Dear Lingling Tian, PhD

Thank you for your comment; we actually performed NK staining using anti-NK1.1 as presented in figure 3a, 3b, and 3c. NK staining allow us to evaluate their phenotype alterations.

We used one of the ideal markers for NK cytotoxicity and it is CD107a (Lysosomal-associated membrane protein 1 (LAMP-1)). In addition, for better characterization of NK cells we further stained them for CD49a marker as to allocate hepatic resident NK cells and not conventional NK cells.
3. Staining for VDR should have been performed in the liver. It is unclear where the vitamin D/VDR interaction is occurring.

Thank you for your comment; we have isolated primary hepatic stellate cells (pHSCs) from mice liver and then we have extracted protein for quantitation of vitamin D receptor (VDR) by western blot analysis. Therefore, we have an evidence (we are the first to show) that VDR is present on pHSCs. This was presented in Figure 2 c "Inhibition of VDR in pHSCs in the chronic model of CCl4 while up-regulation of the VDR were obtained in acute model by western blot." We did not quantitate VDR in hepatocytes as they undergo ballooning and necrosis and the results could not reflect the true quantity of VDR.

4. The authors did not fully evaluate VDR downstream signaling to show changes in activation.

We believe that evaluating VDR downstream signaling pathway is a more wide study and we are performing this pathway in our human subjects.

5. Vitamin D strongly regulates intestinal function and this may be a reason the authors have different outcomes in acute versus chronic settings.

Vitamin D was used in an i.p injections and we as a liver specialized lab we were interested in researching Vitamin D effects on liver. However, this could be nice idea for future plan.

6. The reasoning as to why there are worse conditions for vitamin D in the chronic fibrosis setting is unclear and was not fully explored or explained.

Figure 2 in details explain the following: "The above results suggest increased Ca+2 serum levels in chronic model of CCl4 treated with vitamin D could be a result of liver injury accompanied with vitamin D degradation. Consequently, these effects were associated with inhibited VDR and therefore, unlike the acute model, chronic mice model of CCl4 were unresponsive to vitamin D treatments (Fig. 2 b and c). Moreover, due to the up regulation of VDR in the acute model of CCl4, vitamin D treatments were most probably up taken/ consumed and could explain the low vitamin D serum levels while calcium serum levels remained the same."
7. The authors only looked at alpha-SMA as a fibrotic marker, but other factors should have been evaluated.

Indeed, we have showed in figure 1e Collagen 1 in addition to aSMA.

8. HSCs should have been stained in the model.

Fig. 3d shows isolated primary HSCs form mice livers from all groups and were stained for aSMA as a marker for HSCs. Indeed, we have HSCs monocultures that were also stained for aSMA, however, data were not shown. We have included this sentence in the text in the result section “To cite, HSCs monocultures staining revealed 90% aSMA (data not shown).