NYC, 20th May 2020

RE: Revised manuscript by Matteo Tardelli.

MS ID#: 55458

MS TITLE: Monoacylglycerol lipase reprograms lipid precursors signaling in liver disease.

Dear Editors,

Please find enclosed the revised manuscript (MS ID#: 55458.R1), which I would like to respectfully resubmit for publication in WJG.

I would like to express my sincere thanks to you and the Reviewers for the careful evaluation of this manuscript and giving an opportunity for further improvement. As suggested by the Reviewers, I have addressed their remaining comments and included additional new figures in the revised manuscript.

I am confident that revision of my manuscript according to your and the Reviewer's helpful suggestions has resulted in a significantly improved version.

A detailed point-by-point response is included here. All changes in the revised manuscript are underlined in the text and discussed in this letter. I am confident that revising my manuscript according to the helpful suggestions has resulted in a significantly improved paper, which I hope will now be suitable for publication in WJG.

I am very much looking forward to your positive response in the near future.

Sincerely yours,

Matteo Tardelli, PhD

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Reviewer #1:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Minor revision

Specific Comments to Authors: The review addresses the enzyme monoacylglycerol lipiase (MGL) in reprogramming lipid precursors. MGL activities are involved in the arachidonic acid metabolism. The important study using mice lacking MGL exclusively in the myeloid lineage study is cited.focused on the prediction of dyslipidemia after liver transplantation. In a very good clinical setting the pro-inflammatory cytokine IL-12 was identified as a potential marker predicting post-transplant dyslipidemia (PTDL). Dendritic cells are suggested as the important source of IL-12. Comments 1. The interesting part of the manuscript concerning the putative role of MGL in the liver-gut axis should be illustrated with a scheme.

I thank Reviewer 1 for the positive feedback, and interesting comments on the relation with MGL and inflammation. I included a new Figure 3, illustrating gut-liver axis mechanism in cholestatic liver disease.

Reviewer #2:

Scientific Quality: Grade A (Excellent)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: Authors concisely reviewed the MGL, monoacyl glyserol lipase in liver disease and potential therapetic effects of MGL inhibition. the meaning of abrivations should be given at figure legands.

I thank Reviewer 2 for the overall positive feedback and appreciate the constructive criticisms to this work. I added in all figures meaning of abbreviations.

Reviewer #3:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Minor revision

Specific Comments to Authors: In this manuscript, the author review recent findings about MGL. This is a well-written review. I have only a minor comment. 1. The authors discuss beneficial effects of MGL inhibition in the treatment of several disease models, such as diabetes, acute liver injury and HCC. Please summarize the possible therapeutic applications of MGL inhibitor by modifying Figure 2 or drawing an additional figure.

Many thanks Reviewer 3 for this comment. I modified figure 2 with additional therapeutic avenues in cancer and fibrosis based on current literature.

Reviewer #4:

Scientific Quality: Grade C (Good)

Language Quality: Grade A (Priority publishing)

Conclusion: Minor revision

Specific Comments to Authors: Monoacylglycerol transferase 2 (MGAT2) is a pivotal enzyme in the monoacylglycerol pathway for triacylglycerol synthesis. The pathway for triacylglycerol synthesis has provided several attractive targets for drug discovery in the treatment of metabolic diseases. Author writes that MGL inhibition had a protective effect on hepatocyte for ischemia-reperfusion injury and ccl4 induced acute liver injury.I ask some questios to author. 1.Please tell me the detail etiology which MGL inhibitor had a good effect for re-perfusion injury and CCL4 induced liver failure. 2.Author concluded that MGL will have a good effect for insulin resistancs type 2 DM in the future. Please tell me the etiology which MGL is good effevt for type 2 DM.

Many thanks Reviewer 4 for this comment and for asking further evidence on what's discussed in this review:

1. Partial hepatic I/R (1 h of ischemia followed by reperfusion for 2 h, 6 h or 24 h) was induced in WT mice and the MGL inhibitor (JZL184) was administered by i.p. injection at various time points (1 h before ischemia, 1 and 3 h after reperfusion) as indicated by Cao et al (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3608818/). For CCl4- induced liver injury, mice were injected i.p. with 2 ml/kg of 10% CCl4 and then sacrificed 24 h after CCl4 injection. Authors evidenced decreased serum levels of the acute liver damage/necrosis markers alanine aminotransferase (ALT) and aspartate aminotransferase (AST), decreased coagulation necrosis seen in histological sections as well as a decrease in delayed markers of apoptosis in both genetic and preventative pharmacological blockade of MGL models.

