Reviewer’s report

Title: Pitavastatin suppresses diethylnitrosamine-induced liver preneoplasms in male C57BL/KsJ-db/db obese mice

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Reviewer: Diego F Calvisi

Reviewer’s report:

Mounting evidence indicate that obesity and aberrant lipid biosynthesis are involved in the development and progression of human hepatocellular carcinoma. In the present manuscript, Shimizu et al. examined the effects of the hypolipidemic drug pitavastatin on the development of liver preneoplastic lesions in C57BL/KsJ-db/db (db/db) obese mice induced by the hepatocarcinogen diethylnitrosamine (DEN). The results indicate that pitavastatin administration is able to significantly inhibit the development of hepatic preneoplastic lesions, when compared to untreated mice. Treatment with pitavastatin improved liver steatosis, decreased free fatty acid, total cholesterol, and aminotransferases levels, while increasing hepatic AMPK expression and adiponectin levels in the serum. Also, pivastatin decreased the serum levels of tumor necrosis factor alpha and the expression of TNF-alpha and interleukin-6 in the liver. The Authors conclude that pitavastatin significantly inhibits the early phase of obesity-induced hepatocarcinogenesis and it may be useful in the chemoprevention of liver cancer in obese individuals.

The paper by Shimizu et al. is novel, well written, and the methodologies used are appropriate. The data are compelling and solid. The main strength of the paper is the convince demonstration of liver antineoplastic potential in the absence of major side effects of the cholesterol lowering drug pitavastatin.

To undoubtedly add value to the present manuscript, few issues need to be addressed by the Authors.

Minor Essential Revisions:

1.) The Authors determined the levels of total and activated (phosphorylated) AMPK protein. Is this AMPK-alpha? Please clarify this point in the revised version of the manuscript.

2.) Authors should briefly summarize either in the Introduction or in the Discussion section the findings of aberrant lipogenesis in human HCC with the appropriate references.

3.) In the Materials and Methods section, the Authors should briefly describe the criteria to define foci. This would be highly helpful to the Readers who are not expert in the field.

4.) In Figure 1B only the graphs of FCA number in treated and untreated mice are shown. The Authors should add a low magnification picture from livers of
both groups (treated and untreated) showing the morphologic differences.

5.) Authors should determine whether pitavastatin treatment results in decrease of proliferation and/or increase of apoptosis in FCA. These data will add mechanistic evidence to the present study.

6.) It is known that antineoplastic activity of statins might be also partly independent on their activity toward cholesterol levels. The Authors should briefly comment this issue in the Discussion section.

**Level of interest:** An article of outstanding merit and interest 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