Reply to reviewer's comments

Reviewer #1 (Comments for Authors):

This is a good review that summarizes the current knowledge on the role of HFNs in HBV replication. It is generally well written and I believe it will be of interest for the readers of WJG. I have some specific suggestions that may help improve the manuscript:

1- On pg 3, lane 14, "... four types of HBV RNAs..." and on pg 5, lane 22, "... five types of viral RNAs...". Please, adopt one criteria.

→ Reflecting the reviewer's comment, we changed the text (pg3 lane 14) from "four" to "five".

2- Pg 4, lane 14, I would rather say "... more stages than those of most other viruses;"

→According to the reviewer's comment, we revised the text.

3- Pg 5, lane, 14, influenza is not a large virus as well as HBV cannot also be considered a large one. Please, correct the sentence.

→ We just tried to mention that influenza virus (80–120 nanometers) is larger than HBV (42 nanometers) in original manuscript. However, to avoid the readers' confusion, we omitted the 'large' word.

4- Pg 6, second paragraph, would benefit if the reference cited is not a book chapter but rather the original papers.

→ Following the reviewer's recommendation, we have cited with an original paper [27].

[27] Ponsel D, Bruss V. Mapping of amino acid side chains on the surface of hepatitis B virus capsids required for envelopment and virion formation. *Journal of virology*. 2003; **77**(1):416-422 [PMID: 12477846]

5 -Pg 9, references are needed in subsection "Structure of HBV enhancers and their regulatory transcription factors". Also, this subsection is the sole in section "promoters and enhancers in HBV cccDNA". They can, perhaps, be merged.

→Following the reviewer's comments, two subsections are now merged. All references in "Structure of HBV enhancers and their regulatory transcription factors" were already cited and summarized in Table 1.

6- Pg 10, 3rd paragraph: The statement about stimulation of HBV replication as a consequence of mutations is not very precise. Mutations in HBV genome can also have the opposite effect. I understand the authors are referring to a specific mutation but the sentence is very general.

→According to the reviewer's comment, we now added the negative effect of mutation on HBV transcription in revised manuscript.

"On the contrary, a naturally occurring double nucleotide mutation in the HBV core promoter converted a nuclear receptor binding site to an HNF1 binding site resulting in suppression of RNA transcription via interaction between HNF1 and the mutant HBx[51]."

51. Li, J., V. E. Buckwold, M. W. Hon, and J. H. Ou. 1999. Mechanism of suppression of hepatitis B virus precore RNA transcription by a frequent double mutation. J. Virol. 73:1239-1244.

Reviewer #2 (Comments for Authors):

This is an excellent review. HBV infection is a global public health problem. As a template for HBV transcription, cccDNA plays a central role in HBV transcription and replication. Hepatocyte nuclear factors (HNFs) play an important role in cccDNA transcription. This review summarizes and discusses the role of HNFs in HBV life cycle: HNFs regulate cccDNA transcription by directly interacting with HBx, which enhances the DNA-binding activity of HNFs.