THE UNIVERSITY OF
TENNESSEE
KNOXVILLE

Re: World Journal of Gastroenterology-38869, The production of extracellular lysophosphatidic acid in the regulation of metabolism and liver fibrosis

April 23, 2018
Dear Dr. Wang:

Thank you for your e-mail on April, 18, 2018. We have revised the manuscript accordingly. The revised places were highlighted by red font. Here are our responses to the reviewers' comments line-by-line, which are underlined.

Reviewer 1

In this manuscript the authors review the history of research on lysophosphatidic acid (LPA) biological functions, including the mechanisms of LPA production, the discovery of LPA receptor subtypes, and LPA receptor signaling pathways. The contribution of autotaxin (ATX) to LPA production and of LPA receptors to the physiopathology of obesity, to insulin resistance and fibrosis in different liver diseases is discussed. Though the review is fine as is, I suggest a significant number of minor corrections and additions:

Comment 1: Page 5 (line 28) and Figure 2: Phosphatidic acid is not generated by a lysophospholipase D (lysoPLD). It is rather produced through the hydrolysis of phospholipids by phospholipase D enzymes (PLD1 and PLD2). This mistake needs to be corrected.

Response: Thank you very much for your correction. We have revised this in line 12 on page 9 and Figure 2 on page 8. Please see the revision for the changes.

Comment 2: Page 6, line 18: I would rather say that lipid phosphate phosphates (LPPs) are also involved in the LPA turnover (or recycling). Saying that LPPs are involved in LPA production is a little bit misleading.

Response: Thank you for your helpful suggestion. We have revised sentence in line 5 on page 10. Please see the revision for the changes.

Comment 3: Page 6, last line: I would state that the biologically active LPA-like products generated by this non-enzymatic oxidation co-migrated with an authentic LPA standard in thin layer chromatography.

Response: Thank you for your worthwhile suggestion. We have revised the sentence according to the reviewer's suggestion, which can be seen in lines 17-18 on page 10.

Comment 4: Page 8, line 3: I would rather say that extracellular LPA was found to be present in sub-micromolar or micromolar ranges.

Response: Thank you for your good suggestion and we have revised this in line 23 on page 11.

Comment 5: Page 9, line: I would rather state that the ATX human and mouse ATX gene structures are conserved.

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Response: Thank you for your good suggestion and we have revised this in the last line on page 12.

Comment 6: Page 9. The authors should highlight that a polybasic insertion corresponding to exon 12 in ATXα confers binding to heparin sulfates (Houben AJ et al., 2013, PMID: 23150666). This is another potential mechanism for localizing ATXα to cell membranes and for LPA production in close proximity to LPA receptors.
Response: Thank you for your worthwhile suggestion. We have highlighted this part in lines 7-11 on page 13. We have added the citation as well. Please see the revision for the changes.

Comment 7: Table 1, and page 13. With regard to expression of LPA3 receptor in mouse tissues, including the reproductive organs, I would cite the study by Zhao C et al. (Transgenic Research, 2015, PMID: 25982332).
Response: Thank you very much for your helpful suggestions and we have revised this in lines 10-11 on page 22 and Table 1 on page 18.

Comment 8: Page 17, end of the paragraph, line 20. The last part of the sentence should be revised.
Response: Thank you so much for the suggestion. The last part of the sentence mainly focus on the pro-fibrotic activity of PLA, we have discussed this in "POSSIBLE ROLE OF LPA SIGNALING IN LIVER FIBROSIS" section. So we added the feedback regulation by LPA and S1P in the last sentence on page 27.

Comment 9: Page 18, line 12: "in them" can be deleted.
Response: Thank you for your good suggestion and we have deleted it.

Comment 10: Page 18, line 13: … ATX knockout mice fed with a high-fat diet …
Response: Thank you for your good suggestion, and we have added "with" in this sentence of line 23 on page 28.

Comment 11: Page 18. The authors may highlight that LPA can negatively regulate ATX expression in adipose tissues (Benesch MG et al., 2015, PMID: 25896349).
Response: Thank you for your worthwhile suggestion. We added this part at the end of "LPA receptor signaling regulates adipogenesis", which can be seen in the last sentence on page 27.

Comment 12: Page 18, line 24: … obese-only subjects … -Please check symbols and Greek letters that did not display properly in the word document.
Response: Thank you for your good suggestion and we have added "-" in this sentence in line 5 on page 29 and check symbols and Greek letters in the whole manuscript and figure file.

Reviewer 2

This paper by Yang and Chen presents an in-depth review of LPA and its signaling in metabolism and liver fibrosis. The review is generally well organized and written. However, the majority of the review is about the general information on LPA synthesis and LPA-mediated signaling and effects, and the actual discussion on metabolism and fibrosis takes a back seat. This review seems a bit misleading in this. Although there is increasing interests on LPA and autotaxin in the pathogenesis of diabetes and other liver diseases, most of the studies are correlative findings with a few exceptions.

Comment 1: The “metabolism” in the title should be changed since this has a much broader implication than the review presents.
Response: Thank you for your suggestion. We agreed with the reviewer and have revised the title to “The production of extracellular lysophosphatidic acid in the regulation of adipocyte functions and liver fibrosis”.

Comment 2: Increasing evidence demonstrate the expression and secretion of autotaxin by adipocytes, but the authors downplay this fact for unknown reasons.
Response: Thank you so much for the suggestion. We have discussed this part on page 27.

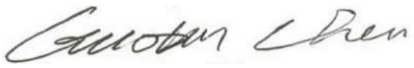
Comment 3: There is a fair amount information liking diabetes to liver fibrosis, but the review lacks a clear link between these pathologies.
Response: Thank you so much for the worthwhile suggestion. We have added two sentences and two paragraphs to discuss this issue in the section “POSSIBLE ROLE OF LPA SIGNALING IN LIVER FIBROSIS”. Please see the revised manuscript for the changes.

Comment 4: Top of pg 20: “LPA from HCC cells ….fibroblasts associated with the tumor” Please check.
Response: Thank you so much for the suggestion. We have revised this sentence in lines 13-14 on page 31.

Reviewer 3
Comment 1: Authors reviewed the role of LPA in the regulation of metabolism. This work is well-written and informative. Authors should discuss about the association between metabolic disorder and liver fibrosis, especially about the contibution of LPA.
Response: Thank you so much for this helpful suggestion. We have added two sentences and two paragraphs to discuss this issue in the section “POSSIBLE ROLE OF LPA SIGNALING IN LIVER FIBROSIS”. Please see the revised manuscript for the changes.

We hope this will make it more acceptable for publication. Thank you and all the reviewers for the kind advice.

Sincerely yours,



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