Answers to suggestions from the editor,

World Journal of Gastroenterology-24943-Review

PreC/C region mutations of hepatitis B virus related to clinical severity

Dear editor and reviewers,

We appreciate your kind comments and suggestions. All the comments were helpful and received careful consideration. We revised the manuscript according to reviewer's suggestions as follows:

[Reviewer(02936306)'s comment and answer]

This review focused on the association between the presence of several distinct types of mutations and the progression of liver disease in patients with chronic HBV infection. To judge from the review article, I think the author grasped wholly the problems engaged in the clinical significance of C gene mutations very well. Especially, the author highlighted that mutations in the immune recognition part of C gene, the MHC class II restricted region, are more significantly related to the disease severity than any other mutations. In addition, he mentioned that mutations inhibiting nucleocapsid formation and inducing ER-stress may be associated with progressive liver disease and hepatocarcinogenesis. **However, the combined mutations, including the accumulation of the above C gene mutations, their complex combinations, and the linkage with specific mutations in other gene regions of HBV genome are not included in this article.**

Answer) There are some well-known mutations causing serious liver disease because they are activated multiply rather than independently in the HBV genome. The representative variation is the G1896A mutation and this mutant represents a complex type of serious illness, especially in combination with other mutants than itself. Although the combined variations have well known for inducing the various clinical implications such as resistance to anti-viral treatment, immune escape, vaccine failure, and occult HBV infection, we focused on the correlation of just only HBV core mutations with clinical severance in this review. We would investigate the specific mutations in other gene regions of HBV genome if given a chance to writing another review.

In the next phase, more comprehensive bioinformatic analyses throughout the whole will be necessary to identify more complicated mutational patterns and to understand their clinical utility.

Answer) We also hope that more comprehensive bioinformatics about HBV full genome containing complicated

mutational patterns would be included in our next study. It would be help to understand their clinical utility.

[Reviewer(02527569)'s comment and answer]

The authors concisely summarized the current knowledge about the effects of prec/c region mutations in HBV sequences on clinical severity. This is a nice review and I have no specific comments.

Answer) Thank you very much for your comment.

[Reviewer(00503536)'s comment and answer]

The manuscript written by Kim et al. summarizes the significance of PreC/C region mutations in the severity of hepatitis and hepatocarcinogenesis. The mutations are analyzed in association with MHC, which is important to understand the effect of the mutations in relation with immune responses against HBV-derived peptides. The review is well-written and well-summarized. There is one point that should be considered. **Minor point, It has been shown that HBV-related liver injury is associated with promoted replication of HBV. Therefore, it would be better to show the changes in replication potential by various mutations within PreC/C region.**

Answer) Among the various mutations that are found in the core region of HBV full genome, we have reported that P5T/H/L mutants could lead to the increase of HBsAg secretion via endoplasmic reticulum (Lee H, Kim H, Lee SA, Won YS, Kim HI, Inn KS, Kim BJ. *Journal of General Virology* (2015) 96;1850-1854). But, relationships between this mutation and HBV replication still remains not to be solved. And, we have previously reported that the lower level of HBV DNA in patients infected with mutated strains in preC/C region than in those with wild strains were found [27], suggesting preC/C mutations could lead to HBV replication, generally. But, the identification of mutation types affecting HBV replication should also be done via functional study in the future. We added the above sentences into the revised version (Page 11, line 243 to 247).