Reviewer's report

Title: Downregulation of Toll-like receptor 4 induces suppressive effects on hepatitis B virus-related hepatocellular carcinoma via ERK1/2 signaling

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Reviewer: Vivekanandan Perumal

Reviewer's report:

In this manuscript, Wang et al. describe the role of TLR-4 in HBV-related HCC. The authors demonstrate higher TLR-4 mRNA and proteins levels in a cell line (HepG2.2.15) expressing HBV-protein(s) as compared to other HCC cell lines. The authors also demonstrate an interaction between HBx and TLR-4. The authors also link TLR-4 levels to the phosphorylation of ERK1/2.

While the association of TLR-4 and HCC has been demonstrated earlier, this manuscript sheds light on the role of TLR-4 in HBV-related HCC. This work provides evidence of interaction between a HBV-encoded protein (HBx) and TLR-4. The manuscript is data rich and provides new mechanistic insights on the role of TLR-4 in HBV-related HCC. The manuscript is written in standard English. Appropriate experimental controls are included.

Major comments:

a) The authors describe the use of TLR-4-miRNA (Le-TLR4) and negative control mi-RNA (Le-NC) to study tumorigenicity in nude mice. Do the authors mean si-RNA (and not miRNA) ? If so this is major error and can mislead readers; this error should be fixed throughout the manuscript (in both the text and the figures). If the authors have truly used TLR4-miRNA – what is this miRNA ? Does this miRNA have other known targets that can potentially modulate tumorigenicity ?

b) The authors demonstrate that downregulation of TLR-4 can lead to the inhibition of HepG2.2.15 derived xenografts in athymic nude mice. Since the focus of the manuscript is on HBV-related liver cancer – the authors may consider studying whether or not the downregulation of TLR-4 can lead to the inhibition of HepG cells (without HBV) derived xenografts in athymic nude mice.

Minor comment:

1) The figure legends should be edited for clarity. Each figure and its legend should be sufficient for the reader to understand without having to go back to the text. The authors may consider revising the figure legends.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.
Declaration of competing interests:

I declare that I have no competing interests