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To
Ze-Mao Gong
Science Editor, Editorial Office
World Journal of Gastroenterology

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Heidelberg, 7. 10. 2016

Dear Mr. Gong,

In response to our earlier correspondence, I hereby send you my revised manuscript No.: 29075 entitled

‘Does pressure cause liver cirrhosis? The sinusoidal pressure hypothesis’

Invited for publication in World Journal of Gastroenterology as **Field of Vision**.

First of all I would like to thank you, the editors and the reviewers for the fruitful comments and suggestions. Please find below my point-by-point response addressing these specific points. Changes to the manuscript are highlighted in red within the updated version of the manuscript file (word docx). Briefly, the following major points have been addressed:

1. According to the reviewer’s suggestions, I have significantly shortened the abstract from 301 down to 233 words. I have also shortened the title to be more concise and to stay within the 12 word limit.
2. Supplemental tables and figures are now provided in an independent supplemental material file.
3. With regard to your request, I also upload a Powerpoint file with the editable images.
3. In the reference list, a twice cited reference (former 21 and 68) has been cleared up and reference numbers have been renumbered accordingly.
4. Although being a bilingual native speaker, I have asked one additional native speaker to recheck the manuscript for further improvements. The corrections of these small typos throughout the manuscript are not indicated in the word file for better readability but I can always provide you with tracked words version.

5. Turnitin software from the University of Heidelberg platform has been used to screen for plagiarism. According to the report, less than cumulative 4% show similarities. In addition, top similar sources are my own preliminary abstract publications at international conferences.

6. Since this paper is a hypothesis paper, files related to academic rules and norms are restricted to conflict-of-interest statement and the copyright assignment form that have been uploaded as well.

I would like to thank you again for considering my manuscript. Please do not hesitate to contact me directly in case of further questions.

Sincerely yours,

Sebastian Mueller

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Point-by-point response:

Reviewer I No. 02860895

Comments To Authors: Sinusoidal pressure hypothesis, a really fascinating hypothesis! The author's idea will be sufficiently understood. If possible, please reduce the manuscript amount by avoiding repetitive descriptions. Rather concise writing may lead to readers' better understanding.

Response: I am encouraged by these stimulating comments. To be more concise, I have significantly shortened the abstract from 301 down to 233 words. I also shortened the title. I also have transferred all supplemental tables and figures to an independent file named 'supplemental material'. In addition, I have shortened some extensive paragraphs e.g. on page 9.

Reviewer II No. 52899

Comments To Authors

As an integrative concept, sinusoidal pressure hypothesis is one causes of liver fibrosis or cirrhosis. Moreover, arterialization triggers the vicious cycle of cirrhotic liver with irreversible fibrosis progression. In this manuscript, the author described sinusoidal pressure hypothesis in detail. In macroscopic level, the author analyzed the possible reasons of the phenomenon that different etiologies cause uniform cirrhosis. Furthermore, the author also summarized the role of arterialization in liver cirrhosis. The topic is interesting and the manuscript is well-written. But proteomics and metabolomics are related to liver cirrhosis. The author could discuss them to better present sinusoidal pressure hypothesis and arterialization.

Response: Many thanks for these stimulating comments. Since reviewer I suggested rather shortening of the manuscript I have not added an extensive discussion paragraph on this topic but added proteomics and metabolomics to Table 2, point 4 for potential future studies. I also mention it now on page 5.

Reviewer III No. 2438768

1. General comments: The article tackles an interesting topic. However, I have some comments regarding the paper.

2. Major comments:

2.1) Cirrhosis is caused by chronic liver diseases (CLD) that damage liver tissue. Some chronic liver patients will never develop fibrosis or cirrhosis, whereas others rapidly progress towards cirrhosis in a few years. This variety can be caused by disease-related factors (for example, viral genotype) or host-factors (genetic/epigenetic). The author should include these additional topics and references to make this article more complete.

Response: I would like to thank this reviewer for this important comment. Two respective sentences have been added into the background paragraph on page 8.

2.2) Abstract is too long that should be as concise as possible.

Response: I would like to thank for this helpful comment. According to the reviewer's suggestions, I have significantly shortened the abstract from 301 down to 233 words. I also shortened the title.

3. Minor comments:

3.1 CLD often lead to liver injuries that cause liver fibrosis, which ultimately may progress to liver cirrhosis. It is not all CLD that can lead to liver cirrhosis. Obviously, the expression of "All chronic liver diseases ultimately lead to liver cirrhosis..."that stated in the Abstract is not exactly right.

Response: I completely agree with this important comment and I see how this sentence could lead to misunderstanding. The respective sentence refers to the fact that all kinds of liver diseases independent of their etiology may lead to cirrhosis. It does not mean that all liver-diseased patients will develop cirrhosis. The first sentence of the abstract has been rephrased accordingly to avoid such misunderstanding.

3.2 The format of this manuscript should be revised according to WJG's requirement.

Response: The format has been adapted according to the WJG's requirement.

3.3 The language needs to be improved.

Response: Although being a bilingual native speaker, I and one additional native speaker have rechecked the manuscript carefully. We have further improved the quality and we eliminated typos throughout the paper. These minor changes are not tracked in red within the submitted version for better readability but it could be provided at any time.