



February 7, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 8385-review.doc).

**Title: Immunopathogenesis of chronic hepatitis B**

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**Name of Journal:** *World Journal of Gastroenterology*

**ESPS Manuscript NO: 8385**

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

**Reviewer 02527808:**

**The review is well written comprehensive but missing some clinical aspects& recent data:**

**-The recent discovery that  $\alpha$ -taxilin plays an essential role for release of HBV-DNA containing particles. Needs to be discussed. ( Hoffmann et al - Journal of Hepatology , Pages 934-941, November 2013)**

Reply: We thank this reviewer for his/her insightful comments. The role of  $\alpha$ -taxilin has been added in “Hepatitis B virus, its structure and replication” (in red), as well as the reference.

**- Acute-on-chronic liver failure (ACLF) is a relatively common complication in CHB patients following certain precipitating events. Previous reports have indicated that certain immune cells such as myeloid DCs (mDCs), plasmacytoid DCs (pDCs) and T cell subsets, are enriched into the livers of ACLF patients; (this must be clarified) 33 Zhang et al J. Hepatol. 2008; 49: 396–406.**

Reply: Liver enrichment of plasmacytoid DCs in livers of ACLF patients has been added in “Dendritic cells” (in red), as well as the reference.

**-The issue of using immune markers as indices to guide clinicians in formulating prognosis and treatment decisions ex:**

**\* when CHB patients receive entecavir therapy, the restored cytokine production of NK cells participates in viral clearance. Tjwaet al . J. Hepatol. 2011; 54: 209–18.**

**\*During IFN-a treatment, the dampened Z39Ig (a novelinhibitor of the B7 superfamily) signals from macrophages are also found to be associated with IFN-a responsiveness in CHB Patients Guo et al Clin. Immunol. 2010; 136: 282–91.)**

**\*Restoration of peripheral mDCs was observed during the course of adefovir treatment and may represent a prognostic marker for favorable responses. Similarly, the recovery of functional pDCs during IFN-a therapy may also have the same predictive value.**

**\* A recent study further reported that lamivudine therapy is able to reduce HBV DNA to an undetectable level, but the patients may only exhibit a transient restoration of circulating DC (Zhang et al ,Journal of Gastroenterology and Hepatology 27 (2012) 223–230 ).**

Reply: These points have been added before “Conclusion” (in red).

**- The role of immune molecules such as micro RNAs & The proposed immunotherapeutic strategies for HBV disease include blockade of PD-1/PD-L1 interaction, an anti-apoptotic drug<sup>9</sup> and a monoclonal antibody that specifically recognizes peptide/MHC class I complex (HBc18-27: HLA-A2) on the HBV-infected cell surface or adoptive TCR-redirectioned T cells need to be more clarified & discussed.**

Reply: These points have been added before "Conclusion" (in red).

**- The number of references is in need to be reduced (delete the old one).**

Reply: The list of references has been updated.

Reviewer 02521807:

**This is a thorough and valuable review of the HBV pathogenesis. This reviewer only suggest to include some topics:**

**(i) The role of intrahepatic antibodies to HBc in the pathogenesis of acute liver failure (Farci et al., PNAS 2010);**

Reply: We thank this reviewer for his/her insightful comments. The reference has been added accordingly (in red).

**(ii) Consider to include the study performed by Lang et al (PNAS 2012; 109:1210-5) who described an additional NK cell role in HBV-induced immunopathogenesis.**

The reference has been added accordingly (in red).

**(iii) Typing error should be amended. On page 13 line 3 (actively) and line 6 (double negative NKT).**

Reply: These typos have been corrected (in red).

**(iv) Two abbreviations (FoxP3 and PD-1) appear extensively explained after their first inclusion on the text. Please relocate. Likewise, the abbreviation "Stat1" needs an explanation (page 16, line 9).**

Reply: These abbreviations have been updated.

**(v) The expression "anti-inflammatory cytokines (IFN $\gamma$ )" could be misinterpreted and needs a brief explanation (page 16, line 3).**

IFN $\gamma$  represents Interferon gamma. The expression has been clarified (in red).

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

Sincerely yours,



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