

February 14, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 6636-revised review.docx).

Title: Hypoxia and Fatty Liver

Author: Tomohiro Suzuki, Satoko Shinjo, Takatomo Arai, Mai Kanai, Nobuhito Goda

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 6636

The authors formatted the revised version according to the Journal request. In addition, the authors draw all figures in black and white and added figure legends for the readers to understand correctly.

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

Reviewer 00006459

Thank you for the reviewer's suggestions. According to the comments, the authors revised the conclusion (page 15), figures, and figure legends. Although the authors would like to modify the first sentence in the last paragraph of page 8, the other reviewer requests us to delete the description about the roles of HIF-1 in heart to focus on its roles in the liver. Therefore we decided to delete the paragraph with the following one.

Reviewer 00011378

Thank you for your comments.

According to the reviewer's suggestion, the revised version focused on the role of HIF in fatty liver. Therefore, the authors delete two paragraphs (from line 18, page 8 to line 16, page 9 in the first version). The authors added the sentences describing controversy as to the importance of SCD-1 in FLD and beneficial effects of PPAR γ agonist with references 12-15 and 18-21, respectively (line 8-10 and line 18-20, page 5, respectively). The authors also added description as to possible involvement of mitochondria in the prevention of NAFLD with a new reference the reviewer indicated (last sentence, page 10). In OSA part, we added an important report showing relationship of OSA and liver injury, fatty liver, and fibrosis (line 17-19, page 13). These modifications clearly improve the manuscript and the authors would like to appreciate the reviewer's suggestions.

Reviewer 00053727

According to the reviewer's suggestion, we added a table of HIF target genes (table 1), and put a new paragraph describing the role of HIF target genes in FLD, especially focusing their roles in liver fibrosis (last paragraph in page 11 and page 12). The authors greatly appreciate the reviewer to improve the quality of our manuscript.

Reviewer 00058441

The authors thank for reviewer's suggestion. The authors discuss the importance of "hypermetabolic state" for liver hypoxia in FLD in page 8. Figure 1 was renewed and drawn in black and white.

Reviewer 00068657

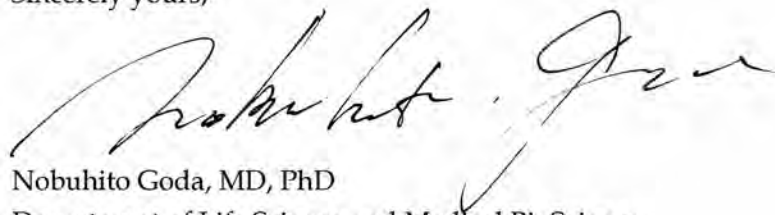
The authors greatly appreciate the reviewer's comments to improve our manuscript. The authors described the effects of loss of HIF-1 α on SREBP expression and its activity in detail (2nd paragraph, page 10) according to the reviewer's comments. The authors hope these changes help the readers understand the relationship between the two transcriptional factors in the development of FLD. In addition, we deleted all our unpublished results in the revised version.

Reviewer 00069618

According to the reviewer's suggestion, we added a new paragraph describing the role of HIF target genes in FLD, especially focusing their roles in liver fibrosis (last paragraph in page 11 and page 12). Although little information as to possible application of chemicals modulating HIF activity for liver disease is now available, the authors described one example showing protective effects of DMOG, HIF activator, for alcoholic fatty liver in mice model (line 18-20, page 10). The authors greatly appreciate the reviewer to improve the quality of our manuscript.

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

Sincerely yours,

A handwritten signature in black ink, appearing to read 'Nobuhito Goda', with a stylized flourish at the end.

Nobuhito Goda, MD, PhD

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