July 7, 2016

Dear Editors and Reviewers:

I was glad to read your favorable response concerning my highlight manuscript untitled “Inhibition of apoptosis by oncogenic HBx protein: implications for the treatment of hepatocellular carcinoma” (No. 2668), submitted earlier to *World Journal of Hepatology*. I am grateful to the Editor and the Reviewers for their considerate and thoughtful advices and comments. I have now taken the time to carefully address each remark as described below. A revised version of the manuscript, and a manuscript with rebuttal, was included. I hope that with these modifications my manuscript will be deemed acceptable by your office.

In response to the first reviewers: (Reviewer’s code: 00068723)

This manuscript focuses on HBx and HURP. HBx activates HURP through p38/MAPK pathway. In HCC cells, HURP induces p53 degradation. These pathways lead to anti-apoptosis of HCC. This concept is interesting. More information on HBs would make this manuscript easier to understand.

Response: There are extensive reviews on HBV biology and its role in liver diseases. Researchers and public population have been educated well in this topic. This short review/highlight is focused on the functional role of HBx, a key HBV gene product, in HCC growth/apoptosis. So, detail information on HBs would not repeated in this manuscript.

Are there any literatures on pathological investigation of HBx and HURP in surgical specimens? If HBx and HURP co-exist in the same HCC cells, the concept is more convincing. How are the expression patterns of HBx and HURP in surrounding non-HCC tissues? If they are not expressed in non-HCC tissues, the authors’ proposal would be more feasible.

Response: Thank you very much for these important questions/suggestions. We have searched for the related information. Unfortunately, the out-come is disappointing. It lacks enough evidence to correlate HBx and HURP in surgical specimens. Our experiments indicated that it is difficult to detect HBx in HCC specimens by Western blotting and IHC staining. So far, no clinical data could support our lab findings. This may be partly explained by complex gene expression in HCCs.

Conclusion seems relatively long. It was hard to know what is the take-home messages.

Response: I shortened the conclusion paragraph (please see deletion of sentences highlighted in grey, and also reference 58, in the manuscript with rebuttal) in order to reveal “the take-home messages”.

In response to the second reviewers: (Reviewer’s code: 00032728)

To my opinion the authors well summarized the possible role of HURP with HBx and SATB1 in HCC. Minor comment: Page 6, line 4: ... increases cell growth in Response to Serum starvation"? This sounds unusual.

Response: Indeed, HURP increases cell growth under serum starvation [Tsou et al., *Oncogene* 2003; 22: 298-307; Yu et al., *Mol Cell Biol* 2005; 25: 5789-5800]. HURP can be phosphorylated and stabilized by oncogenic Aurora-A in cell culture. This may partly explain the functional role of HURP in regulating cell growth and possibly oncogenesis.

Thank you very much for your consideration to this highlight article.

Sincerely yours,

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