Reviewer's report

Title: Decreased PCSK9 expression in human Hepatocellular Carcinoma

Version: 2
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Reviewer: Bertrand Cariou

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In this article, Bhat et al addressed an important question concerning the potential link between PCSK9 and liver carcinogenesis. Some preclinical data in mouse suggest that PCSK9 could play a role in liver regeneration and potentially carcinogenesis. However, there is no data available in humans yet. Unfortunately, the data presented here don't support the extensive conclusions drawn by the authors.

Major Revisions:

1. Concerning the immunohistochemistry data, some controls are lacking. Indeed, the authors only compared PCSK9 expression in HCC and in adjacent cirrhotic liver. What is the expression of PCSK9 in normal liver? At this time, it remains unclear whether PCSK9 is downregulated in HCC or overexpressed in fibrotic liver?

2. The patients are heterogeneous with a mix of hepatitis B & C, NASH, alcholic cirrhosis, etc... It should be remind here that it has been suggested that PCSK9 can play a role in the pathophysiology of hepatitis C by controlling the expression of some specific receptors involved in the uptake of the viruses (LDL-R, CD81). The authors should perform a regression analysis to determine whether the etiology of liver disease alters the results of PCSK9 expression in HCC.

3. It's a pity that plasma PCSK9 levels were not measured in the same population than those for PCSK9 expression in HCC. The number of controls is very small...What are the clinical characteristics (etiology of liver disease) of the patients?

4. Since it has been demonstrated that the effect of PCSK9 in liver regeneration is dependent of cholesterol intake in mice, the plasma lipid parameters of the studied patients for PCSK9 expression analyses must be described.

Minor points:

1. The quality of the figure 2 is poor

2. For Q-PCR analyses, more than only 1 house-keeping (18S) gene must be used.

3. The discussion is very speculative (notably concerning the link between PCSK9 and LDL-R expression, in the absence of LDL-R expression data....)
**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

I declare that I have no competing interests below.