Dear Editor,

We would like to thank the World Journal of Clinical Cases for giving us the opportunity to revise our manuscript (ID# 54479) entitled “Functions and mechanisms of chemokine receptor 7 in tumors of the digestive system”. We really appreciated editor and reviewers for their positive comments and constructive suggestions on our previous draft. We have thoroughly revised the manuscript by addressing the relevant questions and commons point-by-point, which has made the revised manuscript clearer and more concise. For your convenience, all the changes have made revision which marked in red and highlight in the revised manuscript. We have tried to our best revise our manuscript according to your comments.

**Reviewer #1:**

**Speific Comments to Authors:** The manuscript by Xin et al critically summarized the expression and role of the chemokine (C-X-C motif) receptor 7 (CXCR7; also termed ACKR3), a GPCR that binds to CXCL11 and 12, and its prognosis in cancers of the digestive system. As a newly discovered receptor for CXCL12, CXCR7 has attracted increasing attention in the field. The authors have sufficiently elaborated and critically reviewed the most relevant topics in their chosen topic. Overall, it's a balanced, comprehensive and critical review.

The authors really appreciate reviewer 1 for his/her very positive comment and recognition of our paper. We tried our best to revise the article according to the opinions of other reviewers.

**Reviewer #2:**

**Speific Comments to Authors:** Review Function and mechanism of chemokine receptor 7 in tumors of the digestive system In this submission from Qi Xin’s group, the authors reviewed functional role of CXCR7 in tumor of digestive system. Based on many previous reports the authors reviewed the role of CXCR7 in detail for each organ. This review was well written, but to add quality to this manuscript, the authors should consider the following comments. Major 1) CXCR4 has been studied as a receptor for CXCL12, and its involvement in metastasis and angiogenesis has

been reported. CXCR7 is certainly a receptor that binds to CXCL12. However, it is still unknown whether CXCR7 plays a role in cancer malignancy more than CXCR4. Readers want to know about this. I recommend that the authors should describe the point that CXCR7 is more important than CXCR4. 2) The authors used both SDF-1α and CXCL12 as ligands for CXCR7. I think it should be unified. 3) I'm not sure which CXCR4 or CXCR7 is important for anticancer drug resistance. 4) Page16, Patients (neoadjuvant-treated colorectal cancer liver metastases patients (CRLM) from a phase 2 clinical trial) with KRAS mutational status were considered in the CXCR7-overexpressing patients[62]. CXCR4-expressing SW480 cells are more chemosensitive (5-Fu) than CXCR7-expressing SW480 cells in a CXCL12-secreting environment [20]. CXCL12/CXCR7 contributes to the 5-FU sensitivity of chemokine receptor-expressing colon cancer SW480 cells, whereas CXCL11/CXCR7 has no effect [20]. 5) The authors should add reference after this sentence in page18. Pancreatic stellate cells (PSCs) and transforming growth factor β play a role in this process, which also involves CXCR1/CXCL8 signaling.

1. **CXCR4 has been studied as a receptor for CXCL12, and its involvement in metastasis and angiogenesis has been reported. CXCR7 is certainly a receptor that binds to CXCL12. However, it is still unknown whether CXCR7 plays a role in cancer malignancy more than CXCR4. Readers want to know about this. I recommend that the authors should describe the point that CXCR7 is more important than CXCR4.**

Thanks for your meaningful question which we which we have been focusing on. This might be the current understanding that both CXCR4 and CXCR7 play important roles in the development and metastasis of tumors, however the published literatures did not show which of these two receptors played a greater role. Current published literature shows that in tumors of the digestive system, hepatocellular carcinoma, colorectal cancer, and pancreatic cancer, both receptors are expressed in the same cell. CXCR4 and CXCR7 have been studied most thoroughly in terms of their presentation and function in colon cancer, and the existence and mechanism of CXCR4 and CXCR7 have not been reported in other digestive system tumors. In colon cancer, CXCR4/CXCR7 can form heterodimers that promote tumorigenesis. At present, our research team is conducting a comparative study on the role of CXCR4/CXCR7 in gastric cancer and its mechanism. Our study found that CXCR4 and CXCR7 can form heterodimers in gastric cancer cells, which play a stronger role in gastric cancer than CXCR4 and CXCR7 alone. This study will be published soon. Of course, CXCR4/CXCR7

heterodimers is still relatively new, there are still a lot of unanswered questions. More studies are needed to be better understanding about this question.

**2. The authors used both SDF-1α and CXCL12 as ligands for CXCR7. I think it should be unified.**

Thank you very much for the question raised by the reviewers, which we have corrected in the article.

**3. I'm not sure which CXCR4 or CXCR7 is important for anticancer drug resistance.**

Published studies did not compare whether CXCR4 or CXCR7 is more important for anticancer drug resistance. The reason may be that CXCR4 and CXCR7 interact with each other in tumor cells. In some malignancies, such as colon cancer cells, CXCR4 and CXCR7 form heterodimers, and the heterodimers are more potent than the homodimers of CXCR4 or CXCR7.

The following research showed that characterization of the CXCL12/CXCR4-axis revealed that neither bortezomib nor pomalidomide had an effect on CXCR4 in multiple myeloma. CXCL12 and CXCR7 are relevant targets to reverse cell adhesion-mediated drug resistance in multiple myeloma. Oroxylin A reverses the drug resistance of chronic myelogenous leukemia cells to Imatinib through CXCL12/CXCR7 axis in bone marrow microenvironment. By up-regulating the expression of CXCR7, promoting the drug resistance is an important way for it to interfere with esophageal cancer.

**4. Page16, Patients (neoadjuvant-treated colorectal cancer liver metastases patients (CRLM) from a phase 2 clinical trial) with KRAS mutational status were considered in the CXCR7-overexpressing patients [62]. CXCR4-expressing SW480 cells are more chemosensitive (5-Fu) than CXCR7-expressing SW480 cells in a CXCL12-secreting environment [20]. CXCL12/CXCR7 contributes to the 5-FU sensitivity of chemokine receptor-expressing colon cancer SW480 cells, whereas CXCL11/CXCR7 has no effect [20].**

I'm sorry for the ambiguity caused by this statement. We had already modified the article, and the following is the description after the modification. (COLORECTAL CANCER: Page 16, Line 18-20.)

In the presence of SDF-1 secretion, although CXCR7-expressing colon cancer cell line SW480 was sensitive to 5-FU, CXCR4-expressing SW480 was more sensitive to 5-FU.

**5. The authors should add reference after this sentence in page18. Pancreatic stellate cells (PSCs) and transforming growth factor β play a role in this process, which also involves CXCR1/CXCL8 signaling.**

The authors are really sorry for the careless mistake found by the review. I have added the corresponding reference in the article. (PANCREATIC ADENOCARCINOMA: Page 19, Line 12-14.)

Bertran, E., Caja, L., Navarro, E., Sancho, P., Mainez, J., Murillo, M. M., Vinyals, A., Fabra, A., Fabregat, I., Role of CXCR4/SDF-1 alpha in the migratory phenotype of hepatoma cells that have undergone epithelial-mesenchymal transition in response to the transforming growth factor-beta. Cell Signal, 2009. 21(11): 1595-606.DOI: 10.1016/j.cellsig.2009.06.006

**Reviewer #3:**

**Speific Comments to Authors:** The review manuscript by Xin et al. provides a descriptive overview of the functions and mechanisms of CXCR7 in digestive system tumors. Although the authors provide an extensive literature review on this topic, several aspects should be revised and the structure of the review should be revisited in order to obtain a more straightforward reading and comprehension. 1 – Regarding the title, I would suggest to include “Function and Mechanism” in the plural; 2 – In general, all the manuscript should be revised by an English native speaker in order to improve the language. There are some sections that are really difficult to follow. 3 – Most of the times, abbreviations are not explained the first time they appear in the text. Furthermore, a list of abbreviations should be provided. 4 – In vitro, in vivo and et al must appear in italics. 5 – I strongly suggest to revise the structure of the review. I would say it would be easier to make one section for each type of cancer, instead of dividing it by cells, in vivo, mestastasis, etc.. In this way, the authors may explain everything from each tumor in the same section. If wanted, the authors may subdivide then each tumor section in the subtopics explained in the text. 6 –

Although the figures presented in the manuscript, related to each type of cancer are relevant, I would suggest to do only one general figure about the roles of CXCR7 in cancer, since the mechanisms between different types of cancer overlap. And a final figure, with the involvement of CXCR7 in different types of cancer (and their relevance to different processes) might be included. Finally, figures and tables must be referenced in the text. 7 – Rather than presenting only an extensive literature review, it would be important also for the authors to provide their critical point of view. Most importantly, the authors should discuss how CXCR7 might impact on cancer therapeutics and how all these findings might be translated into clinics.