2. In the paper from Taschler et al. (https://www.ncbi.nlm.nih.gov/pubmed/21454566) Authors demonstrated that MGL KO mice challenged with a high fat diet had significantly improved glucose tolerance and insulin sensitivity in comparison with WT controls despite equal weight gain. In our work (https://www.ncbi.nlm.nih.gov/pubmed/31048404) instead we also demonstrated diminished body

weight gain when mice where challenged with western diet, which was also according to another work (https://www.ncbi.nlm.nih.gov/pubmed/25842377). These data suggest that MGL deletion could be a helpful strategy towards diet induce obesity and insulin resistance.

Reviewer #5:

Scientific Quality: Grade C (Good)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: Comments for ESPS Manuscript NO 55458 This Minireview is a well written one. I have no specific comments.

I thank Reviewer 5 for the very positive feedback.

Reviewer #6:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Minor revision

Specific Comments to Authors: The manuscript written by Tardelli M. review the role of monoacylglycerol lipase (MGL) in the lipid metabolism, inflammation and cell growth. The author also demonstrates the possible contribution of MGL to the development of cholestatic liver disease, NAFLD, fibrosis or HCC, and summarized the underlining molecular mechanisms that have been reported so far. Although there are many unclear points how important MGL is in the pathogenesis of various liver disease, the review provides important information to the readers. Minor point 1. It would be better, if a scheme showing the role of MGL in the inflammation, cholestasis or tumorigenesis could be provided.

Many thanks Reviewer 6 for this comment, I modified Figure 2 summarizing possible therapeutic avenues

Reviewer #7:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: Currently many literatures reveal that monoacylglycerol lipase (MGL) is involved in the mechanisms of in liver diseases. In this manuscript, the authors review the relevant details. The manuscript contains provide novel imformation to the readers. It is suggested that abstract should focus on monoacylglycerol lipase instead of some things else.

I thank Reviewer 7 for raising this point and modified and refocused the abstract.

Reviewer #8:

Scientific Quality: Grade A (Excellent)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (High priority)

Specific Comments to Authors: This is a nice basic review focus on the monoacylglycerol lipase function and fatty acids partitioning in the horizons of liver disease. Well manuscript written and clarify mechanism descript.

Thanks Reviewer 8 for this positive feedback.

Step 6: Editorial Office's comments

The author must revise the manuscript according to the Editorial Office's comments and suggestions, which listed below:

(1) Science Editor: 1 Scientific quality: This is a minireview of the liver disease. The topic is within the scope of the WJG. (1) Classification: 2 Grade A, 4 Grade B, and 2 Grade C; (2) Summary of the Peer-Review Report: This is a nice basic review focus on the monoacylglycerol lipase function and fatty acids partitioning in the horizons of liver disease. Well manuscript written and clarify mechanism descript. Although there are many unclear points how important MGL is in the pathogenesis of various liver disease, the review provides important information to the readers. Please summarize the possible therapeutic applications of MGL inhibitor by modifying Figure 2 or drawing an additional figure. The questions raised by the reviewers should be answered; and (3) Format: There are 2 figures. A total of 52 references are cited, including 14 references published in the last 3 years. There are 2 self-citations. 2 Language evaluation: Classification: 8 Grade A. The manuscript is from the United States. 3 Academic norms and rules: The authors provided the signed Conflict-of-Interest Disclosure Form. The authors need to provide the Copyright License Agreement signed by all authors. No academic misconduct was found in the Bing search. The highest single-source similarity index in the

CrossCheck report showed to be 8% and 6%. According to our policy, the overall similarity index should be less than 30%, and the single-source similarity should be less than 5%. Please rephrase these repeated sentences. 4 Supplementary comments: This is an invited manuscript. The study is without financial support. The topic has not previously been published in the WJG. The corresponding author has not published articles in the BPG. This manuscript is the resubmission of manuscript 53274. 5 Issues raised: (1) I found no "Author contribution" section. Please provide the author contributions; (2) I found the authors did not provide the original figures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor; (3) I found the authors did not add the PMID and DOI in the reference list. Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references. Please revise throughout; and (4) the author should number the references in Arabic numerals according to the citation order in the text. The reference numbers will be superscripted in square brackets at the end of the sentence with the citation content or after the cited author's name, with no spaces. 6 Re-Review: Required. 7 Recommendation: Conditionally accepted.

Thanks for this comments, I changed all the sections accordingly : 1. I am the only Author: therefore I wrote, proofread the manuscript (added this section before the abstract). 2. I attached now the original Figures in a Powerpoint file. 3. I corrected the reference list and adapted citations for point number 4. Also I revised the ms thoroughly as demonstrated by the underlined changes.

(2) Editorial Office Director: I have checked the comments written by the science editor.

(3) Company Editor-in-Chief: I have reviewed the Peer-Review Report, the full text of the manuscript, the relevant ethics documents, and the English Language Certificate, all of which have met the basic publishing requirements of the World Journal of Gastroenterology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors.