ANSWERING REVIEWERS

January 9th, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 6786-review.docx).

Title: Mechanisms of fibrogenesis in liver cirrhosis: The molecular aspects of epithelial-mesenchymal transition

Author: Sun-Jae Lee, Kyung-Hyun Kim, Kwan-Kyu Park

Name of Journal: *World Journal of Hepatology*

ESPS Manuscript NO: 6786

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

2. References and typesetting were corrected

3. Revision has been made according to the suggestions of the reviewer as below.

Reviewer: 1
Comments to the Author
The article "Mechanisms of fibrogenesis in liver cirrhosis: The molecular aspects of epithelial-mesenchymal transition" is original and informative. The paper describes the possibility that Epithelial-mesenchymal transition could contribute to hepatic fibrogenesis in chronic liver diseases. The topic is an overview to the knowledge of possible the pathogenesis of liver fibrosis. It is clearly written and readably **but the paper is too long in general and should be considerably shortened. The abbreviations are inconsequent and should be corrected.** The paper fulfils the field of the World Journal of Hepathology and is appropriate for publication after minor revision. There are no ethic imperfections. The paper fulfils grade B classification. The language do not need any polishing.

Answer to Reviewer: 1
We are grateful to reviewer 1 for the critical comments and useful suggestions that have helped us to improve our paper considerably. As indicated in the following responses, we have incorporated all of these comments into the revised version of our paper.

Comment #1: It is clearly written and readably but the paper is too long in general and should be considerably shortened. :

Answer:
As your suggestion, we eliminated some sentences.
These are as follows:
1) "During regression from carbon tetrachloride (CCl_4) induced hepatic fibrosis, bone marrow-derived mesenchymal stem cells migrate into the fibrotic liver, where they can express MMP-13 and MMP-9. Subsequently, two studies have demonstrated the bone marrow origin of fibrogenic cell populations in the CCl_4 mouse model of fibrosis and in the bile duct ligation (BDL) model of biliary hyperplasia.

Roderfeld *et al*. hypothesized that bone marrow-derived circulating CD34+ fibrocytes represent key mediators of liver fibrogenesis in the Abcb4/mice, which represent a highly reproducible, well-characterized non-surgical mouse model for cholangiopathy in humans. In addition, granulocyte colony-stimulating factor and hepatocyte growth factor treatment significantly enhance migration of bone marrow-derived cells into the fibrotic liver and accelerate the regression of liver fibrosis. Over-expression of hepatocyte growth factor together with granulocyte colony-stimulating factor, synergistically stimulate MMP-9 expression, which is followed by accelerated resolution of fibrotic scars." **(page 4, line 23) in Fibrogenesis of HSCs, myofibroblasts and hepatocytes in liver cirrhosis**

2) "Activated Kupffer cells release reactive oxygen species (ROS) and cytokines that are crucial for HSC activation as well. They are a major source of TGF-β1 and PDGF, two potent profibrogenic cytokines that traditionally have been considered key fibrogenic and proliferative stimuli to HSC, respectively. In addition, the Kupffer cell phagocytic activity generates large amounts of ROS that could further activate HSC and induce their fibrogenic potential. Furthermore, addition of ethanol and arachidonic acid synergized to activate Kupffer cells and modulated the fibrogenic response by a mechanism involving TNF-α and TGF-β1. It has been also demonstrated that in vivo ablation of TNF-α, TLR4, CD14, and lipopolysaccharide-binding protein protects from the fibrogenic response."
(page 6, line 9) in Fibrogenesis of HSCs, myofibroblasts and hepatocytes in liver cirrhosis

3) "In a report analyzing serial liver biopsies of a patient who underwent orthotopic liver transplantation for PBC, Robertson *et al*. described EMT features in biliary epithelial cells before the recurrence of PBC was clinically relevant. At time-zero and 9 days after transplantation, there was no evidence of FSP-1 expression in biliary epithelial cells. However, most bile ducts were positive for FSP-1 and vimentin expression 9 months after transplantation."
(page 13, line 19) in EMT in cholangiocytes.

Therefore, 333 words were decreased in general.

Comment #2 : The abbreviations are inconsequent and should be corrected.

Answer: As your suggestion, we reviewed whole manuscript and revised the abbreviations properly.

Reviewer: 2

Comments to the Author
Introduction, line 5: Please expand ECM.

Answer to Reviewer: 2
Thank for your precise suggestion for our manuscript. As your suggestion, we revised this sentence as below.

Original sentence: One of the most important alterations is hepatic fibrosis, which is characterized by deposition of **ECM** components around the sinusoidal layer in the space of Disse, together with molecular reorganization of the matrix components resulting in an altered composition.

Revised sentence: One of the most important alterations is hepatic fibrosis, which is characterized by deposition of **extracellular matrix (ECM)** components around the sinusoidal layer in the space of Disse, together with molecular reorganization of the matrix components resulting in an altered composition.
(Revised and blue highlighted in introduction part)

Thank you again for your kind and helpful suggestion and for publishing our manuscript in the *World Journal of Hepatology*.

Best regards,

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