Reviewer’s report

Title: The occurrence of mesenchymal-epithelial transition and the role of hepatocyte nuclear factor 4alpha in metastatic tumor formation of hepatocellular

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Reviewer: Udayan Apte

Reviewer’s report:

In this manuscript, the authors have studied expression of HNF4a and E-cadherin in human HCC metastasis. The authors show a positive correlation between increased expression of HNF4a and E-cadherin in these metastases. They go on to further show the correlation in expression of E-cadherin and HNF4a in HCC cell lines Hep3B and Huh-7, and increased E-cadherin expression in SK-Hep-1 cells following expression of HNF4a using a human HNF4a expression vector. These are very preliminary studies, which require further examination using animal models and additional number of human samples.

Major Compulsory Revisions.

1. In this study the authors use the presence of E-cadherin as the primary means of showing MET. In figure 4 they also show staining for Vimentin. It may be a good idea to look at multiple marks of MET (vimentin, fibronectin, N-cadherin, etc.). This would help strengthen one of the main themes of this manuscript. It would be nice to see staining for more of these markers throughout the clinical samples.

2. Studies include only 10 human samples. Additional samples are required.

Minor Essential Revisions:

1. It is confusing as to what the y-axis in Figure 1B and 2B is. There is no label. Is this referring to the scoring system based upon E-cadherin expression (none, weak, intermediate, strong)? Also, the figure legend needs rewritten. This is also confusing as to what we are looking at in this figure.

2. In the text describing Figure 1D and 2D it is said that the normal adjacent tissue has increased expression of E-cadherin as compared to distant metastases. It may be a good idea to show the distant metastases as well for a direct comparison.

3. In Figure 2C the distant metastases show increased expression of HNF4a, but it looks to be diffuse throughout the cell and not at a high concentration within the nucleus. Is there any explanation for this? Would this alter its activation of E-cadherin expression?

4. What may be an explanation for the comparable Vimentin expression in
SK-Hep-1 cells and Hep3B cells since Vimentin is another marker for MET? Does HNF4a have nothing to do with Vimentin expression? This is where it may be nice to have Vimentin staining done throughout the clinical samples to help with this comparison and make things a little more clear.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests