Reviewer's report

Title: IL-6, through p-STAT3 rather than p-STAT1, activates hepatocarcinogenesis and affects survival of hepatocellular carcinoma patients

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Reviewer: Federico Moriconi

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Major points of criticisms:

1) The authors write that tissue p-STAT-3 presents a predominant immunostain rate unlike p-STAT-1 in all HCC specimens. On the upper side of Fig. 4-1 (Picture p-STAT-1 Level I) there is too much background that makes this picture not comparable with the lower figure (p-STAT-3 Level I) showing a significant positivity for STAT-3. This figure must be removed and replaced by a new one with less background. Moreover, I see a strong positivity for STAT-1, but not for STAT-3, for Level II mostly in the peripheral parenchyma of the slide. This is in contrast with your results. How do you explain it and which cells are these? According to the IHC studies presented, I can see a difference of detection in favor of STAT-3 only for Level I but not for Level II and III, as is reported by the authors.

2) Are only hepatocytes to express STAT-3? Did the authors make an Heppar-1 staining?

In a recent published brilliant study, Dokduang H et al. (J Hepatobil. Pancreat. Sci. 2014 Jul 16; doi: 10.1002/jhbp.131. Epub ahead of print) analyzed the expression of STATs proteins in human cholangiocarcinoma tissues. Interestingly, the expression of STAT-3 was significantly associated with a shorter survival of tumor patients supporting the theory of Kao JT et al. Moreover, Dokduang et al. detected STATs protein mainly in the cytoplasm of the inflamed bile duct and in bile duct cancer cells.

The authors must show more in detail and with better quality of IHC studies STAT-3 expression profile and comment their results in the discussion section also according to the study of Dokduang et al. Differences in the expression of STAT-3 in two biologically and histologically different tumor entities, such as HCC and CC, could open a new scenario in explaining the role of STAT-3/IL-6 at the precancerous stage and possibly in identifying a new biological marker for HCC.

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.