39103-Answering Reviewers

Reviewer's code: 03646639

SPECIFIC COMMENTS TO AUTHORS

I suggest that they should describe the other metabolic syndrome-associated-HCC models (for example, dietary NAFLD induced HCC C57Bl/6 J mice fed a high fat, high carbohydrate diet developed HCC at week 52).

We agree with the reviewer's comment to our manuscript. However, we focused only on selected NASH mouse models which unfailingly generate HCC in a limited duration and which are most representative of human metabolic syndrome-associated steatohepatitis in this review paper.

Reviewer's code: 02528832

SPECIFIC COMMENTS TO AUTHORS

Authors should either include a list with the abbreviations or define all of them in the text. Minor problems with English language (for instance, page 8 "proceeded" (?) Perhaps preceded?)

We agreed with that we should define all of the abbreviations and correct English language problems, even though we got the English Editing Certificate from Filipodia.

Reviewer's code: 02861131

SPECIFIC COMMENTS TO AUTHORS

1) The original findings of this manuscript – that is review article; the new hypotheses that this study proposed- summarized data about NASH-HCC progression animal models; the hypotheses that were confirmed through experiments in this study – not relevant review article

2) The quality and importance of this manuscript - the authors of this article

have been assessed the mouse models for investigating the underlying mechanisms of nonalcoholic hepatitis-derived hepatocellular carcinoma. The importance and significant of the research is high because research on NASH pathogenesis and carcinogenesis is ongoing and till now we do not have clarity in this point; the new findings of this study – the molecular mechanisms underlying progression to hepatocellular carcinoma from nonalcoholic steatohepatitis that have been identified to date using the array of mouse models currently available and popular in the experimental field the new concepts that this study proposes - the author has presented different animal model which confirmed tumorigenic mechanisms of NASH-HCC progression; the new methods that this study proposed - do not propose new methods; the conclusions do not appropriately summarize the data that this study provided; the unique insights that this study presented - mouse models are essential for investigating the underlying mechanisms of NASH-HCC progression; the key problems in this field that this study has solved - the author has presented different animal model which confirmed tumorigenic mechanisms of NASH-HCC progression

3) The limitations of the study and its findings - the considerable demerit of genetic mouse model, however, is the obscurity of the original gene of tumorigenesis for HCC due to lack of genetic manipulation and the inclusion of diabetes and hyperlipidemia in the background. Genetic manipulation in mouse models, such as of the PTEN-KO or ALR-KO, is a useful means by which to clarify the role of a specific gene in the molecular foundation of NASH-HCC progression; although, the sequential progression to HCC in these models has a

relatively long duration and HCC occurrence is uncertain; the future directions of the topic described in this manuscript - the future research targets may move forward towards gaining a more comprehensive NASH-HCC evaluation by using these mouse models; the questions/issues that remain to be solved - it is still questionable whether or not these available mouse models represent the initiating and/or progression processes of bona fide human NASH-HCC; the questions that this study prompts for the authors to do next - further inquiries are expected by researchers upon selecting an appropriate NASH mouse model according to the specific mechanisms and/or therapeutic targets of interest; this publication impact basic science and/or clinical practice – help to understand mechanism of NASH-HCC progression

Thank you for the comments. We agreed with the comments and revised our manuscript referencing the comments.