Reviewer’s report

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

Version: 2 Date: 13 Feb 2019

Reviewer: Reviewer 2

Reviewer's report:

PEER REVIEWER ASSESSMENTS:

OBJECTIVE - Full research articles: is there a clear objective that addresses a testable research question(s) (brief or other article types: is there a clear objective)?

Yes - there is a clear objective

DESIGN - Is the current approach (including controls and analysis protocols) appropriate for the objective?

Yes - the approach is appropriate

EXECUTION - Are the experiments and analyses performed with technical rigor to allow confidence in the results?

Yes - experiments and analyses were performed appropriately

Statistics - Is the use of statistics in the manuscript appropriate?

Yes - appropriate statistical analyses have been used in the study

INTERPRETATION - Is the current interpretation/discussion of the results reasonable and not overstated?

Yes - the author's interpretation is reasonable
OVERALL MANUSCRIPT POTENTIAL - Is the current version of this work technically sound? If not, can revisions be made to make the work technically sound?

Probably - with minor revisions

PEER REVIEWER COMMENTS:

GENERAL COMMENTS: This study is well conducted and has important results and conclusions. The experiments are well planned and include appropriate controls. Some experimental details are missing and their addition should facilitate the comprehension of the experiences outcome.

REQUESTED REVISIONS:

- Because this study follows a previous study already published on CNN3 expression in the tumor tissue (that was shown to be much higher than the surrounding "healthy" tissue, it would be interesting to show the relative level of expression of CNN3 in the tumor/ in the surrounding tissue/ in the tissue of a normal liver. This will allow a better appreciation of the relative amounts of protein in each tissue region. Because the effect observed on HSC could be the result of diffusion of CNN3 excreted by cancer cells (and not by healthy hepatocytes surrounding the tumor).

- The authors should describe the protocol for "activation" of hepatocytes by HSC in vitro. How long are the cells co-cultured? what is the ratio between HSCs and hepatocyte cell line...

ADDITIONAL REQUESTS/SUGGESTIONS:

Note: This reviewer report can be downloaded - see attached pdf file.

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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