Editor-in-Chief
World Journal of Gastroenterology
Lian-Sheng Ma

Dear Dr. Ma:

Thank you for considering our manuscript “Targeting Wnt/ β-catenin Pathway in Hepatocellular Carcinoma Treatment” for publication at the World Journal of Gastroenterology. We will respond to the reviewers’ comments in a point by point basis:

Reviewer 1:

1 - Author contributions: “devoping” -> in developing
We have change the spelling on page 1.

2 - (Abstract): “The main focus of this review is underlie the role of β-catenin pathway on hepatocarcinogenesis, liver cancer stem cell (LCSC) maintenance and small molecules targeting the Wnt/β-catenin pathway with potential application for treatment of HCC.“ - Please correct this sentence”.
We have changed the last sentence of the abstract (Page 2).
“We aim to review the role of β-catenin pathway on hepatocarcinogenesis and liver cancer stem cell (LCSC) maintenance. We also evaluated the use of small molecules targeting the Wnt/β-catenin pathway with potential application for treatment of HCC.”

3 - Page 7, third paragraph: “Based on recent studies indicating the important role of Wnt/β-catenin signaling an in the maintenance of CSCs,…” - Please clarify this statement.
We have addressed this comment by changing the sentence as follows (see page 9):
“Based on recent studies indicating the important role of Wnt/β-catenin signaling in the maintenance of CSCs, there is increasing interest in developing new compounds to inhibit this pathway”

4 - Figure 1: Was this figure produced by the authors or was it taken from somewhere else?
This was done by the first author based on the description of the pathway.

5 - Lingustic and stylistic problems/typing errors ("Liu et al. shown that…" (p. 5), "Others reports" (p. 6), "desctruction complex" (p. 8), etc.).

"Liu et al. shown that…" (p. 5, now page 7): Liu *et al*[1] showed that human zinc finger protein 191 (ZNF191) is a potential regulator of the β-catenin transcription, found to be significantly overexpressed in human HCC specimens and associated with growth of human HCC cells

"Others reports" (p. 6; now page 8): Other reports

"desctruction complex" (p. 8, now page 10): destruction complex

Reviewer 2:

1 - CD44 and CD133 are popular as cancer stem cell markers. As for HCC, CD44 is less popular. But the authors state both markers at the same weight. Did the author think CD44 as a cancer stem cell marker of HCC?

2 - PLC is positive with CD44.

3 - What is "non-liver cancer stem cell lines"?: It was changed to HCC cell lines (see page 8).

CD133+ cells were first reported as a marker of a CSC subset in HCC by Suetsugu et al. CD44, another LCSC marker, has been associated with tumor cell invasion and migration in liver cancer. In HCC studies, CD44 showed to be an important marker used in combination with other markers to enrich LCSCs. Cells co-expressing CD133 and CD44, or CD90 and CD44, present a more aggressive phenotype than cells with a positive expression of either CD133 or CD90 alone. We think that CD133 and CD44 are two important markers of LCSC but there are many others described as well. See references below.

Regarding to PLC being positive for CD44, we completely agree with the reviewer's comment. The most commonly used HCC cell lines to study liver cancer in experimental models such as Huh7, PLC, Hep3B and others have a small subset of cells expressing LCSC markers such as CD133, CD44, EPCAM, etc. Our group has isolated CD133+ and CD44+ alone and in combination from Huh7 using cell sorting by flow cytometry.

1. Suetsugu A, Nagaki M, Aoki H, Motohashi T, Kunisada T, Moriwaki H. Characterization of CD133+ hepatocellular carcinoma cells as cancer stem/progenitor cells. *Biochemical and biophysical research communications* 2006; **351**(4): 820-824

2. Hou Y, Zou Q, Ge R, Shen F, Wang Y. The critical role of CD133+CD44+/high tumor cells in hematogenous metastasis of liver cancers. Cell Research 2012;22:259-272.
3. Zhu Z, Hao X, Yan M, Yao M, Ge C, Gu J, et al. Cancer stem/progenitor cells are highly enriched in CD133+CD44+ population in hepatocellular carcinoma. Int. J. Cancer 2010;126:2067-2078.
4. Tovuu LO, Imura S, Utsunomiya T, Morine Y, Ikemoto T, Arakawa Y, et al. Role of CD44 expression in non-tumor tissue on intrahepatic recurrence of hepatocellular carcinoma. Int J Clin Oncol 2013;18:651-656.

We addressed spelling issues in the text as suggested by the reviewers.

Thank you for your time and consideration in this matter,
Let us know if we need to do anything else.
Sincerely,

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