

November 24, 2023

Dear Prof. Lian-Sheng Ma,

*World Journal of Clinical Oncology*

RE: # NO: 89067, Inflammatory response in gastrointestinal cancers: overview of six transmembrane epithelial antigens of prostate in pathophysiology and clinical implications

Dear Prof. Lian-Sheng Ma,

On behalf of my co-authors, we are very grateful to you for giving us an opportunity to revise our manuscript. We appreciate your positive and constructive comments and suggestions on our manuscript entitled **"Inflammatory response in gastrointestinal cancers: overview of six transmembrane epithelial antigens of prostate in pathophysiology and clinical implications"** (ID: 89067). We have studied reviewers' comments carefully and tried our best to revise our manuscript according to the comments. The following are the responses and revisions we have made in response to the reviewers' questions and suggestions on an item-by-item basis. Our Manuscript was also polished by a native English speaker with biological background to make it easy understanding to readers. The revised portions are highlighted in yellow in the paper. Thank you again for the hard work of the editor and reviewers.

With many thanks and best wishes.

Jing Liu

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*The main corrections are in the manuscript and the responds to the reviewers' comments are as follows point-to-point (the replies are marked in blue).*

**To Reviewer #1:**

**Scientific Quality:** Grade E (Do not publish)

**Language Quality:** Grade C (A great deal of language polishing)

**Conclusion:** Rejection

**Specific Comments to Authors:**

The abstract did not summarize the study and it is too long.

**Response:** Thank you for your in-depth analysis and practical comments. In this study, we focused on the role of inflammation in increasing the risk of gastrointestinal cancer. It is known that the STEAPs is a family of metal reductases, and its structure and function are closely related to intracellular oxidative stress and inflammation. To investigate whether it can inhibit or activate the inflammatory process, and to provide theoretical basis for the treatment strategy of gastrointestinal tumors. According to the reviewer's critical and professional comments, we re-wrote the abstract and reduced the content on Page 2, with yellow highlight.

(2). The introduction does not highlight the issu.

**Response:** Thank you very much for your critical comments. In accordance with this study, we have made comprehensive revision in the Introduction section. Chronic inflammation is a risk factor for gastrointestinal malignancies, and it is also the molecular and pathophysiological basis of gastritis, inflammatory bowel disease, and upper and lower gastrointestinal cancers. Environmental changes or microbial stimulation, such as gut microbiota, activate the inflammasome and NF- $\kappa$ B pathways, which are inflammatory features involved in the development and progression of

gastrointestinal tumors. As a key metal oxidoreductase, the prostate six transmembrane epithelial antigen protein family is associated with the overexpression of a series of proinflammatory cytokines, and is considered to be a promising therapeutic target for various cancers, especially prostate cancer. Therefore, this study aims to further understand the mechanism of the occurrence and development of gastrointestinal tumors by exploring the inflammatory response of STEAPs in GICs and providing a new strategy for the prevention and early intervention of gastrointestinal tumors. All the changes were highlighted with yellow for tracking on Page 3-4.

There are a lot of inadvertence. Here are few examples: Do you mean that CRC and GC are both the 3rd cause of cancer-related death in the world?" Among them, colorectal cancers (CRCs) are not only the fourth most common malignancy but also the third main cause of cancer-related death in the world. Meanwhile, gastric cancers (GCs) and esophageal cancers (ECs) rank as the third and sixth causes of cancer-related deaths worldwide, respectively [1]." Although effective colonoscopy and upper endoscopy screening can detect polyps and precancerous lesions in the gastrointestinal tract, many patients are still at an advanced stage for their first diagnosis, and the prognosis is poor with existing treatment methods [2]. I disagree, there is a huge differentiation between CRC and GC in terms of screening and diagnosis.

**Response:** Thank you very much for your critical and rigorous comments. It is very important to distinguish the differentiation between different types of GICs. We have timely made such modifications as the reviewer mentioned. Meanwhile, we went through the whole manuscript to clarify the specific type of GIC, avoiding confusing the readers. In addition, although there are differences in screening and diagnosis between colorectal cancer and gastric

cancer, the early detection of gastrointestinal tumors is limited, which is very useful to improve the patients' survival and living quality. Therefore, it is very necessary to further understand the mechanism of the occurrence and development of gastrointestinal tumors and to provide new strategies for early intervention of gastrointestinal tumors. To improve our manuscript, we also sent to a native English speaker with biological background. The language certificate was also uploaded along with our manuscript. All the changes were highlighted with yellow for tracking.