**1 – Regarding the title, I would suggest to include "Function and Mechanism" in the plural;**

Thank you for your comments. I have fixed them as required: Functions and mechanisms of chemokine receptor 7 in tumors of the digestive system.

**2 – In general, all the manuscript should be revised by an English native speaker in order to improve the language. There are some sections that are really difficult to follow.**

We had submitted the language modification to the language modification company as required and submitted the proof of language modification.

**3 – Most of the times, abbreviations are not explained the first time they appear in the text. Furthermore, a list of abbreviations should be provided.**

Thank you for the shortcomings of this article, which we will all pay attention to in the following articles. We explained the first abbreviations as required and provided a list of abbreviations in the article. (Page 3-4)

**4 – *In vitro*, in vivo and et al must appear in italics.**

Thanks, we have made modifications in the article.

**5 – I strongly suggest to revise the structure of the review. I would say it would be easier to make one section for each type of cancer, instead of dividing it by cells, in vivo, mestastasis, etc.. In this way, the authors may explain everything from each tumor in the same section. If wanted, the authors may subdivide then each tumor section in the subtopics explained in the text.**

Thank you very much for your constructive comments and suggestions. We have restructured the article according to the suggestions given for clearer show.

**6 – Although the figures presented in the manuscript, related to each type of cancer are relevant, I would suggest to do only one general figure about the roles of CXCR7 in cancer, since the mechanisms between different types of cancer overlap. And a final figure, with the involvement of CXCR7 in different types of cancer (and their relevance to different processes) might be included. Finally, figures and tables must be referenced in the text.**

Thank you very much for your comments. The mechanisms of CXCR7 in different types of gastrointestinal tumors overlap, but the mechanisms of CXCR7 in different types of gastrointestinal tumors also differ. These differences is one of the purpose of writing this article, the functions and mechanisms of the display in different digestive tract tumor CXCR7, and the research development of CXCR7 in all kinds of digestive tract tumor, let readers to read this article to see in which more research is needed to find in the digestive tract tumor CXCR7 mechanism. That is why we designed the separate figures to focus on different mechanisms of CXCR7 in different gastrointestinal tumors. Thank you very much.

**7 – Rather than presenting only an extensive literature review, it would be important also for the authors to provide their critical point of view. Most importantly, the authors should discuss how CXCR7 might impact on cancer therapeutics and how all these findings might be translated into clinics.**

Thank you very much for your suggestion. This opinion is also due to our negligence caused the biggest deficiency of this article. Our research team has been working on the functions and mechanisms of SDF-1 /CXCR4/CXCR7 in gastric cancer. Our related article was published on WJG in 2017, **Xin, Q**. Zhang, N. Yu, H. B. Zhang, Q.*et al*. CXCR7/CXCL12 axis is involved in lymph node and liver metastasis of gastric carcinoma. World J Gastroenterol, 2017. **23**(17): 3053-3065. Our new research will be published soon.

We have added to this article the impact of CXCR7 on cancer treatment, and thank you very much for your comments. (Page 21-22.)

**Review of science editor**

Thanks for the scientific editor's careful revision and good advice.

Ed1-4, 6: It's what we want to say.

Ed3 We changed “main” in the text.

**Ed4: Abbreviations and acronyms are typically defined the first time the term is used within the main text and then used throughout the remainder of the manuscript. Please consider adhering to this convention. The target journal may have a list of abbreviations that are considered common enough that they do not need to be defined.**

Thank you very much for your suggestion. We have modified it in the article.

**Please provide the ORCID Numbers of all authors.**

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