

Dear Editors and Reviewers:

Thanks for your letter and for the reviewers' comments concerning our manuscript (NO: 63410). Those comments are all valuable and very helpful for revising and improving our paper. We have studied comments carefully and have made correction which we hope meets with approval. The corrections in the paper and the responds to the reviewer's and editor's comments are as flowing:

Reviewer 1#:

Comment 1: Less convincing is the explanation presented by the authors about the molecular mechanism of action of CTS in gastric cancer, and in particular its link with CagA. It is known that CTS acts as an irreversible inhibitor of SHP2, and this is the effect observed on the growth of GC cells. But the link between CagA and SHP2 is indirect, demonstrated only by the presence of CagA-IgG (Table 1). Is the phosphorylation of SHP2 directly performed by CagA, or does CagA induce the phosphorylation process? Can the author, for example, test that CTS does not act directly on CagA, blocking SHP2 phosphorylation? Perhaps this part in the discussion could be somehow attenuated, making it more hypothetical.

Response to comment 1: It is discovered that CagA interacts with SHP2 and causes SHP2 activation in GC (reference 28). Our experiment further identified the positive correlation between the expression levels of IgG against CagA in patient serum and phosphorylated SHP2 protein in GC tissues. Together, phosphorylation of SHP2 induced by CagA is one of critical parts in HP associated GC. Next, we explored the effect of CTS on above process and the evidence showed that CTS inhibited the CagA-induced proliferation and EMT of GC cells. Moreover, CTS significantly decreased the expression levels of SHP2 and p-SHP2 except CagA protein in GC cells. Together, CTS inhibits CagA-induced cell growth and metastasis through inhibiting SHP2 rather than CagA. Therefore, we added the critical parts into the discussion, avoiding the misunderstanding about the conclusion (file: 63410_Auto_Edited.docx).

Comment 2: The meaning of Table 2 is not clear (at least for me), a legend should be included. What's the difference among the four groups?

Response to comment 2: The difference among the four groups is added in the legend of table 2 (file: 63410-Table-File-revision.docx).

Comment 3: If the hypothesis of the authors is correct, the cartoon of Fig. 7 should be redrawn. The message of the paper, if I understand correctly, is that CTS blocks the activity of SHP2 (in particular of SHP2-P), blocking GC proliferation etc. CTS should be moved to the lower part of the figure.

Response to comment 3: As reviewer termed it, CagA promoted proliferation and metastasis of GC cells by inducing the phosphorylation of SHP2, which was blocked by CTS. Therefore, we redraw the Fig. 7 (file: 63410-Image-File-revision.ppt).

Science editor:

Comment 1: The "Author Contributions" section is missing. Please provide the author contributions.

Response to comment 1: The "Author Contributions" section is added into submission system.

Comment 2: The authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s).

Response to comment 2: The funding of National Natural Science Foundation of China (No. 81572350) is presented in file: 63410-Approved Grant Application Form.PDF. Regrettably, the funding of Anhui Academic and Technical Leaders Fund (No. 2019D229) is a kind of internal funding without documentary evidence. Thus, we deleted the information of funding (No. 2019D229) in revised manuscript (file: 63410_Auto_Edited.docx).

Comment 3: The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor.

Response to comment 3: The original figures is presented in file: 63410-Image-File-revision.ppt.

Comment 4: PMID and DOI numbers are missing in the reference list. Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references. Please revise throughout.

Response to comment 4: PMID and DOI to the reference list is added and all authors are also listed (file: 63410_Auto_Edited.docx).

Comment 5: The “Article Highlights” section is missing. Please add the “Article Highlights” section at the end of the main text.

Response to comment 5: The “Article Highlights” section is added in the manuscript (file: 63410_Auto_Edited.docx).

We tried our best to improve the manuscript and made some changes in the manuscript. We appreciate for Editors and Reviewers’ warm work earnestly, and hope that the correction will meet with approval.

Best regards
Aman Xu