

To
Professor Subrata Ghosh & Professor Andrzej S Tarnawski
Editors, World Journal of Gastroenterology

Athens, April 9th, 2020

Submission of a Re-Revised Review Article to the World Journal of Gastroenterology

Dear Editors,

We wish to thank you for your decision letter from April 2nd 2020 regarding our invited review article titled 'Metabolic inflammation as an instigator of fibrosis during non-alcoholic fatty liver disease' (WJG No: 54329) and for allowing us to resubmit a revised version of our manuscript.

In addition we would like to thank the Science Editor, Dr. Le Zhang, for his comment from April 8th regarding the image file of our revised manuscript (submitted April 7th 2020).

In order to provide an overall update pertinent to our revised manuscript, within this response letter we provide replies to both the Science Editor and the Reviewers.

Please find attached our revised manuscript (changes are highlighted in yellow).

Looking forward to hearing from you in due course,

With best regards,
Antonios Chatzigeorgiou (MD, PhD)
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&
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RESPONSE TO THE SCIENCE EDITOR (EDITORIAL REPLY FROM APRIL 8th)

In his comment from April 8th 2020, the Science Editor, Dr. Le Zhang, asked for a decomposable version of our figure, whose parts are movable and editable. Upon communication with Dr. Zhang, we provided him our figure in its original vector art format, which was Adobe Illustrator. Dr. Zhang kindly replied that the picture is qualified and we thank him for this quick reply. Therefore, we currently uploaded in the online system of the Journal the Illustrator version of our figure. In any case, we are still able to provide our figure in ppt format.

RESPONSE TO THE REFEREES (EDITORIAL REPLY FROM APRIL 2nd)

We wish to thank the reviewers for their constructive comments, which helped us improve our manuscript. We have revised the manuscript, according to the Referees' comments.

Major points:

Reviewer #1:

I revised the manuscript entitled “Metabolic inflammation as an instigator of fibrosis in the liver”. The manuscript is well written and interesting. It discusses an important issue regarding the progression of NAFLD into NASH. I recommend its publication as it is.

We thank the reviewer for his/her positive comments.

Reviewer #2:

This manuscript has a quite good quality, it is interesting and summarizes an important information about role of inflammation and some principal molecules in hepatic fibrosis development. Paper could be published after correction of some typos and language mistakes.

We thank the reviewer for his/her positive remarks and the helpful critique. The revised version of our manuscript underwent language editing by the native-speaker author of our manuscript Panagiotis Lembessis and typos and language mistakes were corrected.

Reviewer #3:

The review is highly relevant as the incidence and prevalence of NAFLD continues to grow worldwide. The abstract summarizes and reflects the review described in the manuscript. The authors reasonably cite the latest and relevant references. Self-citation was appropriate ($\approx 5\%$). The review can certainly be published in the WJG, but a minor revision is required.

We thank the reviewer for his/her positive remarks and the constructive critique to improve our manuscript.

- 1. First, despite the presence of Figure 1 (Innate immune pathways and mediators involved in the development of liver fibrosis during NAFLD), it is desirable to**

summarize all described pathways and mediators involved in the development of liver fibrosis during NAFLD in a table, which will make the review more understandable and readable.

We thank the reviewer for this comment. We followed the reviewer's advice and summarized the main pathways and mediators of liver fibrosis during NAFLD in a new table (Table 1) that is included in the revised version of our manuscript.

2. The link to Figure 1 should be in the text.

We thank the reviewer for this comment. We added the link to Figure 1 in the first paragraph of the section 'Conclusion'.

- 3. Although the authors give the correct definition of NAFLD, hereinafter such phrases as “the progression of NAFLD into NASH or cirrhosis”, for example, are found. It may be misleading that NAFLD is steatosis only. Such phrases should be replaced, for example, by “the progression of steatosis into NASH...”.**
- 4. I also propose concretizing the title of the article, for example, “Metabolic inflammation as an instigator of fibrosis during non-alcoholic fatty liver disease”.**

We thank the reviewer for comments 3 and 4. Indeed, NAFLD is not only defined by steatosis, but may also be accompanied by cellular injury characterized by enlarged swollen hepatocytes with or without Mallory-Denk bodies in the cytoplasm as well as ongoing inflammation. In the revised version of the manuscript, we replaced phrases such as “the progression of NAFLD into NASH or cirrhosis” with “the progression of steatosis into NASH”. Along this line, we also improved the title of the manuscript according to the reviewer's suggestion.

- 5. In addition, I would recommend a brief overview of the metabolic interaction of gut microbiota and the liver, discussing some microbial metabolites in the context of their association with NAFLD and its progression.**

We thank the Reviewer for raising this point. Indeed, gut microbiota emerges as an important factor for the pathogenesis and the progress of the disease. To address this issue, in our revised manuscript we have added a new section discussing the role of gut microbiota and its metabolites in the development of liver steatosis and fibrosis, under the title 'GUT MICROBIOME AND NAFLD'.