

Dr. Lian-Sheng Ma  
Founder and Chief Executive Officer  
***Baishideng Publishing Group Inc***

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Dear Dr. Ma,

We are most grateful to you and the reviewers for the valuable comments made concerning our manuscript entitled “Mutual interaction between the oxidative stress and the endoplasmic reticulum stress in the pathogenesis of diseases” by Junichi Fujii, et al. We wish to resubmit this revised paper for publication in the ***World Journal of Biological Chemistry***.

We are sincerely grateful for relevant criticisms that helped us to improve the manuscript significantly. We have addressed all the comments and amended the manuscript in the light of these comments and included Audio Core Tip.

We hope that the revised manuscript will now be found to be suitable for publication in ***World Journal of Biological Chemistry***, and we look forward to receiving a decision from you at your earliest convenience.

Thank you very much for your consideration.

Sincerely yours,

Junichi Fujii, Ph.D.

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## Comments from editor

Please offer the audio core tip, the requirement are as follows:

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Response: We have uploaded the audio core tip.

Reviewer 1: Anonymous

Review Date: 2018-08-03 22:28

Specific Comments To Authors: - There some typo errors, e.g. communicate. - Please use full names of abbreviations before using abbreviations, e.g GPX. - The title is not representing the study. The study mainly focused on NALFD and this not appear in the title. - Some references are old references and there are new versions of the manuscript. Please use the new papers instead of the old papers.

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments To Authors  
(File):

Responses: Thank for your critical comments on our manuscript.

1. We have corrected all errors throughout the manuscript.
2. Because PRDX4, GPX7 etc. are genetic names but not conventional abbreviations, so we used without further explanation. Now we have spelled out all at the first appearance for readers' convenience.
3. We have changed the title according to the advice as follows.  
"Mutual interaction between oxidative stress and endoplasmic reticulum stress in the pathogenesis of diseases specifically focusing on non-alcoholic fatty liver disease (NAFLD)"
4. We believe that important new original articles were mostly cited. We tried to cite original papers, which report for the first time new molecules or novel mechanism, for the purpose of giving scientific priority to them. In some cases, fairly old review papers were cited because recent review articles describe only limited subject and do not overview the field. Now we have reconsidered and replaced the old review papers, which need to be updated, to recent ones when possible.

Reviewer 2: Anonymous

Review Date: 2018-08-05 21:59

Specific Comments To Authors: The manuscript provides a comprehensive review of the molecular events taking place in the endoplasmic reticulum to maintain homeostasis and prevent oxidative damage. The figures are clear, informative and useful. A large part of the review covers the mechanisms governing the repair of misfolded proteins in oxidative stress conditions but the relation of these mechanisms to the pathogenesis of diseases in general or with NAFLD in particular and the therapeutic approaches used to treat these diseases is not apparent. A table indicating the pathways or the molecules targeted with a specific therapeutic approach (ascorbic acid, GW501516, GW0742 or other therapies) to treat NAFLD would make it easier for the reader to follow and increase the value of the review as source of information. A more extensive section indicating future directions of the research in the topic would be useful and improve the quality of the review. Figure 2, page 49: "Oxidases" instead of "oxydases" In page 4 the word "extemporaneous" is not the right choice in the context of the subject discussed in the text.

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments To Authors  
(File):

Responses: Thank for your valuable advice. NAFLD is a disease condition recognized fairly recently and not well understood mechanically. In addition, the topic of this review article, interplay between oxidative stress and ER stress, is also new research

field, so that clinical data concerning them are very limited and mostly cited in the text. Moreover, we believe that World Journal of Biological Chemistry is dedicated to basic science and that readers are mostly working on basic research and wish to know the molecular mechanism. Accordingly, we have overviewed the subject by emphasizing on the basic, molecular mechanisms on oxidative stress-triggered ER stress and pathogenesis of the related disease, notably NAFLD, in mostly animal models and tried to assemble information to gain insight for future, clinical studies.

Regarding molecular mechanism, precise targets of ascorbic acid in amelioration of NAFLD are rather ambiguous. GW501516 and GW0742 are activators for PPARdelta, and in fact some papers report carcinogenic activity of the compounds, as mentioned in the text. Moreover, precise target genes and protective mechanism by PPARdelta are still not fully identified either. Thus, we consider that it is not possible or adequate to make such Table, which presents the protective mechanisms against NAFLD of these agents, without misleading.

As mentioned above, the roles of activators for PPARbeta/delta in this issue are under debate, and we are not sure whether PPARbeta/delta becomes prosperous or unapplicable as therapeutics. Thus, we proposed possibility for clinical application based on reliable reports but had to limit the description as written.

Thank for pointing out the misuse of the words. We have corrected them.

Reviewer 3: Anonymous

Review Date: 2018-08-19 14:18

Specific Comments To Authors: In this review, the authors summarized the mechanisms of oxidative stress and endoplasmic reticulum stress in the pathogenesis of MAFLD. The manuscript was well written. However, the topic of the review should be demonstrated clearly in the title. NAFLD could reflect the content more exactly.

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (General priority)

Specific Comments To Authors

(File):

Responses: Thank for your critical comments on our manuscript. We have changed the title according to the advice as follows.

“Mutual interaction between oxidative stress and endoplasmic reticulum stress in the pathogenesis of diseases specifically focusing on non-alcoholic fatty liver disease (NAFLD)”