August 30, 2015

To:

Editorial Board of World Journal of Hepatology

RE: Manuscript ID: 19855

Highlights Title:
Pathogenesis of Hepatocarcinogenesis in Non-Cirrhotic NAFLD – Potential Mechanistic Pathways

We would like to express our appreciation to the reviewers and editor for spending time and effort to improve our manuscript. Your suggestions were valuable to help us strengthen our work.

Reviewer(s)' Comments to Author:

Reviewer: 1

The authors report the impact of NAFLD on HCC and association to the metabolic syndrome. The prevalence has dramatically increased last decade in industrialized country. The work is well carried out. Minor formatting or typing errors remains.

> **RESPONSE**: We appreciate the reviewer's positive feedback. We have reviewed the formatting and typing elements and revised accordingly.

Reviewer: 2

This review article mean to talk about the pathogenesis of hepatocarcinogenesis in NAFLD, it raises a good topic, actually. With the epidemic of NAFLD, and the increasing number of the related hepatocarcinoma, it is urging to get understand of the potential mechanisms. However, it seems that the authors talked a lot of pro-inflammatory mechanisms of NAFLD and related diseases, while the specific mechanisms that targeting hepatocarcinogenesis are not sufficient.

> **RESPONSE**: We appreciate the reviewer's suggestion regarding the addition of information pertaining specifically to mechanisms underlying hepatocarcinogenesis. We have added an additional paragraph and three references to further elucidate this concern as included below:
>
> "Intrahepatic lipid accumulation, derived from either lipolysis or excess dietary lipid intake, followed by lipid peroxidation contributes to inflammation and ultimately hepatocarcinogenesis.[21] PPARα upregulates

fatty acid disposal in response to increased free fatty acid levels. However, in murine models, PPARα variants accelerate risk for hepatocarcinogenesis. Genetic variants affecting cell signaling (Akt, E-cadherin, β-catenin, ERK, MEK, MET, PI3K, Ras, Rat, mTOR and Wnt) as well as cell cycle regulation (p16, p53, INK4, cyclin's and cdk's) have all been implicated in HCC.[21-23] As differing classes of HCC have been observed in both humans and murine models, unique pathogenetic mechanisms linked to specific genetic variants may explain each class of HCC.[22, 23]"

References:

21. Hill-Baskin AE, Markiewski MM, Buchner DA, Shao H, DeSantis D, Hsiao G, Subramaniam S, Berger NA, Croniger C, Lambris JD, Nadeau JH. Diet-induced hepatocellular carcinoma in genetically predisposed mice. Hum Mol Genet 2009; **18**: 2975-2988. [PMID: 19454484]

22. Tward AD, Jones KD, Yant S, Cheung ST, Fan ST, Chen X, Kay MA, Wang R, Bishop JM. Distinct pathways of genomic progression to benign and malignant tumors of the liver. Proc Natl Acad Sci USA 2007; **104**: 14771-14776. [PMID: 17785413]

23. Coulouarn C, Gomez-Quiroz LE, Lee JS, Kaposi-Novak P, Conner EA, Goldina TA, Onishchenko GE, Factor VM, Thorgeirsson SS. Oncogene-specific gene expression signatures at preneoplastic stage in mic define distinct mechanisms of hepatocarcinogenesis. Hepatology 2006; **44**: 1003-1011. [PMID: 17006931]

In addition, subtitles might be needed to make it more readable.

RESPONSE: We have added subtitles to the manuscript to improve readability.

Once again, we appreciate the time that the reviewer and the editor have spent in bringing these points to our attention. We believe that the manuscript is now much improved, and we hope that the response has been adequate. We again appreciate your consideration for publishing this manuscript in *World Journal of Hepatology*.

Sincerely,

Aijaz Ahmed, MD