The authors extracted false conclusions from different studies, some of them are not in concordance with the issue or subject. For example: "In the acute lung injury model caused by sepsis, inhibition of STEAP1 reduced the inflammatory response and ROS production, improving cell viability and restoring mitochondrial morphology [63], while in obesity, anti-STEAP4 antibodies can cause increased ROS level and decreased cellular ATP production, resulting in reduced insulin-induced glucose uptake [64]. These investigations indicate the potential role of STEAPs in inflammatory response for Hp-related GC."?????? I do not understand, the authors rely on which studies??? Are the acute lung injury, obesity, Hp and GC related?

**Response:** Thank you very much for your critical and professional comments.

We re-wrote these sentences to clarify the potential function of STEAPs in the metabolism of ATP and ROS, associated with the cellular oxygen stress, on Page 12. Meanwhile, we went through the whole manuscript to clarify the conclusions from different studies, avoiding confusing the readers. To improve our manuscript, we also sent to a native English speaker with biological background. The language certificate was also uploaded along with our manuscript. All the changes were highlighted with yellow for tracking.

The paper is too long, is not clearly written, there are some misunderstandings. From my point of view the paper is not suitable for the journal.

**Response:** Thank you very much for your critical and professional comments.

The whole content of the manuscript was revised comprehensively and polished by a native English speaker. The language certificate was also uploaded along with our manuscript. All the changes were highlighted with yellow for tracking. We accepted the Editor's suggestion to transfer our manuscript to *World Journal of Clinical Oncology*. We believe that the manuscript is improve greatly and will be interest to the readers of the *World Journal of Clinical Oncology*.

**To Reviewer #2:**

**Scientific Quality:** Grade D (Fair)

**Language Quality:** Grade C (A great deal of language polishing)

**Conclusion:** Major revision

**Specific Comments to Authors:**

The manuscript by Fang et al. entitled "The inflammatory response in gastrointestinal cancers: an overview of STEAPs as novel biomarkers in pathophysiology and clinical implications", describes the relationship between inflammation and the implications of STEAPS in gastrointestinal cancers. The paper is interesting; however, it needs major corrections.

-The writing of the manuscript needs to be reviewed by a native English speaker because it has grammatical errors (some verbs and words are written incorrectly; e.g., was exposed for...).

**Response:** Thank you for your serious and rigorous comments. The whole manuscript has been revised based on the reviewers' comments and suggestions and polished by a native English speaker with biological background. All the changes were highlighted with

yellow for tracking. The language certificate was also uploaded in the system.

-The abstract section should be focused on inflammation and STEAPs implications in gastrointestinal cancers. For instance, the main effects of the inflammatory process and STEAPs (processes that inhibit or activate to promote the development of gastrointestinal cancers).

**Response:** Thank you for your critical and professional comments. We re-wrote the abstract to focus on inflammation and STEAPs implications in GICs. Meanwhile, according to the valuable suggestion from Reviewer 1, we also reduced the content of abstract to summarize this study and make it clear to the readers.

-In vivo is written in different ways, please write only “in vivo”.

**Response:** Thank you for your professional and valuable comments. We went through the whole manuscript and changed such description into “*in vivo*” in italic, on Page 7 and Page 8, with yellow highlight for tracking.

-In the keywords section, the word treatment should be eliminated because the manuscript does not contain this information.

**Response:** Thank you for your critical comments. According to the professional views and the results of our study, the word “treatment” had been eliminated in the keywords on Page 2.

-In the core tip section, systematic review is used incorrectly due to this manuscript is only a review.

**Response:** Thank the expert for the rigorous and critical comments. According to the professional views and the results of our study, the “systematic review” had been changed to “review” on Page 2.

-In the introduction section, the authors should define which types of gastrointestinal cancers are included in the paper.

**Response:** Thank you for the reviewers' valuable and professional suggestions and comments. Based on the professional views and research results, gastrointestinal cancers including gastric, colorectal, and liver cancers are redefined in the introduction section. The revised introduction section is shown on Pages 3-4.

