

Sep 25, 2015

Dear Editor,

I appreciate the important comments and suggestions which help us to revise the manuscript for high quality manuscript

Please find the enclosed the revised manuscript in Word format (file name: 20946-revised manuscript.docx)

**Title:** Hepatic non-parenchymal cells; master regulators of alcoholic liver disease

**Authors:** Wonhyo Seo and Won-Il Jeong

**Name of journal:** *World Journal of Gastroenterology*

**Manuscript NO.:** 20946

The manuscript has been improved in accordance with the suggestions of reviewers: The individual response is provided below each comment.

#### **REVIEWER1**

This is an interesting review addressing the roles of the hepatic non-parenchymal cells in the pathogenesis of alcoholic liver disease. A few suggestions: The sinusoidal endothelial cells are also one kind of non-parenchymal cells which play many important roles in the pathogenesis of liver diseases. The roles of sinusoidal endothelial cells in the alcoholic disease should be mentioned.

#### **RESPONSE**

Thanks for your careful reviewing out the manuscript. Albeit liver sinusoidal endothelial cells (LSEC) are participated in the clearance of macro-sized molecules in liver pathophysiology, the exact role of LSEC in alcohol-mediated liver injury has not been fully understood. However, the description of the role of LSEC must be needed to understand the modulatory role of hepatic non-parenchymal cells. According to previous studies, LSEC is affected by alcohol consumption and undergoes morphological and functional changes. In addition, LSEC are equipped with specialized receptors to eliminate viruses, colloids, and macromolecular wastes from the circulation. Therefore, the general role of LSEC was briefly described in the introduction section and its morphological/functional change during acute/chronic alcohol consumption was also explained in the manuscript as the reviewer1 suggested.

The roles of different kind of cells should be illuminated and replenished in separate paragraphs. The manuscript

would clarify the different role of cells, such as sinusoidal endothelial cells, hepatic stellate cells, Kupffer cells, immune cells, etc.

#### **RESPONSE**

The brief categorized description of hepatic non-parenchymal cells (liver sinusoidal endothelial cells, Kupffer cells, liver lymphocytes and hepatic stellate cells) in the manuscript will help to readers for better understanding about their general roles in liver pathophysiology. Therefore, in the section of introduction, brief explanation about the hepatic non-parenchymal cells (LSEC, KC, liver lymphocytes and HSCs) was introduced.

#### **REVIEWER2**

The review does not unequivocally convince that non-parenchymal cells are the master regulators. Perhaps change the title by adding ‘?’ at the end.

#### **RESPONSE**

Thanks for your valuable comments regarding appropriate title in the manuscript. We revised the title to “Hepatic non-parenchymal cells; master regulator of alcoholic liver diseases?” as the reviewer2 suggested. Hepatic non-parenchymal cells are the important factors to modulate the progression of ALD, however, there are a large number of other factors to modulate alcohol-mediated liver injury. Merely we only focused on the novel roles of hepatic non-parenchymal cells in the aspect of the modulation of alcoholic liver disease. Therefore, the changed title might be more appropriated.

Abbreviation full form when used first time. e.g NLRP3 NON-PARENCHYMAL CELLS IN ALCOHOLIC STEATOSIS AND INFLAMMATION OF LIVER section is very confusing as is.

#### **RESPONSE**

We changed the abbreviation with the full name the reviewer2 figured out (e.g. NLRP3).

It covers several pathways/molecules in many cell types and overlaps with human and experimental systems. It needs some sub-sections/sub-headings to clearly explain the relationships and/or interactions of cell types and overlap of pathways. Perhaps cover steatosis, then inflammation, and then interaction.

#### **RESPONSE**

This manuscript describes the progression of ALD from inflammation to liver fibrosis. As reviewer2 suggested, the sub-section/sub-headings might be valuable for better understanding to readers. Because, the interactions

between hepatic non-parenchymal cells are complicated in the progression of ALD and its description must be well-organized for better understanding. Therefore, in the manuscript, sub-sections, based on different cell types in the stages of ALD were further categorized and described their interactive roles during the progression of ALD. In detail, “Contribution of activated Kupffer cell in development of hepatic steatosis and inflammation” “HSC activation and its retinol metabolism in alcoholic hepatic steatosis” “Dysfunction of LSEC and role of liver NKT cells during alcohol-mediated liver injury” “Interaction with activated HSCs and Kupffer cells during alcohol-mediated liver fibrosis” “Interaction with activated HSCs and liver lymphocytes in the pathogenesis of alcohol-mediated liver fibrosis” were further categorized and described in the manuscript. For better understanding, the order of certain sentences and paragraphs in the manuscript were changed in a permissible range.

Pg 7, line 7: "...intra-gastric ethanol feeding to mice ." Which mice? KO or WT? Please clarify.

#### **RESPONSE**

We changed the incomplete sentence (feeding to mice → feeding to WT mice).

Pg 8, line 5: "In chronic alcohol consumption, the number of NKT cells contributes in an inverse manner.." What does this mean? Clarify if it is increased or decreased number of NKT cells?

#### **RESPONSE**

We changed the incomplete sentence (the number of NKT cells contributes in an inverse manner → the significantly increased number of NKT cells contributes in an inverse manner).

Pg 8, Treatment line 3: Moderate alcohol is also reported to cause breast cancer. Pg 8, Treatment line 8: change mechanical to 'mechanistic'

#### **RESPONSE**

We added the information the reviewer2 suggested, which is about breast cancer caused by alcohol in Page8.

We changed the expression (mechanical → mechanistic).

Pg 8, Treatment line 9: change therapeutic to 'therapy'

#### **RESPONSE**

We changed the expression (therapeutic → therapy).

Figure legend 2: does not describe clearly what the image is.

**RESPONSE**

We changed figure 2 and figure legend to understand better in the aspect of the interaction between activated HSCs and liver lymphocytes.

Best regards

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