Reviewer's report

Title: Hypoxia induces epithelial-mesenchymal transition via activation of SNAIL by hypoxia-inducible factor -1a in hepatocellular carcinoma

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Reviewer: Cecilia Sahlgren

Reviewer's report:

Although the question posed by the authors is interesting and important, the work does not raise our knowledge on the association between hypoxia and aggressive metastatic tumor growth nor does it enhance the molecular insight of the link between HIF and Snail, an inducer of epithelial mesenchymal transition (EMT). The link between hypoxia and EMT is already demonstrated for a number of cancer types, as is the direct regulation of Snail by HIF. The novelty is restricted to the extension of this already quite established paradigm to hepatocellular carcinoma and hence is of highest interest for those focused on this particular disease. As the authors include data pointing to the clinical relevance of the findings the work merits publication given that the comments below are addressed. This will require a major revision as the data as it stands is merely correlative and not conclusive.

Major:
The authors do not conclusively show that Snail is responsible for the hypoxia/HIF induced EMT. Experiments with down regulation of Snail should be included.

The authors demonstrate that Co2Cl treatment and HIF induces expression of luciferase form a snail promoter construct containing HRE sequences. The direct association of HIF on the Snail promoter should be demonstrated by ChiP assays.

The statistical data in the first result section is not correctly expressed.

The experiments with Co2Cl treatment should be repeated with hypoxia.

The authors should include references to work establishing both direct and indirect links between hypoxia and Snail expression.

The reoxygenation mechanisms should be studied in more detail. What happens on the protein and cellular level? Is it a EMT-MET transition?

Minor

The text should be proof read and corrected

The E-cadherin blots should be repeated and quantified
A control/normoxia image with more confluent cells in Figure 2A should be included.