Answering Reviewers

Dear Reviewers:

Thank you very much for your precious suggestions on our manuscript. We have resubmitted new version accordance with recommendations of the reviewers. We have addressed the comments raised by the reviewers in the documents below, and the amendments are highlighted in red in the revised manuscript. We hope that revision is acceptable and look forward to hearing from you soon.

Best Regards,

Zhu Ranxu

1 Response to Revierwer1:

Comment 1. There were not consistence between Title - study aim- hypothesis - conclusion

Author's Reply: Thank you very much for your suggestion. We have carefully revised the manuscript according to your suggestion.

They are corrected in 4th lines in 3 th paragraghs in the introduction section, 1th line in 1th paragragh in the result section, 6th line in 2th paragragh and 2th in the last paragragh in the discussion section, respectively.

2. This article was not the novel study as mention the article .... "Over all, our diverse functional assays revealed a novel molecular mechanism underlying the anti-proliferative nature of GAS2 in hepatocyte and HCC cell line". Zhu R et al. J Pathol 2015; 237: 38–49 published an article with the title " Truncated HBx-dependent silencing of GAS2 promotes hepatocarcinogenesis through deregulation of cell cycle, senescence and p53-mediated apoptosis "

Author's Reply: Thank you very much for your suggestion. We revised the

paper in the revised manuscript according to your suggestion.

They are modified in 1th in the last paragragh in the discussion

3. there was not sequence mentioning to mRNA GAS2 target.

Author's Reply: Thank you very much for your suggestion.

They are modified in 6th and 7th in the 3th paragragh in the materials and methods. For example, the sequence mRNA level of GAS2(F5'-TGCAAA TGCCCAAACAAGTTC-3 '; GAS2-R5'-TTCTCCCACTCGGTATCTTCCTT-3') in the revised manuscript.

Response to Revierwer2:

RE: Manuscript NO: 47571 Zhu et al, Growth arrest-specific gene 2 suppresses hepatocarcinogenesis by intervention of cell cycle and p53-dependent apoptosis.

Zhu et al investigated the role of GAS2 in liver cells and found that GAS2 inhibited the growth of certain HCC cells in a p53-dependent manner. The authors further showed that GAS expression was down-regulated in clinical HCC samples compared to corresponding non-HCC liver tissue. The data presented here include interesting findings in HCC biology, however data are not enough to support the authors conclusion. The authors showed that GAS2 overexpression suppressed growth of SK-hep1 cells and knockdown of GAS2 in MIHA cells stimulated the proliferation. However, these experiments were conducted only in cell with wild type 53. Alteration of p53 gene is relatively common events in HCC, mutations of p53 that acquires dominant-negative function and deletion of p53 are reported. Therefore authors' conclusion seems to be too much extended and data are not enough to generalize the role of GAS2The in HCC.

Author's Reply: Thank you very much for your suggestion. We add some explanations in the discussion of revised manuscripts.

They are corrected in 11th and12th lines in the 3th paragraph and 6th paragraph in the discussion section

1. Hep3B cells without p53 expressed GAS2(Fig 1A). What is the result of GAS2 knockdown in Hep3B cells?

Author's Reply: Thank you very much for your suggestion. We add the data in the extended experiment(Supplementary experiment).

They are modified in 6th -8th in the 3th paragraph in the result section.

2. There are no experiments in Huh7 and/or PLC5 cells that carry mutant p53 geones. These two cell lines do not express GAS2. Therefore overexpression of GAS2 is necessary to confirm whether it can suppress HCC cells with mutant p53.

Author's Reply: Thank you very much for your suggestion. We add the data in the extended experiment(Supplementary experiment).

They are corrected in 4th ,9th -11th lines in the 2th paragraph in the result section.