-The following information should be reviewed to confirm the prevalence of the cancers. In addition, the authors should include that this data is from the United States. "Among them, colorectal cancers (CRCs) are not only the fourth ..... rank as the third and sixth causes of cancer-related deaths worldwide, respectively [1]."

**Response:** Thank you very much to the reviewer for your critical and professional comments. In the introduction section, following your professional advice, we changed the information about colorectal cancer in more detail to be from US data on Page 3.

-In the introduction section, the molecular mechanisms or pathological processes caused by inflammation that promotes the different types of gastrointestinal cancers should be addressed.

**Response:** Thank you for your in-depth analysis and practical comments. According to previous studies, it mediates the production of proinflammatory cytokines such as IL-6. Environmental changes or microbial stimulation (such as intestinal flora) mediate the production of proinflammatory cytokines such as IL-6 to varying degrees, and then activate inflammatory features that are involved in the occurrence and development of colorectal cancer, namely inflammasome and NF- $\kappa$ B pathway. Similarly, smoking, drinking,

various infections and other environmental factors, susceptibility gene mutations, epigenetic changes and other genetic factors are related to the occurrence of gastric cancer and liver cancer. The details are shown in the discussion section on Page 3-4.

-The next information is already considered in the abstract section, in fact it is exactly the same "The gastrointestinal tract was exposed to diverse food and/or drugs daily, which may be related to various degrees of inflammatory response and kinds of diseases."

**Response:** Thank the reviewer for providing professional suggestion. We re-wrote the abstract and the introduction section to avoid the same description on Page 2 and 3.

-In the following paragraph, please add another reference related to cancer because the reference 6 is about skin disorders: "Recently, the six-transmembrane epithelial a..... has been associated with the overexpression of a range of proinflammatory cytokines [6],"

**Response:** Thank you very much for your professional opinions. Based on this content, the correct references have been added as Reference 13, on Page 4.

-In the introduction section, please add more information about STEAPs related to different types of gastrointestinal cancers, such as how they promote or inhibit cancer progression.

**Response:** Thank you for your suggestions. According to the professional and rigorous comments, STEAP plays its role of metal reductase by regulating the action of a series of pro-inflammatory cytokines, and then further promotes or inhibits the occurrence of gastrointestinal cancer. We had added the suggested content to the manuscript on Page 3-4.



-There is no information on the molecular weight of STEAP1 in the references 11 and 14, please add another reference: "STEAP1 is the first reported STEAP family member with a molecular weight of 39.9kDa and an intramembrane heme binding site [11, 14]."

**Response:** Thank you for your precious advice. To be more clearly and in accordance with the reviewer and readers, relevant reference information is added to the STEAP1 molecular weight as Reference 18 and 21, on Page 5.

-The Rosman folding motif is not mentioned in the references 18 and 19, please add another reference: "the N-terminus of STEAP2-4 (except for STEAP1) have the Rosman folding motif, which is thought to be vital for binding nucleotides such as flavin adenine dinucleotide (FAD) [18, 19]."

**Response:** Deeply appreciate the reviewer's suggestions. Since the Rosman folding motif of STEAP proteins was not described in detail in this study, to avoid confusing the readers, this section was deleted for the consistency of the whole manuscript on Page 6.

-The acronym DMT1 is not defined correctly, please review their definition, thus the word iron should be eliminated: "divalent metal-iron transporter 1 (DMT1)".

**Response:** We are extremely grateful to the reviewer for pointing out this problem, "divalent metal transporter 1 (DMT1)" was revised and modified according to the references on Page 6.

-The reference 25 is not appropriate for the next paragraph: "STEAP3 co-localizes with Tf, TfR1, and divalent metal-iron transporter 1 (DMT1) to participate in iron-uptake mediated by transferrin endosome in erythroid cells [25]".

**Response:** Thank you for your precious advice. In order to enable readers to access the relevant content more correctly, we have modified the citations as Reference 20 and 30, on Page 6.

-In the heading "THE STRUCTURAL CHARACTERISTICS OF STEAP FAMILY MEMBERS", please only add information related to the structural characteristics of the STEAPs; for example, the following information is not related to the structural characteristics of the STEAPs: "Latest studies reported that STEAP3 is up-regulated in non-alcoholic fatty liver disease (NAFLD) and that its overexpression.....regulating liver ischemia-reperfusion injury, hepatocellular carcinoma, myocardial hypertrophy and other diseases [26]."

