

We thank the reviewer for valuable comments on our manuscript. We have carefully addressed the criticisms and have modified the text and figures, and incorporated additional data as requested. We have given below a point-by-point response to the reviewer. The changes in the revised text file are highlighted.

We hope that we have satisfactorily addressed the concerns of the reviewer and that the revised manuscript will be favorably considered for publication in the *WJG*.

COMMENTS TO AUTHORS

In this study, the authors investigated the role of SOCS1 in the invasion ability of HCC. Based on the previous study, the authors assumed that SOCS1 may regulated the MET signaling pathway to make it. However, there are some questions appearing in the text needed to be answered.

Response to comments

Comment: 1. There are a great many of HCC cell lines, why the Hepa, Hep3B, HepG2 were chosen for this study?

Response: We have chosen these cells because (i) they represent mouse (Hepa) and human (Hep3B, HepG2) HCC, and (ii) we have previously shown that they respond to HGF by inducing MET phosphorylation and initiating downstream signaling events (Gui et al., *J Hepatol.* 2011;55(6):1300-8; *Oncogene* 2015; 34(46):5718-28). These reasons are added to page 8 of the revised manuscript.

Comment: 2. In the figure 1A, only Hepa cells was disposed for the phase contrast microscopy although the authors cited that Hepa1-6 cells could better utilize endogenous HGF, it is necessary to study the circumstance of others HCC cell lines.

Response: We have done this experiment in Hep3B-vector and Hep3B-SOCS1 cells, and the results are added to Fig. 1A in the revised manuscript.

Comment: Moreover, the authors also need to explain the concentration of HGF(25 ng/ml).

Response: We have previously determined that this concentration was effective in inducing proliferation and migration of Hepa and Hep3B cells (Gui et al., *J Hepatol.* 2011;55(6):1300-8). This is indicated on page 8 of the revised manuscript.

Comment: The figure 1c reveals the number of migrated cell of HepB-V and Hep3B-socs1 in control group was no significance, and the picture of migrated cells showed that the number in Hep3B-V was more than Hep3B-SOCS1, please explain it and provide other picture.

Response: The control groups, which did not receive HGF, show the basal level of migration. There was no difference in this background migration between vector and SOCS1 expressing cells, whereas HGF stimulation significantly increased migration in both, but significantly less in SOCS1-expressing cells. We had indicated only the difference between vector and SOCS1 expressing cells within the HGF-treated group in the original figure. We have indicated all statistical comparisons in the revised figure 1C.

We agree with the reviewer that the representative image for untreated Hep3B-SOCS1 does not truly reflect the quantification data shown. We have replaced the images for untreated Hep3B-V and Hep3B-SOCS1 with another area of the membrane from the same experiment, as suggested by the reviewer.

Comment: 3. figure3 revealed the number of colonies, while in figure 3A the average colony size of colony and picture were provided, there was no similar histogram and picture in figure 3B, it is necessary to supply it.

Response: We have re-evaluated colony size and found that to be significantly reduced in SOCS1 expressing Hep3B and HepG2 cells compared to vector control cells as well. The colony size distribution (as area in μm^2) for these cells is shown in the revised figure 3.

Comment: 4. In the figure 4, the authors chose the tumors from mice to do the western blot, why not select cells. Furthermore, the number in legend was different, the number of Figure 4A was 4, while in Figure4B-D the number was 6, why?

Response: We have previously published the *in vitro* results on cell lines, and in xenografts that SOCS1 inhibits HGF-induced MET signaling and reduces MET expression. Showing them again would represent data duplication. Therefore, here we have provided only the *in vivo* data on orthotopic tumors.

Fig 4A and 4B represent two different types of experiment, in (A) the cells were injected via the i.v. route, whereas in (B) the cells were delivered via the intrasplenic route. As two mice in vector group died in (A), we had only 4 mice to compare. Nevertheless, all mice in control and SOCS1-expressing tumors showed similar difference in growth.

Comment: 5. In figure 5B the cells were stimulated with HGF for 30min or 2h, why not choose other time?

Response: The indicated proteins are transcriptional regulators and their genes are induced early after HGF stimulation (Reference 40), while their protein expression can last longer. We have done a time course experiment to confirm this (please see below), and thus have used the chosen time points of 30 min for *EGR1* and 2h for *SNAIL* for gene expression analysis.

