

May 25, 2016

Professor Lian-Sheng Ma

Editor-in-Chief

*World Journal of Gastroenterology*

**Manuscript's invitation number 02570358, written by Koji Fujita and Tsutomu Masaki.**

Dear Professor Lian-Sheng Ma,

Thank you for editing our manuscript and improving the quality of this article. We have modified our manuscript in accordance with your comments and the reviewers' suggested revisions.

To reviewer *03452795*,

Thank you for kindly proposing detailed revisions to our manuscript.

- a. We corrected 'Kessler I. I.' to 'Kessler' by deleting 'I.I.' in line 3 of page 7.
- b. We cited two publications addressing cell cycle arrest induced by metformin and the downregulation of p21<sup>CIP</sup> and p27<sup>KIP</sup> in line 8-10 of page 15.

To reviewer *02860846*,

Thank you for your contribution to improving the quality of our manuscript.

- a. We modified the manuscript's title to 'Diabetes mellitus and metformin in hepatocellular carcinoma' in line 1 of page 1 because metformin's anti-cancer activity in HCC was discussed only in a diabetes-specific context.
- b. We expanded the miRNA-related section in line 6-9 of page 16, particularly with respect to miRNAs related to metformin's anti-cancer activity and their target messenger RNAs in HCC. We added a review article by Pulito *et al* in 11-13 of page 16, regarding miRNAs downstream of metformin in malignancies to benefit readers interested in miRNAs.
- c. We expanded the conclusion in line 19-23 of page 17, by mentioning newly developed topics, such as an AMPK-independent pathway, miRNAs and cancer stem cells.

To the editors ,

- a. We had the language in our manuscripts polished again by native speakers. We

touched in a draft certificate about language polishing published by American Journal Experts.

- b. We had to correct first name of a co-author, Dr Tadokoro in line 4 of page 1.

We are greatly honored by the fact that you are considering our manuscript for publication. Thank you.