

February 26, 2017

Dr. Jing Yu
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Dear Drs. Jing Yu,

Thank you for your email dated on February 20, 2017 regarding our manuscript (32310) entitled "HBx protein induces HpSC-like features in hepatocellular carcinoma by activating KDM5B ". We appreciate the constructive comments of the reviewers and the opportunity to resubmit a revised manuscript. Accordingly, we have made a concerted effort to address all comments raised by the reviewers. As suggested by the reviewers, some new experiments were carried out. New results have been included as new panels in Figures 3 in our revised manuscript. Our point-by-point responses are described below.

I hope that our revised manuscript is now acceptable for publication in World Journal of Gastroenterology. I greatly appreciate your time and look forward to your decision.

Yours sincerely,

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The point-by point responses:

Reviewer: 1

Comment 1: It is necessary to explain that the cohort2 cases are HBV-related HCC samples.

Response: We agree with this comment. We have revised the human subjects section to include a detailed description of this cohort.

Comment 2: Though KDM5B was positively related to Hepatic stem cell (HpSC) markers (EpCAM, AFP, PROM1, and NANOG) in HBV-related HCC, there lacks the data of HBx relating to Hepatic stem cell (HpSC) markers.

Response: We appreciate the constructive comments. We have included new data demonstrating the relation between HBx and HpSC markers in Fig. 3. Experimentally, we have shown that introduction of HBx upregulated HpSC markers in HepG2 and Huh7 cells.

Comment 3: It seems like that the effects of HBx siRNA on the expression of KDM5B and stemness markers were also necessary in Huh7 cells.

Response: We have included new data demonstrating that HBx introduction upregulated KDM5B and HpSC markers in Huh7 cells in Fig. 3. We got same data with HepG2 cells. We think these data confirmed that HBx upregulated KDM5B and HpSC markers in HCC cells.

Comment 4: Page 31, line 9-11 described that “Effect of c-Myc siRNA on the endogenous levels of c-Myc (D), KDM5B (E), and EpCAM (F) in Huh7 cells”, but there is no data of EpCAM (F) in Figure 3.

Response: We sincerely apologize to the reviewers for our negligence. In accordance with the reviewer's comment, Figure 3F has been added.

Comment 5: The characters of HepG2, Huh7 and Hep3B cells need to be described in this article.

Response: In accordance with the reviewer's comment, the characters of HepG2, Huh7 and Hep3B cells have been added in the cell lines section.

Comment 6: The abbreviation of “HBV, HCV, ALD and NASH” in Figure 1 should have the full names in the legend.

Response: In accordance with the reviewer's comment, we have changed the following text in Figure1 legend from:

‘A nonparametric test was used to compare the 5 groups and p-values are indicated.’

to

‘A nonparametric test was used to compare the 5 patient groups of hepatitis B virus (HBV), hepatitis C virus (HCV), alcoholic liver disease (ALD), nonalcoholic steatohepatitis (NASH) and others respectively as indicated by p-values’

Reviewer: 2

Thank you for providing your valuable time to review this manuscript.