ANSWERING REVIEWERS

December 21, 2013

Dear Editor,

Please find enclosed the edited and revised manuscript in Word format (file name: 7455-Revised.doc).

Title: Chronic liver inflammation: Clinical implications beyond alcoholic liver disease

Author: Byoung-Jin Park, Yong-Jae Lee, Hye-Ree Lee

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 7455

The manuscript has been improved according to the suggestions of reviewers:
1 Format has been updated. Also we have written 'Core tip' in the revised manuscript.

2 Revision has been made according to the suggestions of the reviewer as follows.

Reply to Reviewer #1
1) Author should describe the role of IL-6 and IL-10 on the alcohol liver disease because of these cytokines are related with the inflammation induced by chroic alcohol intake.

Response: As suggested by the reviewers, we have described the role of IL-6 and IL-10 on the alcoholic liver disease as follows in 'CARDIOVASCULAR DISEASE' section and 'Activation of immunity' section:
"Moreover, pro-inflammatory cytokines such as tumor necrosis factor-α (TNFα), interleukin-6 (IL-6), interleukin-8 (IL-8), and interleukin-17 (IL-17) are produced by Kupffer cells in the liver in response to LPS, which, in turn, play a key role in inducing acute phase reactants in the liver, such as C-reactive protein (CRP), ferritin, and amyloid A[10,11]."
and
"…Interestingly, activation of TLR4 also induces Kupffer cells to produce hepatoprotective cytokines such as IL-6 which reduces hepatocyte necrosis-associated inflammation, albeit having proinflammatory roles, and anti-inflammatory cytokines such as interleukin-10 (IL-10)[53]. However, long-term alcohol consumption may…"

2) Moreover, authors should review more antioxidants intervention study in animals or patients with alcohol liver disease such as resveratrol, carotenoids, betaine and so on.

Response: As the reviewer mentioned, we have added more explanation about antioxidants intervention study as follows in 'Antioxidants' section: "S-adenosylmethionine could increase cellular antioxidant glutathione in patients with alcoholic liver disease[70]. Betaine, precursor to S-adenosylmethionine, has also been reported to attenuate alcoholic liver disease[71]. In clinical trials, S-adenosylmethionine has shown improved survival in patients with less advanced liver cirrhosis[72] but has not been consistently effective in treating alcoholic liver disease[73]. Antioxidants including phytochemicals such as resveratrol and carotenoids are successful for treating

alcohol-fed animals, but lack convincing benefits in human patients[7, 74-76]. Oxidative stress may be more pronounced in early stages of alcoholic liver disease, which is found in most animal models, but plays a minor role in later stages of alcoholic liver disease."

3) Hyperhomocysteinemia also is the risk factor of CVD induced by chronic alcohol consumption. Author should describe the relationship between hyperhomocysteinemia and chronic alcohol consumption.

Response: As suggested by the reviewer's comment, we have addressed the relationship between hyperhomocysteinemia and chronic alcohol consumption as follows in 'CARDIOVASCULAR DISEASE' section: "Lastly, chronic alcohol consumption has a tendency for increased plasma homocysteine levels, albeit the results are inconsistent according to amount and types of alcoholic beverage consumed, or underlying disease[19]. However, hyperhomocysteinemia induced by chronic alcohol consumption may be one of the important risk factors for CVD[20,21]."

Reply to Reviewer #2

1)This paper is well written about current topics on alcoholic liver diseases.

Response: We greatly appreciate your kind consideration of our manuscript.

Reply to Reviewer #3

1) Thank you for your comments and suggestions. We had addressed your points as shown below.
Please correct 1st word in the abstract. Please correct spelling and grammatical errors like "in addition the hepatitis B virus" "to lipid peroxidation of hepatocytes" "Kuppfer cells" "ROS could activate NF-κB and subsequent inflammatory cytokines such as TNF-α." Line 76, please add IL-6 because of its central role in CRP induction "Therefore, alcohol-derived ROS may be important for preventing liver damage and further systemic inflammation as well as understanding the mechanism of alcoholic liver disease. " Please check this sentence, is this correct? Fig. 2 Targeting antiinflammation may be changed to targeting inflammation

Response: As the reviewer pointed out, we have changed inappropriate words or sentence as follows in the revised manuscript:
"ABSTRACT" to "Abstract"
"in addition the hepatitis B virus" to "in addition to the hepatitis B virus"
"to lipid peroxidation of hepatocytes" to "to lipid peroxidation"
"Kuppfer cells" to "Kupffer cells"
"ROS could activate NF-κB and subsequent inflammatory cytokines such as TNF-α."
"ROS could activate NF-κB, which leads to production of inflammatory cytokines such as TNF-α."
"Therefore, alcohol-derived ROS may be important for preventing liver damage and further systemic inflammation as well as understanding the mechanism of alcoholic liver disease." to "Therefore, alcohol-derived ROS may be important for understanding systemic inflammation accompanied with alcoholic liver disease."
Figure 2: "Targeting antiinflammation" to "Targeting inflammation"
Also, we have added IL-6 in 'CARDIOVASCULAR DISEASE' section according to the reviewer's recommendation.

3 References and typesetting were corrected.

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

Sincerely yours,

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