November 1, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 5228-review.doc).

Title: Mitochondrial DNA alterations and mitochondrial dysfunction in the progression of hepatocellular carcinoma

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Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 5228

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) According to the reviewer's suggestions, we have added two paragraphs and references in the text as following:

"Although mtDNA alterations have been identified in HCC, it remains controversial whether mtDNA alterations are correlated with the initiation and progression of HCC. To dissect the role of mtDNA alterations in HCC, a larger sample size of HCC is required in future research. Moreover, some lines of evidence suggest that mitochondrial dysfunction and the dysfunctions caused by mtDNA alterations have the potential to contribute to tumor progression. However, whether a specific mtDNA mutation plays a driving force or is an indirect consequence of HCC progression requires further evaluation. Therefore, it is important to develop a strategy to dissect the role of specific mtDNA mutations in cancer progression and/or to exclude non-causal epiphenomena.

Because the coordination between the nDNA and mtDNA is important for the maintenance of mitochondrial structure and function [14, 17], mutations in the nDNA-encoded genes that are responsible for mtDNA integrity and/or mitochondrial function may play an important role in tumorigenesis and cancer progression. For example, it was recently reported that defects in P53 [70], mitochondrial DNA polymerase γ [71], and mitochondrial deacetylase SIRT3 [72] may affect mtDNA integrity and promote tumorigenesis. In addition, not only mtDNA mutations but also mitochondrial dysfunction caused by nDNA mutations, oncogenes, and tumor microenvironments (hypoxia and inflammation) are suggested to underlie energy metabolism reprogramming (or the Warburg effect) [73, 74]. In summary, the interaction between mtDNA and nDNA may play an important role in the initiation and progression of HCC."

3 References and typesetting were corrected.

4 The manuscript has been was edited for proper English language, grammar, punctuation, spelling, and overall style by one or more of the highly qualified native English speaking editors at American Journal Experts.

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

Sincerely yours,

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