

RESPONSE LETTER

Dear Editors and Reviewers:

First , we would like to thank the editors and the reviewers for the positive and constructive suggestions and comments concerning our manuscript entitled as “**Ghrelin and gastrointestinal stromal tumors**”, whose NO. is 30337.

Those suggestions and comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied comments carefully and have made correction which we hope meet with approval. **All of the revisions has been highlighted in red in the updated version of the manuscript.** The main corrections in the paper and the responds to the reviewer's comments are as flowing:

For peer reviewers

1. COMMENTS 1 (Reviewed by 01404215):

The authors suggest that ghrelin could activate the development of GISTs based mainly on that ghrelin stimulate the PI3K/AKT/mTOR pathway in cardiac muscle cells and pulmonary artery endothelial cells under hypoxia, but this has not been demonstrated yet. If this assertion would be true, a therapy directed against gastrointestinal stromal tumours development could be developed based only on ghrelin inhibition. Minor point The referenced article number 13 is also duplicated as article number 23. Reference 23 should be skipped.

Reply:

Dear Reviewers :

Thank you for your valuable advice at first. My responses are as followings:

1) Dear peer reviewer:

There is no relevant reports whether Ghrelin is involved in the occurrence and development of GIST, no matter at home or abroad at present. However, Clinical observation found, Gastric stromal tumors are mainly produced in fundus ventriculi, and ghrelin is mainly produced in fundus ventriculi too. Research has proved that Ghrelin can activate the PI3K/AKT/mTOR pathway in cardiac muscle cells and pulmonary artery cells, which indeed plays an important role in the occurrence and development of GIST. Therefore, this hypothesis was made: Ghrelin promotes the occurrence and development of GIST through the PI3K/AKT/ mTOR pathway. The main purpose of this article is to objectively state the research status about ghrelin and

GIST, and to point out possible research directions. Dear editor, Thank you for your advice again.

2) As you said, the referenced article number 13 and 23 are the same one, I have corrected them.

2. **COMMENTS 2** (Reviewed by 03646550) :

Please correct the numbers for the references.

Reply:

Dear peer reviewer:

Thank you for your valuable advice at first. As you said, there indeed existed some problems in the references. I have corrected all the problems in the references. You can see the corrections in detail in the revised version. Thanks again for your comments.

3. **COMMENTS 3** (Reviewed by 00503623) :

This manuscript presents a brief review of the literature implicating peptide hormone, ghrelin, and the expression of its receptor, growth hormone secretagogue receptor (GHS-R1a) in the development of gastrointestinal stromal tumors (GISTs). Based on the provided literature citations (48 + one not numbered), the conclusion is that GISTs affected intestinal cells express ghrelin as well as ghrelin receptor, and that ghrelin-activated PI3K/AKT/mTOR signaling pathway plays a major role in the development and progression of GISTs. Although the paper suggest the involvement of RTKs in the process and provides the data pointing to possible benefits of RTK-targeted therapy, the included diagram (figure) does not show the pathways of ghrelin action and the consequences of GHS-R1a activation, and hence this requires remediation and referencing (see Inflammopharmacology, vol 21 (2013) 241-251) and vol. 22 (2014) 251-263) and Journal of Biosciences and Medicines vol.2 (2014) 20-33. Also, the paper requires a short summary followed by the clearly marked Introduction.

Reply:

1) Dear peer reviewer:

Thank you for your constructive suggestion. I have added another figure to illustrate the pathways of ghrelin action and the consequences of GHS-R1a activation, the relevant referenced article has been added at the same time. **Revised portion are marked in red in the paper.**

- 2) as you demanded, we have marked introduction and made a brief summary at the same time.

Thanks again for your comments.

4. COMMENTS 4 (Reviewed by 00646395) :

This is an interesting and concise manuscript on the relevance of ghrelin and its receptor for GIST. The manuscript discusses potential targets for new therapies.

Minor comments:

- Neither an abstract nor a clear structure for the main text is provided.
- The first reference has no number.
- The figure has no legende.
- The source of the figure needs to be mentioned (from another review article?)
- On page 2 there seems to be an oversight: "Whether ghrlein is involved in,

Can we finde ..." These two sentence contain grammatical errors and need to be revised.

- There seems to be something wrong with the first sentence on page 4.

- Page 4: Did the authors mean the EXTENT of ghrelin (receptor) expression? Because in the previous paragraph the authors stated that all GIST were ghrelin (receptor) positive.

Reply:

Dear Reviewers :

Thank you for your valuable advice at first. My responses are as followings:

- 1) I have reorganized the structure of the article according to the requirements of the magazine; You can see the corrections in detail in the revised version.
- 2) As you said, there indeed existed some problems in the references. I have corrected all the problems in the references and marked them in red.
- 3) The legend has been added to the figure.
- 4) The source has been added to the figure and Figure the is reproduced.
- 5) These two sentences has been revised as "It is currently unknown whether ghrelin is involved in the development or progression of GIST through some certain pathways. Can we find a new target for the treatment of GIST ? .
- 6) The first sentence on page 4 has been revised as "A Japanese study, to our knowledge, is only one study which have examined the expression of ghrelin and its receptors in GIST tissues."

- 7) In the Page 4, what I want to say is that the extent of ghrelin (receptor) expression is different in the GISTs though the expression of ghrelin (receptor) is positive in each GIST tissue.

For dear editor

To dear editor:

As you demanded, PMID and DOI have been added to the reference article. **However, there is one thing I have to explain to you:** Most of the references have PMID and DOI, but some references only have one of them, I really cannot find them both. Maybe those article indeed just have one of them. Sorry

COMMENTS AND REPLIES

1. **You'd better offer us one paper with word format next (such as, .doc or .docx), which is easy to be edited and helpful to accept earlier. Thank you very much!**

Reply: Dear editor, as your requirement, the version I submitted this time is word format.

