Reviewer’s report

Title: Paracrine effects of CCN3 from non-cancerous hepatic cells increase signaling and progression of hepatocellular carcinoma

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Reviewer: Yin-Ying Dong

Reviewer's report:

In this study, the authors sought to assess the role of hepatic cells and HSCs in the malignant progression of hepatocellular carcinoma. The study was conducted using tissue microarrays and cell lines. There are multiple findings in the study, of which the major one is that CCN3 secreted from hepatic cells was related with enhanced potential of EMT, proliferation and metastasis of HCC. They also find that CCN3 was inversely related to cirrhosis, regulating HSCs through a negative feedback loop. HSCs and activated hepatic cells both exert paracrine effects to promote HCC progression.

This is a generally well designed study aimed to addresses a novel question. And the language description is idiomatic. However, the authors need clarify several issues that may potentially strengthen their interpretations, and some minor revisions are still needed.

Comments:

1. In table1 the quantitative unit of AFP is μg/L, while in table2 the unit of quantity is missing. Please correct this minor problem.

2. In figure legend 4, (Page22 line 20) the author described the E and F, while there is lack of relevant instructions in the result part.

3. Cause figures in this manuscript is missing, I am not sure the legend describe well for figures.

4. On page 15 the description may be not accurate enough "we found that CCN3 expression was a useful but insufficient marker alone to predict prognosis of patients with HCC. Thus, exclusive targeting of CCN3 may have limited efficacy in treating HCC progression". And I think the author may want to describe " Although cirrhosis promoting tumors progression is very clearly, while cirrhosis was insufficient factor alone to predict prognosis of patients with HCC, cause of many cytokines such as CCN3 may influence the relationship between
cirrhosis and HCC progression. Maybe that is way anti-fibrosis is not an very effect way to anti-HCC.

5. As described in the part 2 of Results, "Patients were then divided into four groups according to level of cirrhosis (severe, moderate, mild, and no cirrhosis)". What is the criteria used in dividing the severity of cirrhosis. Please instruct it in the part of Method.

6. Please describe the methods that activate Hepatic LO2 cells by HSC LX2 cells in detail.

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

Yes

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Yes

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

Yes

**Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?**
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

**Quality of written English**
Please indicate the quality of language in the manuscript:

Acceptable

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