

To editor, World Journal of Clinical Cases

Dear editor,

We appreciate your comments and suggestions. These comments and suggestions are valuable and very helpful for revising and improving our manuscript (Manuscript NO: 45588). We have carefully revised the manuscript and enrich the content of the article according to the comments. Meanwhile, the article was carefully polished and checked by English native speakers before resubmitted. We would like to submit the revised manuscript for publication as a review in WJCC. The detailed responses are listed below.

We believe that this article will be interesting to general readers of WJCC. In this article, we review the current findings concerning the relationship between the brain-gut axis and GI cancer cells, focusing on the significant role of the brain-gut axis in the processes of tumor proliferation, invasion, apoptosis, autophagy, and metastasis. It appears that the brain might modulate GI cancer by two pathways—the anatomical nerve pathway and the neuroendocrine route. The stimulation and inactivation of the central nervous, sympathetic, and parasympathetic nervous systems, or changes in the innervation of the GI tract, might contribute to a higher incidence of GI cancers. In addition, neurotransmitters and neurotrophic factors can produce stimulatory or inhibitory effects in the progression of GI cancers. Insights into these mechanisms may lead to the discovery of potential prognostic and therapeutic targets.

Looking forward to hearing from you soon.

Sincerely yours,

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Point by point responses

1. REVIEWER 1

- a) The review should be more illustrated. The only figure is hard to follow and located only at the end.

As suggested by the reviewer, we have listed a table to summarize the effect of relevant neurotransmitters and neurotrophic factors on the progression of GI cancer to make the review more illustrated.

- b) The authors left as final conclusions that the interaction between the axis and tumors may be used in the treatment but no references are provided. The authors could explore more this.

In fact, in the article such as the refs: [144], [145] have suggested that DR, 5HT antagonists or inhibitors alone or together with other drugs may have potent inhibitory effects on tumors, which represent a promising therapeutic strategy for cancer in the future. However, these drugs are still being studied in cellular research or animal experiments, and the Clinical Trials have not started yet. Further, this neurobiological view of cancer might enable a better understanding of oncogenesis and open new prospects for cancer diagnosis and treatment

2. REVIEWER 2

- a) There are misspelt words in the text. The word of 'especiall' at page 6 line 14 is wrong, exactly especially. The word of 'showed' at page 7, line 3 is wrong, exactly shown. The word of 'GABRA' at page 15, line 7 is wrong, exactly GABAA. Please check them.

In response to the reviewer's requests, we have carefully check the words and corrected the wrong words in the text.

3. REVIEWER 3

- a) Title: I suggest to change it. It is a bit same as others already published. So my strong recommendation is to first check the databases and see how many similar titles are released yet. Then, using current knowledge in this paper can easily

suggest better ones for you.

We have changed the title with “Role of the brain-gut axis in gastrointestinal cancer”

If it's completely replaced, may it be “Brain-Gut Axis: its crucial function in gastrointestinal cancer”?

b) Introduction is fine and acceptable.

c) Figure 1: Nicely designed but I would prefer to remove it. Reason: All data raise is already discussed in the text! Thus, to reduce the repeating text, please delete it.

Because of the referee's comment, we have deleted the Fig.1 which represents the interaction between the brain-gut axis and GI cancer. But we'd better reserve it, because it may further clarify the structure of the article.

d) In the section: 3.1 Brain-derived nerve growth factor (BDNF) and GI cancer 5- I would recommend to divide it in to the two basic division: Stomach cancer and colon-associated ones. As such you can find other factors attributed in and also discuss it better. Hopefully you can find many infectious agents include bacterial agents and viral ones which are the subjects of this cancer. For sure, you can get more attentions if you add this sort of information in it.

We have divided it in to the two basic division according to the effect of brain-gut axis on the stomach cancer and colon. And we revealed that the BDNF/TrkB axis could promote cell proliferation, migration, and invasion but also be involved in bone metastatic of stomach cancer cells.

e) Due to the importance of gastric cancer, I would suggest authors to first add a new section to well-define it, then addressing necessary items with it. In this regard, authors can read these below listed paper to enrich the text accordingly:

Considering the reviewer's suggestion, we have added some references with updated bibliographical review (40, and 41) to enrich the text accordingly.

4. REVIEWER 4

- a) English should be improved throughout the manuscript. Quantitative information should be provided in the abstract. The conclusion should be concise and to the points indicating the application of the work. Novelty of the work be established. Write one paragraph on the cancer scenario in general with citation of following refs.

We would like to thank the referees for their thoughtful review of our manuscript. We sincerely apologize the Referee for not completely addressing all of the points raised in the response. We have done so below and added additional data in hopes that this reviewer will be supportive of publication.

1. Thank the reviewer for the comments. We've recognized that some of the descriptions in the previous copy were really not so accurate and a little bit arbitrary due to our poor English level and the study on recent literature. The article was carefully polished and checked by English native speakers before resubmitted.
2. The abstract and conclusion part have been rewritten, and we particularly revised some sentences since they are not correct or so confusing. Further, the neurobiological view of cancer might enable a better understanding of oncogenesis and open new prospects for cancer diagnosis and treatment, which may be the novelty of the work.