Reviewer 2:

The manuscript "Derivation and applications of human hepatocyte-like cells" by Li S et al., is a comprehensive description of the latest advances and potential applications of Human hepatocyte-like cells (HLCs). Since HLCs usually exhibit immature features and great heterogeneity, the authors review the main recent advances to improve cell culture conditions and genome editing, which are necessary before translation to the clinic. The authors emphasize the derivation of HLCs from hPSCs, and possible uses of these cells in the study of rare diseases and population genetics, among other applications. The authors' work is relevant since there is an increase in prevalence of liver diseases which requires both: more effective treatments, and the improvement of cell yielding for transplantation. Also, the manuscript describes the current available differentiation protocols and their consecutive steps: endoderm differentiation, hepatic induction, and liver maturation and it provides different optimization strategies to improve maturation and decrease HLCs heterogeneity. Major point: The manuscript is relevant, interesting and well written, however, one of the most critical aspects related with translation of stem cells to the clinic, is that these cells frequently acquire cancer cell properties. Even when the authors state that the cell source for transplantation should have no tumorigenic risk, they don´t analyze this very important problem. Therefore, I would strongly recommend adding a paragraph which includes the relevance of this issue and the improvements and difficulties in this area.

Response: Thanks very much for the valuable suggestion. We included a new paragraph discussing the potential causes of the tumorigenic risks as well as potential approaches to reduce risks in the revised manuscript. The paragraph is also included below for easier assessment.

"Plus, the potential tumorigenic risk of transplanted HLCs has to be carefully considered. Specifically, tumor cells can arise from cells with residual expression of factors in iPSC reprogramming process (e.g., the myc expression), undifferentiated iPSCs remaining in the culture, and cells with mutations or karyotype abnormalities caught in the rather long *in vitro* culture and differentiation processes. Several approaches can be adopted to reduce the tumorigenic risk: 1) use integrating-free viruses or small molecules for iPSC reprogramming[80, 81]; 2) improve the *in vitro* culture conditions and enhance the differentiation efficiency of hPSC-derived HLCs [82]; 3) remove undifferentiated iPSCs, e.g. through treatments with small molecules or antibodies that can specifically target iPSCs[83] [84]; or enrich HLCs using HLC specific surface markers before transplantation[85]; 4) monitor the genome integrity of cells at the iPSC stage and the HLC stage, through karyotype analysis and whole-genome sequencing; 5) engineer a self-killing circuit in cells that would allow the trigger of cell death *in vivo* to remove tumorigenic cells, if necessary, to further assure safety[86]".