Disease (2012) 3, 307; doi:10.1038/cddis.2012.47).* The mechanism of uptake of mtDNA within the endosome is not well studied.
4. We have modified the figure now indicating that the IRS954 inhibitor exerts its effect by inhibiting the TLKR9 activation on Kupffer cells and hepatocytes. Since the authors did not show results associated with fibrogenesis or fibrosis, the effect of the inhibitor on stellate cells remains to be determined, and we have pointed out this caveat in our editorial.
5. We have corrected 'TNFa mRNa' to 'TNFα mRNA' in line 8 on page 6

Sincerely,

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