**Response:** Thank the reviewer's constructive evaluation. This section was revised and modified on Page 4-7, focused on the structural information of STEAPs.

-In figure 2, what do the colored regions and the acronym TM mean? please add this information in the figure legend.

**Response:** Thank you very much your critical suggestions. In FIG. 2, the TM with the colored region represents the transmembrane region and is added in its Figure legend on Page 7.

-In the heading "INFLAMMATORY RESPONSE OF STEAPS IN PHYSIOLOGICAL AND PATHOLOGICAL PROCESSES", please focus this section with the inflammatory response of STEAPs.

**Response:** Thank you for your precious and constructive comments. We re-wrote this section to focused on the inflammatory response of STEAPs on Page 7-9.

-Please add the name of proinflammatory cytokines as examples in the following phrase: ".....revealing a positive association between STEAP1 and

STEAP4 with in vivo proinflammatory cytokines in several neutrophil-driven diseases in humans.”

**Response:** Great thanks for your professional comments. According to your suggestions, proinflammatory cytokines including IL-1, IL-36, CXCL1, CXCL8 were added in such description on Page 9.

-The authors should check reference 57 because it does not relate to the information in the next paragraph: “The latency of Hp leads to a variety of changes in the gastric mucosa, such as gastritis, atrophic gastritis, intestinal metaplasia, dysplasia, and eventually cancer [57, 58].”

**Response:** Thank you very much for your helpful advice. After checking related investigations, we modified the related citation as Reference 65 on Page 11.

-The references 63 and 64 are not related to gastric cancers: “In the acute lung injury model caused by sepsis, .....and restoring mitochondrial morphology [63], while in obesity, anti-STEAP4 antibodies can..... insulin-induced glucose uptake [64].”

**Response:** Thank you for your positive and thoughtful suggestions. According to Reviewer 1’s suggestion, we re-wrote such description and deleted this sentence. So we also removed the references 63 and 64 accordingly on Page 12.

-With respect to the following information: “CRC is the second most common cause of cancer death in the United States and other developed countries, with more than 1 million cases worldwide annually [69].” The reference 69 is from 2009, please update the reference and data.

**Response:** Thank you very much for your professional advice. According to your suggestion, we had amended the relevant part in manuscript on Page 13.

-Please review again if STEAPs are involved in energy metabolism, how do STEAPs regulate energy metabolism?: “As members of metalloredutases, STEAPs are involved in energy metabolism and iron/copper homeostasis [79].”

**Response:** Thank you for the reviewer’s critical comments. We are very sorry for the typing error in this sentence. We have carefully revised this part on Page 14.

- In the following paragraph, the reference 89 is from 2001, please update it. I recommend the next good reference (PMID: 36612019) for this interesting paper.

**Response:** Thank you for your critical comment and helpful suggestion to improve our manuscript. We replaced such citation as Reference 93, on Page 15.

-Please state the units for the value 1.18 (mGy/MBq??): “Another research group constructed ..... and the highest mean absorbed doses to the normal organ was in the liver as 1.18 [95]”.

**Response:** Thank you for your critical comments. According to the relevant references, the unit of 1.18 is mGy/MBq. We revised the description accordingly on Page 16.

-The authors should check reference 98 because it does not relate to the information in the next paragraph: “Interestingly, after HCV infection, STEAP3 was found to be ....., as a potential monitoring biomarker for the development of HCC [98].”

**Response:** Thank you very much for your critical comments. For the content of reliability and readability, relevant citation was supplemented as Reference 102 on Page 16.

-In table 1, please use assigned numbers as references instead of PMID numbers, because it is easier to identify them in the references section. The title should be restructured as “The function/mechanism of STEAPs involved in GICs”, because there is little information on the inflammatory response. In addition, all acronyms used in this table should be defined in the table legend.

**Response:** Thank you for your professional advice. To make it easier for the reader to read, in Table 1, we used the numbers of the references. The title of the table was also changed to a form more consistent with the contents of the table. In addition, all abbreviations that appear in the table are defined on Page 18-19.

-In the next heading: “THE CLINICAL IMPLICATION OF STEAPS IN GIC”, this section does not have enough information with this approach.

**Response:** Thank you very much for your critical and valuable comments and suggestions. We re-wrote this part to expand more information about clinical implications of STEAPs in GICs and provide theoretical basis for further investigation on Page 21.

