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Format for ANSWERING REVIEWERS



April 23, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 10066-review.doc).

Title: The role of Nrf2 in chronic liver disease.

Author: Wei Tang, Yongfang Jiang, Mamadou Diallo, Murugavel Ponnusamy

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 10066

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

1 Format has been updated.

2 Revision has been made according to the suggestions of the reviewer

(1) **Reviewer code:** 02861117: The work is generally pedestrian and poorly written. The paper also needs a great deal of English language polishing. The major advice to authors for improving this review is to incorporate findings of most recent research articles combining it with their own published findings, thus providing the latest information for Nrf2 mediated signaling events in liver diseases. The work is very poorly prepared. This includes issues in English language. The abstract alone is full of grammar and syntax mistakes. I recommend a complete re-write with a sharp eye towards appropriate scientific writing. As is the paper reads like an early draft. Minor comments 1. Too many grammatical and syntax errors in the abstract itself, which are further repeated in the entire manuscript. 2. "And" word is never used to begin the sentence. 3. "be a common mechanism" should be "be a common mechanism" 4. Before start of every bracket sign there should be gap e.g. mechanism (5). 5. In vivo, in vitro should be in italics.

I have revised the review seriously.

- 1). the paper has been revised by two native English speakers.
- 2). "And" word is not used to begin the sentence.
- 3). Changed to be a common mechanism.
- 4). Every bracket sign has been changed.
- 5). In vivo, in vitro had been changed to italics.

(2) **Reviewer code:** 02861340: The authors summarized the role of Nrf2 in the development of chronic liver diseases including viral hepatitis, NASH, and ALD. This is a well-described article, but the reviewer concerns about the below points. 1) In line 21 on page 2, "Cap'n' collar" seems to be a misprinting. 2) In the last line on page 3, "Nr2/ARE" should be "Nrf2/ARE". 3) On page 5, it would be nice to more extensively describe the relationship between HBV replication or proteins and Nrf2 pathway currently known. 4) On page 6, it would be nice to mention about the mechanisms how HCV core, E1, E2, NS4B, and NS5A activate Nrf2. 5) On page 6, activation of Nrf2 by these HCV proteins seems to be an opposite effect against the augmentation of ROS by HCV infection that was reported so far by several research groups . What is the explanation? 6) The authors claimed that Nrf2 activators have great potential as therapeutic agents against oxidative stress. Is there any example known so far for agents that activate Nrf2 pathway? If it is, what is the mechanism for activation of Nrf2

1) Nrf2 is a member of the Cap “n” Collar (CNC) family

2) "Nr2/ARE" is "Nrf2/ARE"

3) We had extensively described the relationship between HBV replication or proteins and Nrf2 pathway.

4) We had mentioned about the mechanisms how HCV core, E1, E2, NS4B, and NS5A activate Nrf2.

5) The biological consequences of Nrf2/ARE pathway regulation are multifaceted. The activation of antioxidant defense system during HCV protein expression, as in acute HCV infection, can mitigate harmful effects of oxidative stress protecting affected cells. However, activation of Nrf2/ARE pathway may also alleviate the ROS-mediated inhibition of virus replication and trigger cell transformation. We have only studied the molecular mechanisms of regulation of Nrf2/ARE pathway by individual HCV proteins during the initial steps of their expression in Huh7 cells. Further studies are required to gain a systematic understanding of the in-put of oxidative stress into the pathogenesis of HCV infection and HCV-related disorders.

6) Recently, dimethyl fumarate (BG-12) was approved by the European Union and the FDA for relapsing-remitting MS. BG-12 seems to be at least equally effective as, if not more effective than, established injectable therapies. Moreover, the ability of DMF to activate Nrf2 underpins the cytoprotective modality that further augments the natural antioxidant responses in MS tissues.



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(3) **Reviewer code:** 02861276: The message would come across better if the language were more succinct. Besides, the patterns of the article need to be modified

The paper had been revised by two native English speakers.
The patterns of the article had been modified.

(4) **Reviewer code:** 02861134: The subject matter of research problem is highly appreciable. It will surely make a contribution to the relevant field of research. The presentation of thoughts in the paper is notable. The paper is well organized. In my opinion, the paper is publishable with no significant revision.

Thanks



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3 References and typesetting were corrected

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

Sincerely yours,

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