A point-by-point response to referees' issues

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Title: Impact of hepatitis B virus infection on hepatic metabolic signaling pathway

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Thanks for your comments on our manuscripts. We appreciate these comments, which help us improve our work. All the new or revised information was marked in red throughout the manuscript. And we would be glad to respond to any further questions and comments that you may have.

And according to the editor's advice, we have used manuscript language editing services, corrected inappropriate grammas and confirmed the revisions. Since the manuscript has been revised significantly, we feel it is better not to highlight the amendments in the revised manuscript. All the revised information was directly marked in red throughout the manuscript.

Reviewer #1 (Reviewer's code: 03257402): *This is a concice review on the impact of HBV infection on hepatic metabolic signaling. This is well written and acceptable.*

Answer: We thank the reviewer for the nice summary and comments.

Reviewer #2 (Reviewer's code: 03521089): *The authors provided a very well written and precise overview about the metabolic responses in the liver during HBV infection, including glucose-, lipid-, nucleic acid- and vitamin-metabolism and the potential consequences for progressive liver disease such as HCC. Format and language a very acceptable, only abbreviations require more consistency throughout the manuscript.*

Answer: Thanks for the insightful comments. Following the reviewer's suggestion, we have revised and kept the abbreviations in a uniform manner throughout the manuscript.

The revised sentence in the manuscript is:

(Page 5) some ~~of them~~ are liver-enriched nuclear receptors such as hepatocyte nuclear factor 4, alpha (HNF4a), CAAT enhancer-binding protein (C/EBP), peroxisome proliferator-activated receptors, alpha/retinoid X receptors, alpha (PPARa/RXRa) and farnesoid X receptor (FXR)[7,8].

(Page 8) Based on HPLC/MS analysis and two-dimensional electrophoresis (2-DE),

(Page 8) ~~Liver fatty~~ Fatty acid binding protein 1 (~~L-FABP or~~ FABP1), responsible for the uptake, metabolism and transport of long-chain fatty acids (LFA)[24], plays a key role in intracellular fatty acid utilization and transport[25].

(Page 10) HBV-infected humanized mice displayed a significant increase in human genes related to the uptake, biosynthesis, and transcriptional regulation of cholesterol, such as low density lipoprotein receptor (LDLR), hydroxymethylglutaryl-coenzyme A ~~(CoA)~~ reductase (~~h~~HMGCR) and ~~h~~SREBP2[40]. Another study provided evidence that HBV exacerbated hepatic cholesterol accumulation *via* up-regulation of LDLR and HMGCR ~~HMGCoAr~~ in HepG2 cells[41].

(Page 11) Previous data provided evidence that retinoic acid could enhance HBV transcription and replication through ~~activating~~ activation of RXRa[53-54].

(Page 11) HBV infection may up-regulate retinoic acid by promoting retinol metabolism and thereby facilitating ~~itself~~ self-replication through activation of RXRa, leading to an increased risk of liver damage, which was considered a positive feedback[56].