-In the next paragraph the reference 113 does not belong to Cherl: “Scherl et al. identified transferable IgA-coated *Odoribacter splanchnicus* .....and production of SCFAs, resulting in limitation of colitis [113].”

**Response:** Thank you very much for your critical comments. We are very sorry for the typing error. We changed the correct author name on Page 20.

-Is there a relationship between supplementation of Vitamin A and STEAPs expression? “The supplementation of Vitamin A also ameliorates ulcerative colitis in a gut microbiota-dependent manner, which restores the intestinal barrier and inhibits inflammation [114].”

**Response:** Thank you for your critical suggestion. There was no direct

interaction between vitamin A and STEAP expression. Vitamin A can affect intestinal inflammation by regulating intestinal microbiota. In recent years, STEAPs have been found to play an important role in the inflammatory response. Therefore, it is speculated that there may be some indirect interaction between vitamin A and STEAPs expression. However, as no direct interaction between Vitamin A and STEAPs was found, we deleted such description to avoid confusing the readers, on Page 20.

***To Revision Reviewer:***

-inflammatory process, change proces to processes -disassociation, change disasociation to dissociation

**Response:** Thank you very much for your critical comments. I have revised the manuscript according to your comments.

***To Science editor:***

1 Scientific classification: Grade D and Grade E. Scientific classification: does not meet the publication standard of WJG.

2 Language classification: Grade C and Grade C.

**Response:** Thank you very much for your critical comments. The whole content of the manuscript was revised comprehensively and polished by a native English speaker. The language certificate was also uploaded along with our manuscript. All the changes were highlighted with yellow for tracking. We accepted the Editor's suggestion to transfer our manuscript to *World Journal of Clinical Oncology*. We believe that the manuscript is improve greatly and will be interest to the readers of the *World Journal of Clinical Oncology*.

3 Peer-Review: Reviewer pointed out that the manuscript describes the relationship between inflammation and the implications of STEAPS in

gastrointestinal cancers. The paper is interesting; however, it needs major corrections. There are many issues with both language and content. The abstract did not summarize the study and it is too long. The introduction does not highlight the issue. There are a lot of inadvertence. There are many issues with the content of the manuscript and the expression is not clear. For example, "Among them, colorectal cancers (CRCs) are not only the fourth most common malignancy but also the third main cause of cancer-related death in the world. Meanwhile, gastric cancers (GCs) and esophageal cancers (ECs) rank as the third and sixth causes of cancer-related deaths worldwide, respectively [1]." Although effective colonoscopy and upper endoscopy screening can detect polyps and precancerous lesions in the gastrointestinal tract, many patients are still at an advanced stage for their first diagnosis, and the prognosis is poor with existing treatment methods[2]. I disagree, there is a huge differentiation between CRC and GC in terms of screening and diagnosis. The authors extracted false conclusions from different studies, some of them are not in concordance with the issue or subject. The paper is too long, is not clearly written, there are some misunderstandings. From my point of view the paper is not suitable for the journal.

**Response:** Thank you very much for the reviewer's critical comments and suggestions. We revised the whole manuscript accordingly and send the manuscript to a native English speaker with biological background for polishing. The language certificate was also uploaded along with our manuscript. All the changes were highlighted with yellow for tracking.

4 Specific comments:

(1) Abbreviations other than COVID-19 and SARS-CoV-2 are not allowed in the title of the article, and no more than 18 words are allowed. The title cannot start with "the, a, an";

**Response:** Thank you very much for the title suggested. According to your

professional suggestion, we will name the article title as:  
Inflammatory response in gastrointestinal cancers: Inflammatory  
response in gastrointestinal cancers: overview of six  
transmembrane epithelial antigens of prostate in pathophysiology  
and clinical implications.

(2) The English-language grammatical presentation needs to be improved to a certain extent. There are many errors in grammar and format, throughout the entire manuscript. Before final acceptance, the authors must provide the English Language Certificate issued by a professional English language editing company. Please visit the following website for the professional English language editing companies we recommend:  
<https://www.wjgnet.com/bpg/gerinfo/240>. 5 Recommendation: Rejection.

**Response:** Thank you very much for your critical comments. The whole content of the manuscript was revised comprehensively and polished by a native English speaker. The language certificate was also uploaded along with our manuscript. All the changes were highlighted with yellow for tracking.