

ANSWERING REVIEWERS



January 4th, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 6771-review.docx).

Title: The clinical implications of hepatitis B virus mutations: recent advances

Author: Ivana Lazarevic

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 6771

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated. According to "Format for Topic Highlights", the abstract was lengthened to reach at least 256 words. The added sentences were highlighted.

2 Revision has been made according to the suggestions of the reviewer

(1) Reviewer No. 00007461

Reviewer's Comment:

Page 5, last paragraph the sentence must be re-written for clarity "During the 1980s, a follow-up study of childhood vaccination in Italy revealed vaccinees who became HBsAg positive, despite the presence of a strong antibody response to HBsAg".

Answer:

The sentence was re-written to clarify the meaning and was highlighted in the text.

Reviewer's Comment:

Page 11, please revise sentences as follows, since these are well established functions of HBx: HBx serves as transactivator and is required for efficient transcription of viral RNAs from CCC DNA in infected hepatocytes[4]. Please add the following references in support of this statement: ? Andrisani OM, Barnabas S. The transcriptional function of the hepatitis B virus X protein and its role in hepatocarcinogenesis. *Int J Oncol* 1999;15(2):373-9. ? Bouchard MJ, Schneider RJ. The enigmatic X gene of hepatitis B virus. *J Virol* 2004;78(23):12725-34. HBx protein has a role in HBV-induced carcinogenesis by number of different mechanisms[71,72]. Please add the following references in support of this statement: ? Terradillos O, Billet O, Renard CA, Levy R, Molina T, Briand P, et al. The hepatitis B virus X gene potentiates c-myc-induced liver oncogenesis in transgenic mice. *Oncogene* 1997;14(4):395-404. Madden CR, Finegold MJ, Slagle BL. Hepatitis B virus X protein acts as a tumor promoter in development of diethylnitrosamine-induced preneoplastic lesions. *J Virol* 2001;75(8):3851-8. ? Buendia MA. Genetics of hepatocellular carcinoma. *Semin Cancer Biol* 2000;10(3):185-200

Answer:

The sentences were revised according to reviewer's suggestion and the suggested references were added in support of these statements. The changes were highlighted in the text.

(2) Reviewer No. 00742524

Reviewer's Comment:

Addressing the following concerns will significantly enhance the manuscript. 1) Drug-resistant and vaccine-escape mutants as well as occult hepatitis B in patients with HBV/HIV and HBV/HCV co-infection should be described in detail. New papers such as Hepatology 58:912-922, 2013 should be cited and discussed.

Answer:

The suggestion for improving the manuscript, by adding information on clinically relevant HBV mutations in HBV/HIV and HBV/HCV co-infected patients, was appreciated and the chapter discussing these matters was added at the end of the manuscript. The suggested reference was discussed and cited.

Reviewer's Comment:

2) A table or diagram summarizing the different mutants would be helpful.

Answer:

The table summarizing mutations mentioned in the text was added at the end of the manuscript. Several references to the table were added in the text and highlighted.

Reviewer's Comment:

3) Truncated HBx is commonly found to be integrated into cellular genome. This should be explained clearly.

Answer:

The sentence clarifying this matter was added in the chapter about X gene mutations and highlighted.

Reviewer's Comment:

4) Some typos such as "weather" (should be "whether") and "CCC DNA" (should be "cccDNA") should be corrected.

Answer:

The typing errors were corrected throughout the text and language polishing was performed.

(3)Editor's comments:

1.) Please write a summary of less than 100 words to outline the most innovative and important arguments and core contents in your paper to attract readers.

Answer:

The core tip was added to the manuscript to outline the core contents of the paper.

2.) Please add DOI citation to the reference list and list all authors. Please revise throughout. The author should provide the first page of the paper without PMID and DOI.

Answer:

DOI citation was added wherever available. PMID is present for all references.

3 References and typesetting were corrected throughout the text.

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

A handwritten signature in blue ink, appearing to read 'I. Lazarevic', is shown on a light blue rectangular background.

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