Format for ANSWERING REVIEWERS

September 12, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 13216-edited.doc).

Title: Involvement of the TAGE-RAGE system in NASH: A novel therapeutic strategy

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Name of Journal: *World Journal of Hepatology*

ESPS Manuscript NO: 13216

The manuscript has been improved according to the suggestions of reviewers:
1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer
Reviewers' comments: Responses to the two reviewers' comments are shown in red.
Reviewer #227509
Comment 1. In this manuscript, the authors represented that liver function inversely correlated with serum TAGE levels in chronic liver diseases, and also represented that serum TAGE levels decreased in NASH patients by using anti-DM drugs. Which is more important in each liver disease (virus associated liver diseases, NAFLD)? Liver functions or glucose tolerance? Please explain precisely.
(A): Serum TAGE levels were positively correlated with HOMA-IR and inversely associated with adiponectin levels. Although serum TAGE levels did not correlate with the severity of hepatic steatosis or fibrosis, these values were not affected by the status of glucose tolerance. No significant difference was observed in TAGE levels between normal and IGT patients. TAGE was detected in the hepatocytes of patients with NASH, whereas its levels were negligible in patients with simple steatosis.

The chronic ingestion of an excessive daily diet increases the levels of the sugar metabolite, glyceraldehyde (a precursor of TAGE), in the liver. NAFLD is considered to be more important than virus-associated liver diseases in the early stages of liver dysfunction.

Glyceraldehyde, a precursor of TAGE, is produced *via* glycolysis and fructolysis in the liver. It is thought that liver functions are more important than glucose tolerance for the formation of TAGE. However, more detailed research is needed to confirm this.

Comment 2. The authors showed that HMG-CoA reductase inhibitor, statins, decreased serum TAGE levels. What is the putative mechanism that decrease TAGE levels by statins? Is this secondary effects of statins?
(A): Yes, this is a secondary effect of atorvastatin; however, it currently remains unknown whether this effect is common to all statins. Decreased production of glyceraldehyde (TAGE precursor), a fructose metabolite, results in reduced TAGE production. Please check page 25.
Comment 3. In conclusion, the authors described serum TAGE levels were significantly higher in NBNC-HCC. How about other HCC patients (HCV, HCB associated HCC)?

(A): We have not yet measured the amount of TAGE in blood samples collected from these patients, but intend to in a future study.

Comment 4. After (TBARS), " , " is missing (Page 25, line 10)

(A): This was corrected.

Reviewer #2726

Comment 1. Fig. 1 is very busy and therefore difficult to understand. It should be simplified by removing the chemical formulas.

(A): The chemical formulas were removed from Figure 1.

Comment 2. The review is long, and there is a lot of information related to diseases and cell types, particularly from that of the authors' work, that is not directly relevant to the liver. These sections should be cut and review focused more on the liver.

(A): The review was shortened in accordance with these directions. The deleted text has been crossed out.

Comment 3. The review is not well organized and quickly switches topics. For example, on page 12 the first paragraph starts about endotherial cells, then within the same paragraph hepatic stellate cells are discussed for a few sentences. The next paragraph discusses hepatocytes. The material should be better organized into more coherent subthemes.

(A): The paragraph about endothelial cells was deleted, while that regarding hepatic stellate cells was transferred to the subsequent paragraph discussing hepatocytes. Please refer to pages 12 & 13.

Comment 4. There are a number of typos, for example, just on page 5: line 6 should read "more significantly", line 13 should read "discuss", line 19, "residues". The manuscript requires extensive editing.

(A): The revised manuscript was rewritten carefully and proofread by a native speaker of English. Please confirm this.

Comment 5. There are a large number of abbreviations, some nonstandard (e.g. OS) and a list of abbreviations would be helpful.

(A): We added a list of abbreviations in accordance with the directions (pages 30-32)

OS was replaced with "oxidative stress".

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Hepatology*.

Sincerely yours,

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