Thanks for your advice.

2. **Please provide language certificate letter by professional English language editing companies (Classification of manuscript language quality evaluation is B).For manuscripts submitted by non-native speakers of English, please provided language certificate by professional English language editing companies mentioned in 'The Revision Policies of BPG for Article'.**

Reply: Dear editor, as your requirement, I have uploaded the language certificate by professional English language editing companies. Thanks for your advice.

3. **Name of journal: World Journal of Gastroenterology**

ESPS Manuscript NO:

Manuscript type:

Reply: Name of journal: World Journal of Gastroenterology

ESPS Manuscript NO: 30337

Manuscript type: MINIREVIEWS

Thanks for your advice.

4. Please revise and perfect your manuscript according to peer-reviewers' comments.

Reply: I have made those correction respectively according to peer-reviewers' comments, which I have displayed above. Thanks for your advice.

5. Running title: (Less than 6 words)

Reply: Ghrelin/gastrointestinal stromal tumors/PI3K/AKT/mTOR pathway.

Thanks for your advice.

6. Author contributions: XXX (family name should be put first in full, followed by middle names and first name in abbreviation with first letter in capital) designed research; XXX performed research; XXX contributed new reagents or analytic tools; XXX analyzed data; XXX wrote the paper. An author may list more than one contribution, and more than one author may have contributed to the same aspect.

Reply: Author contributions: Zhu CZ performed the majority of the writing and prepared the figures; Zhu CZ, Ma ZQ, and Ye X performed the data acquisition and writing; Zhu CZ, Li K, and Liu D provided input in writing the paper; Zhu CZ, Kang WM, and Yu JC designed the outline and coordinated the writing of the paper.

Thank you for your advice.

7. Abstract (no less than 200 words.)

Reply: Ghrelin, as a kind of multifunctional protein polypeptide, is mainly produced in the fundus of the stomach and can promote the occurrence and development of many tumors, including gastrointestinal tumors, which has been proved by the relevant researches. Most gastrointestinal stromal tumors (GISTs, about 80%), as the most common mesenchymal tumor, develop in the fundus too. Scientific research has confirmed that Ghrelin, its receptors and mRNA respectively can be found in gastrointestinal stromal tumors, which demonstrated the existence of a ghrelin autocrine/paracrine loop in GIST tissues. However, no reports to date have specified mechanism whether ghrelin can promote the occurrence and development of GISTs. Studies of pulmonary artery endothelial cells in a low-oxygen environment and cardiac muscle cells in an ischemic environment have shown that ghrelin can activate the phosphatidylinositol 3-kinase/AKT/mammalian target of rapamycin (PI3K/AKT/mTOR) signaling pathway. Moreover, some studies of GISTs have confirmed that activation of the PI3K/AKT/mTOR pathway can indeed promote the growth and progression of GISTs. Whether ghrelin is involved in the development or progression of GISTs through certain pathways remains unknown yet. Can we find a new target for the treatment of GISTs? This review explores and summaries the relationship among ghrelin, the PI3K/AKT/mTOR pathway and the development of

GISTs.

Thank you for your advice.

8. Key words: 5~10 words

Reply: Gastrointestinal stromal tumor (GIST); PI3K/AKT/mTOR pathway; Ghrelin; Occurrence; Development. Thank you for your advice.

9. Core tip: Please write a summary of less than 100 words to outline the most innovative and important arguments and core contents in your paper to attract readers.

Reply: Ghrelin has been proven to promote the occurrence and development of gastrointestinal tumors. Some gastrointestinal stromal tumors express ghrelin and its receptor. However, no previous reports have specified whether ghrelin is involved in the occurrence and development of gastrointestinal stromal tumors. Through a review of the literature, this paper is the first to summarize and discuss the correlation between ghrelin and gastrointestinal stromal tumors.

Thank you for your advice.

10. Audio core tip: In order to attract readers to read your full-text article, we request that the author make an audio file describing your final core tip, it is necessary for final acceptance. Please refer to Instruction to authors on our website or attached Format for detailed information.

Reply: I have made an audio core tip as the journal demands. Thank you for your advice.

11. Please provide all authors abbreviation names and manuscript title here. World J Gastroenterol 2016; In press

Reply: Zhu CZ, Liu D, Yu JC, Kang WM, Ma ZQ, Ye X, Li K. Ghrelin and gastrointestinal stromal tumors. World J Gastroenterol 2016; In press

Thank you for your advice.

12. Abbreviations and acronyms are often defined the first time they are used within the main text and then used throughout the remainder of the manuscript. Please consider adhering to this convention Search all abbreviations in your manuscript and do like this when they were used firstly.

Reply: I have made corrections as your demands. Thank you for your advice.

13. Please check that there are no repeated references!

Reply: I have checked the references as your demands and make sure there is no repeated ones.

Thank you for your advice.

14. Please provide the decomposable figure of Figures, whose parts are movable and editable. So please put the original picture as ppt so that we can edit them easily.

Reply: I have remade the figures in format of PPT as your demands. Thank you for your advice.

15. As your demands "Please subject the final title of the manuscript to Google Scholar search, and store screenshot images of the results. We strongly suggest that you check the final title of the manuscript using Google Scholar at <http://scholar.google.com/>.

Reply: Dear editor, for some reason I cannot control, I have no access to Google Scholar search to search my final title of the manuscript. I subject the final title of the manuscript to PubMed resource instead and stored screenshot images of the results.

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