**ANSWERING REVIEWERS**

February 20, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 7657-review.doc).

**Title:** Phospho-Smad signaling in HCV-related chronic liver diseases

**Author:** Takashi Yamaguchi, Katsunori Yoshida, Miki Murata, and Koichi Matsuzaki

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

**ESPS Manuscript NO:** 7657

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

(1) Revision has been made according to the suggestions of the reviewer (#00054187)

*Section "JNK dependent Smad3 signaling through linker phosphorylation" – in the last paragraph the authors wrote "To address this problem, we….", but there is no reference – a reference should be included, or a major explanation regarding this research should be presented.*

In accordance with your suggestion, we refer the review article entitled "Smad3 phosphoisoform-mediated signaling during sporadic human colorectal carcinogenesis (*Histol Histopathol* 2006;21:645-662 PMID:23871609)" regarding this research (Page 7 line 30).

*Section "Smad3 phospho-isoform signaling: tumor suppressive TGF-b type 1 receptor……" and Figure 1 – the authors describe molecular activation in uninfected and infected hepatocytes. It seems that this is a result of self-research – this should be clearer in the text and figure legend, as well as some more detail regarding this research could be presented (an in vitro study? what kind of sample was used? How were samples selected?)*

In accordance with the suggestion, we extensively revised the relevant part.
Page 8 line 6-Page 9 line 27, and the figure legend

*Figure 2 – which sources of these information? Also self-research? Some aspects seem hypothesis.*

In accordance with the suggestion, we added more detail information in relevant part.
Page 10 line 1 - 2
Page 12 line 11 - 20
Page 12 line 22 - 23

(2) Revision has been made according to the suggestions of the reviewer (#02860875)

*Yamaguchi et al have produced a short review article exploring the relationship between TGF-b and JNK*

*signaling in chronic liver disease. They have revealed an interesting cross-talk between these 2 pathways underpinned by mutually exclusive phosphorylation events of Smad3 and the respective downstream signaling pathways. The article is focused, but rather brief in places. The English is good and concise. I have the following comments.*

*Page 6, para 2. "HCV triggers an immune-mediated inflammatory response that promotes neoplastic transformation of damaged hepatocytes." I am not sure how strong the evidence is to make this kind of assertion. Whilst there is certainly an association with viraemia and level of viraemia in HBV, there is relatively little evidence of direct causation that immune cells drive transformation.*

In accordance with the suggestion, we revised the relevant part as bellow.
Page 7 line 3 - 5
Page10 line 16 - 29

*Page 7, perhaps some example photomicrographs could be included to demonstrate the effect the authors have previously demonstrated. Their pictures from the 2007 Hepatology paper looked really good, perhaps some examples could be used here.*

In accordance with the suggestion, we represent the representative figure concerning immunohistochemical analysis using domain-specific antibodies (Figure 1).

*There needs to be a brief discussion about the mutually inhibitory nature of the SMAD3 phosphorylation events and some discussion of the evidence about how this is achieved in vitro. Then further discussion about how this might occur in the progression to cirrhosis and HCC, with a frank discussion of the current uncertainties. The current speculation about how this occurs (p8, para 2) is rather unconvincing.*

In accordance with the suggestion, we extensively change the relevant part.
Page 10 line 30 - Page 11 line 30
Page 12 line 4 - 10

*Page 8, para 3, "After successful antiviral therapy, patients with chronic hepatitis C have less HCC risk because hepatocytic Smad3 phospho-isoform signaling has shifted from carcinogenesis to tumor suppression…". Again their evidence is purely associative rather than causal. Whilst this effect is interesting, to suggest that it underpins the reduction in HCC risk is not supported by evidence.*

In accordance with the suggestion, we added more information in the relevant part as bellow.
Page 9 line 19 - 24

(3) Revision has been made according to the suggestions of the reviewer (#02538717)

*Manuscript entitled "Smad3 phospho-isoform signaling in HCV-related chronic liver diseases", it has been reviewed completed. The authors might have obtained the interesting data. However, it is unfortunate that the manuscript is not well prepared for readers. Some comments are listed below.*

*References are too old, majority are over 3 years ago, the author should refer the new publish article.*

In accordance with your suggestion, we refer the resent articles as much as possible. However, publication date of some key references are old.

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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