May 5, 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 17789-review.doc).

Title: Genetic and epigenetic aspects of initiation and progression of hepatocellular carcinoma

Author: Mitsuro Kanda, Hiroyuki Sugimoto, Yasuhiro Kodera

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 17789

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 02766291
- In general, the review is well structured, although it lacks figures and/or diagrams for clarification (i.e. a schematic representation of the mechanisms of genetic or epigenetic alteration of the status in HCC). The topic discussed in the review has already been fully covered by others, even recently and also in the WJG (2014 Epigenetics in hepatocellular carcinoma: An update and future perspectives therapy WJG). However, the targets and the miRNA analyzed here are relatively new and there are many recent articles that are cited in this review (2014-2015). It must be said that the paragraphs concerning the individual genes are poorly developed. For example on SIRT1 and HCC there are many recent articles that may help to deepen the topic. (Zhang ZY et al. J Hepatol 2015 62, 121-130; Song S et al. J Coll Physicians Surg Pak 2014 24, 849-854; Bae HJ Oncogene 2014 15 (20), 2557-2567). Furthermore, there are three articles on TPX2 and HCC published in the 2014 that may help to deepen the subject of the review. Also the Authors should clarify what are the criteria by which they choose some genes (very few!) from Table I to be analyzed in detail. Minor points The name of the genes must be written in italics
Reply) We thank the Reviewer for this thoughtful suggestion. The primary goal of this study was to introduce the latest discovery of molecular aspect of HCC. Therefore, the lists of molecules in this review are different from those of the earlier reviews with similar topics. According to your suggestion, some more evidences for *SIRT1* and *TPX2* have been added in the text to deepen the topic. We picked up representative genes by the following criteria; 1) highly-innovative genes or miRNAs, 2) data from relatively large number of patients, 3) solid data by functional analyses or in vivo study. This criteria has been added in the text. In the revised manuscript, the names of the genes are written in italics.

(2) Reviewer 03251929
- This review article has extensively summarized the findings of the following genes in HCC: IL6, MACC1, SIRT1, TPX2, TREM1, MAGE, ARNT, BTG1, GPX3, FBLN5. The review has also summarized some deregulated epigenetically silenced genes (TIF1a, DPTSL3, DPT, PDSS2) and some microRNAs (miR-128-2, miR-148, miR-331). The manuscript has provided substantial amount of information but the rationales for the gene list remain unclear. I think the authors should strengthen the links between the genes and explain the choice of their genes. Otherwise, authors would feel that the manuscript is lack of focus. My major concern is the context of the manuscript. Other than that, the manuscript is written fluently and clearly.
Reply) Thank you for your favorable comments. The primary goal of this study was to introduce the latest discovery of molecular aspect of HCC without confinement to specific gene groups, functions

and pathways. Therefore, there are no rationales for the gene list in this review. We picked up representative genes by the following criteria; 1) highly-innovative genes or miRNAs, 2) data from relatively large number of patients, 3) solid data by functional analyses or in vivo study. This criteria has been added in the text.

(3) Reviewer 03015689
- This article presents a very comprehensive list of genes involved in the field of HCC in a very clear and methodical way, being the sources used excellent and the information very up to date. In my opinion the article could greatly benefit from the addition of a sum up of the most relevant or useful genes in clinical practice so that the reader can have an immediate idea of which are the most important ones.Regarding readability, it has a very reader friendly approach. I have thoroughly enjoyed reviewing your article and I am looking forward to reading the next one.
Reply) Thank you for your favorable comment encouraging us.

3 Languages and typesetting were corrected throughout the manuscript.

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

Sincerely yours,

Mitsuro Kanda, MD, PhD,

Department of Gastroenterological Surgery (Surgery II),
Nagoya University Graduate School of Medicine,
65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan.
Tel: +81-52-744-2249, fax: +81-52-744-2252, e-mail: m-kanda@med.nagoya-u.ac.jp