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Dear Editor Gong,

Enclosed is the revised manuscript of a review article invited by your editorial office, entitled “HCC mouse models: HBV-associated hepatocarcinogenesis and haploinsufficienct tumor suppressor genes” by Teng et al. for publication in the World Journal of Gastroenterology. The manuscript ID: 19724.

We revise the manuscript based on the Reviewer’s comments and in compliance with the guidelines of Revision Instructions (please see the point-by-point responses to the comments of the reviewer). The revised portions are highlighted by colored text in the revised manuscript. We hope the revised manuscript is now acceptable for publication in the WJG.

We apologize for the delay in submission of this revised manuscript, and hope that this does not cause inconvenience for your publication of WJG.

Sincerely yours,

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Responses to reviewer's comments:

Reviewer: 1

Reviewer's Comment #1

As the authors state, mouse model is useful for research of human diseases. How was the rationality on the transgenic mouse of HBV? Did the authors think HBV caused the same conditions to mouse liver as to human? HBV did not infect mouse. This means that HBV might not cause any disease to mouse. Or HBV might cause different conditions from human.

Response: This comment has been well taken. Indeed, HBV replication in transgenic mouse liver is not cytopathic to the host cells. However, transgenic mice carrying the HBV genome have helped scientists to gain insights into the molecular mechanisms of viral replication. HBV transgenic mice were also capable of recapitulating several aspects of the post-infected hepatocytes in natural hosts such as the human. In the revised manuscript, we have added two new paragraphs to review and discuss the advantages and disadvantages of using mouse models in HBV related biology. The newly added text is described on pages 10-11 of the revised manuscript and marked in blue.

Reviewer's Comment #2

What type of changes happened in mouse expressing HBV surface antigen? Were there any similarities to human? Did HCC occur in the mouse expressing HBV surface antigen? Did HBV surface antigen play a role in HCC carcinogenesis?

Response: Mice expressing HBV surface antigen in the livers have been shown to develop HCC (Table 1). The pathological changes in the livers of the transgenic mice are similar to those observed in human patients, including the ground glass cells, necrosis and inflammation (please see Table 1 and text on page 12). Regarding the role of HBV surface antigen in HCC carcinogenesis, several groups previously had provided evidence supporting that the HBV surface antigen was an onco-protein and played an important role in HCC carcinogenesis. The relevant information was reviewed and discussed on page 12 of the revised manuscript.

Reviewer's Comment #3

Many tumor suppressor genes and signaling pathways are described. It would be better to re-organize them to explain the genetic changes in transgenic mouse of HBV related genes.

Response: HBV viral products and mutations of tumor suppressor genes (TSGs) are the two major driving forces of pathogenesis in HCC. These two risk factors have a synergistic effect on HCC development. However, they can also function independently to cause HCC (Table 1). In this review article, we mainly focus on the application of mouse models in relation to HBV-associated HCC and on TSGs that act in either a recessive or haploinsufficient manner. As mentioned by the Reviewer, there are many TSGs and signaling pathways involved in the HCC. We thought that it might be easier for the readers to have a quick glance of information on TSGs linked to the biological pathways.