

## RESPONSES TO THE REVIEWERS

*We are happy that reviewers positively consider our manuscript and we thank them for their time and constructive comments, which help us to further improve our manuscript.*

### **Reviewer #1:**

*“Very nice observation!”*

*We thank the reviewer for her/his very positive opinion on our study and for accepting our manuscript in its current version.*

### **Reviewer #2:**

*“I consider that the authors should underline the clinical implications of their research.”*

*We thank the reviewer for her/his positive consideration of our study and her/his pertinent suggestion to better underline clinical implications of our study. To that end, we have modified the last paragraph of our discussion as followed:*

*“However the mechanism affecting PTEN functions are different depending on the etiologies of the diseases. In this study, we show that we can take advantage of the different molecular mechanisms affecting PTEN activity or expression in liver metabolic disorders to identify their etiology. Thus, the immunohistochemical detection of PTEN protein expression should be added to the diagnostic armamentarium of pathologists and clinicians in the differential diagnosis of NAFLD and ALD in humans.”*

### **Reviewer #3:**

The article is very interesting and useful for clinicians. The small number of patients included in the study is a limit recognized by the authors, but most studies requiring liver biopsy in these types of pathology are difficult to achieve in a single center. A multicenter future study would be useful in this regard. I suggest to the authors to add to Discussion a comment on the beneficial role of statins in nonalcoholic fatty liver disease and in chronic hepatitis C; one of the explanations would be the increased PTEN expression induced by statins.

*We thank the reviewer for her/his positive consideration of our study, her/his pertinent comments and for her/his interesting suggestion to further expand our discussion on the potential PTEN-related mechanisms contributing to the clinical benefits of statins-based therapies in liver diseases. To that end, we*

have now added the following paragraph in our discussion to comment this aspect:

*"The observation linking PTEN downregulation with liver disease progression in NAFLD and hepatitis C may have implications for treatment. Regular statin use has been shown to upregulate PTEN in heart tissue <sup>[1, 2]</sup>, skeletal muscles <sup>[3]</sup> and cancer cells<sup>[4-6]</sup> through various mechanisms including decreased expression of PTEN-targeting microRNAs<sup>[7]</sup>, NFκB inactivation<sup>[4]</sup> and PPARγ activation<sup>[5, 6]</sup>. Regarding the relationship between statins and liver disease progression, the few data in NAFLD suggests some beneficial effect, at least on steatosis<sup>[8]</sup>. More convincing evidence has been reported in patients with chronic hepatitis C, where statin use was associated with a significantly lower liver fibrosis progression, independently of inflammation and viral load changes over time<sup>[9-11]</sup>. Thus, one cannot exclude that the beneficial effects of statins may be mediated by PTEN upregulation in the liver with NAFLD or HCV infection, however direct evidence are currently lacking. Obviously, the long-term use of statins in these conditions should also be weighed against the risk of toxicity, in particular concerning the increased risk of insulin resistance and type 2 diabetes development, which can results from PTEN upregulation in skeletal muscles<sup>[3, 12, 13]</sup>."*

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