

September 28, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 5285-revised.doc).

**Title:** Role of innate immunity in the development of hepatocellular carcinoma

**Author:** Rajagopal N. Aravalli

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

**ESPS Manuscript NO:** 5285

I thank the reviewers for their valuable comments, which helped greatly in enhancing the quality of this manuscript. As per their suggestions, following changes have been made in this revision:

Reviewer 1

*The addition of a glossary explaining the many abbreviations might improve the readability.*

As suggested by this reviewer, a glossary of all abbreviations used in this manuscript has been added to this revision in page 3.

Reviewer 2

*1. Correlation between TLR expression and tumor staging/grading.*

This is a very good point. Unfortunately, however, there is no clear information on the correlation between each TLR expression and tumor staging in the literature. Therefore, this issue has not been covered in this revision.

*2. TLR polymorphisms and HCC susceptibility.*

As per this reviewer's suggestion, a section on TLR polymorphisms and risk of developing HCC has been added to this revised manuscript in page 15.

Reviewer 3

*1. Diet should not be a risk factor of HCC unless author point out what kind of diet increase the prevalence of HCC...*

As reviewer suggested, 'diet' and 'coffee' were deleted from the first paragraph of Introduction.

*2. In the Abstract section, the order of HCC risk factors should be re-organized.*

As per this reviewer's suggestions, the order of HCC risk factors have been changed in the Abstract.

*3. Some contents about HBV should be added, such as TLR-mediated immune responses down-regulate HBV replication, and the interactions between HBV and key molecules on the TLR signaling pathways, etc.*

As per this suggestion, text has been modified in pages 4, to underscore the interaction of HBV components in regulating TLR signaling, and down-regulation of HBV by TLR-mediated immune responses.

4. *I like to believe that chronic infection with HBV and/or HCV and imbalanced immunity contribute to chronic inflammation, while TLR activation might be one of the intermediate steps of the infection-caused chronic inflammation.*

I agree with the reviewer's comment and the sentence in page 12 has been modified accordingly.

5. *Co-infection with HBV and HCV contributes to a higher risk of HCC than the infection with HBV or HCV alone, however the co-infection is generally rare.*

I agree with the reviewer's comment and the sentence in page 10 has been modified accordingly.

6. *The section about microRNAs in this paper should be simplified.*

The section on microRNAs has been modified.

7. *There are too many abbreviations in this manuscript, which make this manuscript difficult to read.*

In response to this comment, a glossary listing all the abbreviations used in this manuscript has been included in this revision on page 3.

#### Reviewer 4

*Although the author mentioned about sorafenib (this drug is usually thought to work on the step of progression), he does not discuss about the role of innate immunity in progression of HCC.*

I would like to clarify that sorafenib was mentioned in the 'Conclusion' section just as an analogy to underscore the importance of targeting multiple signaling pathways simultaneously (rather than a single pathway) as a successful strategy for combating HCC, but not to discuss the progression of HCC.

In addition, figure 1 has been slightly modified to include 'free fatty acids'. All the changes in the text were **underlined**. As you have suggested, DOI citation has been added to all references and all authors were listed.

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

Yours sincerely,

Raj Aravalli