Format for ANSWERING REVIEWERS

May 7th, 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 17674 -review.doc).

Title: Contribution of the toxic AGEs (TAGE)-RAGE axis in NASH-related HCC

Author: Jun-ichi Takino, Kentaro Nagamine, Takamitsu Hori, Akiko Sakasai-Sakai, Masayoshi Takeuchi

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 17674

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

Reviewers' comments:

Responses to the two reviewers' comments are shown in red.

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

<Reviewer #2860585>

This is a nice review about glycation end-products which have been associated with NASH and NBNC-HCC, including NASH-related HCC. Authors are expert in this topic, with several reviews like Med Hypotheses 2015, 84(5):490-3, which should be included. My suggestion is including new figures and tables to be a more easy-reading paper.

(A): We added two figures (Figures 1 and 2). The above article and our recent review article were added as references (Ref. No. 24 & 75).

<Reviewer #2715825>

This review briefly analyses the state-of-art of the TAGE-RAGE axis in NASH-related HCC. In general, English is acceptable, but however, some sentences need to be polished:

- Toxic advanced glycation end-products (TAGE), which is one of its ligands, increase not only in nonalcoholic steatohepatitis (NASH)…
- Glyceraldehyde, which is a precursor of TAGE, is considered to be produced by two pathways…

- The possibility that the catabolism and clearance of circulating CML may be impaired by various liver diseases was initially introduced by…
- Similar findings have been reported by Yagmur *et al*…
- The etiology of HCC has changed in recent years due to slight increases in the incidence of NBNC-HCC…
- Our review showed that TAGE, enhanced by NASH, may contribute to the malignancy…

(A): The above sentences were rewritten.

Moreover, section *Characteristic and formation of TAGE in vivo* is too extensive, so I strongly recommend to abbreviate it.

(A): The section on *"Characteristic and formation of TAGE in vivo"* was rewritten and divided into two sessions. We also added two diagrams (Figures 1 & 2) as descriptions.

<Reviewer # 02860539>

Takino and colleges have discussed in their review article the connection between the different toxic advanced glycation end-products (TAGE), receptor for advanced glycation end-products (RAGE) and the development of NASH and NASH-associated HCC. The review is well written and summarizes current understanding of these metabolic parameters in NASH and HCC. Nevertheless, minor changes would be necessary before I endorse for publication. Minor changes: the figure 1 aims to summarize their proposed model for the contribution of the TAGE-RAGE axis in NASH and HCC. The authors could enhance the understanding of their conclusions by adding more details to the figure such as CML and sRAGE and their role or plausible role in HCC and NASH. Also the potential therapeutic targets for future therapies could be marked in this figure.

(A): We re-illustrated Figure 3 according to the instructions.

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

Sincerely yours,

Masayoshi Takeuchi, PhD.
Department of Advanced Medicine, Medical Research Institute
Kanazawa Medical University
1-1 Daigaku, Uchinada, Ishikawa 920-0293, Japan
TEL: +81-76-286-2211 / FAX: +81-76-286-3652
E-mail: takeuchi@kanazawa-med.ac.jp