November 16th, 2017

Letter of Response

Dear Editorial Board of the World Journal of Hepatology,

Thank you for your suggested revisions for our manuscript #36921 entitled "The Epigenetic Basis of Hepatocellular Carcinoma: a Network-based Integrative Meta-analysis". We have addressed all reviewer and editorial comments below, and hope these adequately address the required revisions. Please also note that we have added another author to our list (Emily Chen), as we had omitted her name although she had contributed significantly to the manuscript.

Reviewer #1:

The objective of this study that investigators wrote in the abstract section doesn't match with that in the end of the introduction section

We thank the reviewer for this comment, and have accordingly modified the statement of objectives at the end of the introduction as follows:

"The goal of this study was to identify key epigenetically modulated genes and pathways in HCC by integrating all major, well-annotated and publicly available methylation datasets datasets using tools of network analysis."

2. What about the sample size and the incomplete information of the 11 databases used? Any comment about that in the discussion section

The characteristics of the datasets are detailed in tables #2 and 3 (revised numbering on pages 7 and 8). The tables previously numbered as Tables 2 and 3 are now renumbered as Tables 4 and 5 on pages 11 and 12.

We have commented on the incomplete clinical information on p.15, last sentence as follows: "Clinicopathological characteristics such as grade, stage and survival were available only for half of the datasets, thereby limiting the ability to correlate these data points with the most aberrantly methylated genes."

3. Include the new 2017 AASLD guidelines on HCC in the references section

We have added this as a reference on p. 13 in the discussion.

4. The supplementary material is not necessarily (table s1) or if you want to include it. You have to summarize.

We had incorrectly labelled the tables with the clinicopathological information as Supplementary tables. These have now been renumbered as Tables 2 and 3.

Reviewer #2

The authors performed an integrative network-based analysis approach of genome-wide DNA methylation data of both the promoter and body of genes. They identified G-protein coupled receptor signalling as the most highly associated with HCC. This finding was in consistent with previous literature on gene expression in HCC. Moreover, the authors also found few novel targetable genes such as HIST1H2AJ that are epigenetically modified, suggesting their potential as biomarkers and for therapeutic targeting of the HCC epigenome. Overall, this manuscript may provide useful data to support further study in HCC. However, the organization of the manuscript needs to be revised.

Table 1 to 3 were embedded in the main text but there also had 2 tables labeled as Table 1 and 2 located after the section of the Discussion.

This has been revised as per the response above to Reviewer 1.

Reviewer #3

Totally, this Manuscript is good, while the ***overall structure of the manuscript is not complete (e.g Introduction, Conclusion), though maybe you have wrote about it, so I think you should arrange the structure again***.

Thank you for this comment, we have accordingly revised the structure and headings according to the recommended format.