

**Please provide specific point-to-point replies to each reviewer's comments.**

**Response to Reviewer #1:**

**[Comment 1]** briefly expand this part indicating the relevance of the oxygen gradient within the hepatic lobule in gene expression. Linked to the above consideration, are the authors aware of any relation between oxygenation and intra-tumoral heterogeneity? It would be nice to briefly discuss this aspect.

**[Answer 1]** This is a valuable comment. Thank you for raising the question of the impacts of hypoxia on heterogeneity. Despite of limited direct evidence of hypoxia-dependent heterogeneity, there are plenty of studies on hypoxia-related stemness and CSCs. We believe it is a conserved mechanism in both physiological and pathological conditions and a potential target for CSC treatments. Hence, we have a brief discussion on hypoxia and stemness in the CSC section as an example of emerging treatment strategies.

**Response to Reviewer #2:**

**[Comment 1]** Title: since the focus almost solely related to HCC it may be possible to update the title to HCC as otherwise the data to cholangiocellular cancer is missing.

**[Answer 1]** Thank you for this comment. We did some retrieval work but hardly find any researches on heterogeneity of cholangiocellular cancer. So, we change the title to HCC for a more accurate description.

**Response to Reviewer #3:**

**[Comment 1]** the manuscript is interesting and well structured.

**[Answer 1]** Thank you for your appreciation.