Reviewer’s report

Title: Endothelial cells do not arise from tumor-initiating cells in human hepatocellular carcinoma

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Reviewer: Matias A Avila

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In this work Ghanekar et al. address the issue of the origin of endothelial cells in new blood vessels formed in the vascularization of HCCs. In particular the aspect evaluated here is whether these endothelial cells derive from the host tissues or are originated from cancer stem cells/tumor-initiating cells (TICs) within the tumor tissue. They employ an experimental model of xenograft in which human HCC cells isolated in their laboratory from primary tumors are implanted by intrasplenic injection in immunodeficient mice, and also study new HCCs developed in human livers from female donors transplanted in male patients. Through different labeling procedures that distinguish human and mouse endothelial cells markers, as well as FISH for X and Y chromosomes, they conclude that new blood vessels formed in tumors only contain endothelial cells derived from the host, not the HCC tissues (TICs). This is a very interesting study, with relevant information, and its limitations have been clearly discussed by the authors. There are some issues that need attention.

Major compulsory revisions

1. The number of experiments performed in the xenograft mouse model need to be clearly mentioned in the Materials and Methods section. To be more conclusive this experiment should be repeated at least three times in duplicates using different HCC cell isolates.

2. The individual panels (A, B, C, etc) presented in Figures 2, 3 and 4 should be better described in the main text. There is not a direct reference for the information presented in each panel, rather the authors make a general reference to the figure in the text, and this is not appropriate for a rigorous description of the results.

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'