Reviewer's report

Title: Higher Proliferation of Peritumoral Endothelial Cells to IL-6/sIL-6R than Tumoral Endothelial cells in Hepatocellular Carcinoma

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Reviewer: Laura Alaniz

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The authors explored interestingly the mechanism involved in HCC angiogenesis, taking into account the peritumoral endothelial cell (PEC) and the modulation of the important cytokines and factors involved in this type of cancer as IL-6, moreover, studies the IL6/sIL6R complex. They showed that these cell could be considered as potential target for anti-angiogenic treatment in HCC, where angiogenesis is critically associated with the hepatocarcinogenesis. Therefore, the question posed by the authors is very well defined and new.

The manuscript require essential revisions and following comments should be considered for manuscript publication in BMC:

1. IHC results shown in figure 1A should include a representative tissue from one or two week after tumor injection in order to visualize difference observed in the 7th week. Beside, should be include a representative IHC showing both tumor and peritumoral issue in order to visualize the curves indicated in part B, C and D in figure 1. A brief description of how tumor microarray was constructed from mouse. The reference [9] describe the method for human tumor, but the size from human tumor is different in mice.

The authors should indicate the n (number) of mice used in the experiment and How many experiments they were performed?

2. The figure 2 A should be enlarged to distinguish the described increase of HIF-1a and IL-6. Figure 2D shown that IL-6 expression assayed by RT-PCR is lower in hypoxia than normoxia, this right? It is not in concordance with the results in figure 2 B and C.

3. Western blot results require densitometry and statistical analyses. Since the authors have observed variations in proteins expression by this method, only this conclusion could be reached by performing a densitometric analysis and then determining by statistical significance, indicating the number of experiments performed.

4. The authors could discuss the results about the differences observed within peritumoral and tumoral liver tissue after tumor implantation in mice. They should discuss about IL-6 function in liver tumor, taking into account the role of this cytokine in underlying cirrhosis that usually accompanies these tumors. Because a controversial result was found by the authors about gp130 expression unmodulated in PECs under hypoxia condition, they must discuss a possible
mechanism.

5. As suggestion in vitro studies could be performed in different hypoxia protocol in order to confirm the results observed by the authors in PECs.

Minor revision
Several references are indicated as superscript in the text, must be corrected.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests