August 08th, 2016

Dear Editor,

Please find enclosed the revised manuscript in Word format (file name: 28019-Revised Manuscript). Below, we address all comments by the reviewers, and discuss them point-by-point.

Title: *Role of RNA Secondary Structure in Emergence of Compartment Specific Hepatitis B Virus Immune Escape Variants*
Authors: *Sibnarayan Datta, Runu Chakravarty*
Name of Journal: *World Journal of Virology*
ESPS Manuscript No: *28019*

Reviewer's Comments [00504486]

This study has shown that HBV subtype A1 and A2 have entirely different pgRNA secondary structure, which may explain compartment specific selection and preponderance of specific HBV subgenotype with unique mutational pattern. This study has novel findings but there is no direct evidence connection of different pgRNA secondary structure to compartment of HBV subgenotypes and prevalence of specific HBV subgenotype with unique mutational pattern. Therefore, we would like to point out conclusion part: their argument is too strong without direct evidence. Please rewrite this part.

Response: We sincerely thank the reviewer for his/her encouraging comments. We also acknowledge that the results are based on predictions. We have now suitably modified the conclusion part as per the reviewer's comments.

Reviewer's Comments [00504271]

The manuscript by Datta & Chakravarty compares RNA secondary structures of HBV subtypes A1 and A2 to show their differences relating to their clinical and biological feature. Between sequence 341 and 660 the sequences are highly homologous among HBV types A to H (That of type H shows a little difference). Their secondary structures should be compared to demonstrate those between subtypes A1 and A2 are biologically.

Response: We completely agree with the reviewer's comments. However, we wish to add that despite having homology in the sequences (nts 341-600) among HBV genotypes/ subgenotypes of A to H, there are a number of regions/nucleotides that are genotype/subgenotype specific. When looked from the perspective of nts 341-660, sequences belonging to HBV genotypes/subgenotypes of A-H appear to be quite homologous. However, we have observed that when compared from the perspective of global secondary structure of the pgRNA, the homology in the nts 341-660 appear to be not strong enough to conserve the secondary structure of this region of the pgRNA, probably due to other non-homologous or highly variable sequences of the pgRNA. This has already been shown in the present manuscript from the perspective of two different subgenotypes (A1 vs. A2) of the genotype A.

We further wish to inform here that we have already completed a

comparative study on the pgRNA secondary structures for different HBV genotypes/subgenotypes and we have observed very interesting differences in the structure and the base pairing patterns among the genotypes as well as subgenotypes of the same genotype. Since the manuscript has already been communicated elsewhere and is presently '*under review*', we cannot include the suggested comparisons in the present manuscript.

Reviewer's Comments [00503536]

The manuscript written by Datta & Chakravarty describes the difference in the structure of pgRNA between A1 and A2 subgenotypes of HBV and its relation to compartment specific selection and preponderance of specific HBV subgenotype with unique mutational pattern. The data are interesting, but the data are mostly based on the prediction and direct evidence is lacking. Therefore, the discussion and conclusion need to be revised according to the uncertainty.

Response: We sincerely thank the reviewer for his/her interest in our work. We also acknowledge the fact mentioned by the reviewer. We have now modified the relevant sections in the revised manuscript, as per the reviewer's comments.

Thank you again for considering our manuscript for publishing in the World Journal of Virology.

Sincerely yours,

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