Nov 29, 2022

Dear Prof. Lian-Sheng Ma,

World Journal of Gastroenterology

RE: # NO: 80852, A review of ferroptosis in colorectal cancer: Friends or Foes?

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 with revised title **"A review of ferroptosis in colorectal cancer: Friends or Foes?" (ID: 80852).** 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

Cancer Hospital of Shantou University Medical College

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 A (Excellent)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: First, focusing on CRC, this manuscript illustrates the molecular mechanisms and pathways of ferrochrysetic disease and proposes that cancer therapy based on ferrochrysetic disease may not be suitable for all cancer types, or even for different clinical stages of the same type. The TP53-induced glycolysis and apoptosis regulator (TIGAR) is a potential regulator of iron sag in the development of colorectal cancer, and TIGAR is a potential negative regulator of iron sag. In addition, factors regulating gpx4 may be involved in the regulation of ferrolapse. GTP loop hydrolase 1 (GCH1), a rate-limiting enzyme that synthesizes free radicals to capture the antioxidant tetrahydrotrexate (BH4), has been found to inhibit ferrolapse in a GPX4-independent manner, and it has been clinically proposed that inducing ferrolapse in cancer cells may induce vaccine-like effects. The idea of stimulating anti-tumor immunity to overcome immunotherapy resistance and of immunosuppressive cells in TME contributing to immunotherapy resistance is constructive and instructive. Second, this manuscript mainly plays a role of summary and inspiration in this field. The content structure is logical, the language narrative is organized, and the illustrations are concise and clear. The background investigation and summary are carried out by the literature discovery method, and the summary is comprehensive and complete. It will further help the specific mechanisms involved in the occurrence, development and metastasis of colorectal cancer. Third, many studies have proposed possible pathways for iron sag in colorectal cancer, but the specific mechanisms of its involvement in the onset, progression and metastasis of colorectal cancer remain unclear. In

the classical pathway, GPX4 can be used as a target for tumor therapy, but inhibition of GPX4 may have side effects on its protective effect against beta-amyloid toxicity in neurons. In addition, p53 has conflicting effects on iron lobe, but its mechanism in colorectal cancer is unique. Future research could explore how to switch between the "brake" and the "accelerator" in the regulation of iron sag. In addition to classical mechanisms, other potential regulatory pathways need to be discovered. Therefore, it is very necessary for the majority of researchers to learn from the systematic knowledge framework of the paper on the basis of theory combined with clinical practice to further research on colorectal cancer iron ptosis.

Responses: Thank you very much for your time involved in reviewing the manuscript and your very encouraging comments on the merits. We have revised the manuscript according to reviewer's valuable comments and suggestions. The revised manuscript has been polished by an English-native speaker with biological background. All the revision was highlight with yellow for tracking.

To Reviewer #2:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: In this paper, the authors aimed to elucidate the underlying mechanisms of ferroptosis in colorectal cancer by literature review. This study is some interesting and the results may be useful. However, some critical concerns should be addressed before publish.

Responses: Thank you for your positive comments and valuable suggestions to improve our manuscript. We have revised the manuscript according to your valuable comments and suggestions. The revised manuscript has been polished by an English-native

speaker with biological background. All the revision was highlight with yellow for tracking.

1 Title: Appropriate. But, I suggested to add study design or article type in the title.

Responses: Thank you for your positive comments and valuable suggestions. We changed the title as "A review of ferroptosis in colorectal cancer: Friends or Foes?" with its article type.

2 Abstract: Well described in the manuscript.

3 Key words: Appropriate.

Responses: Thank you for your positive comments.

4 Background: Please add references about review article related to similar issue.

Responses: Thank you for your valuable suggestions. In response, we have added a brief introduction to the background section on "Morphological changes in ferroptosis" and "Genes associated with ferroptosis predict prognosis in colon cancer patients", along with relevant references. For details, please refer to Line 4-7 and Line 24-27 on Page 4.

5 Methods: Appropriate.

6 Results: Appropriate.

Responses: Thank you for your positive comments on this part of our content.

7 Discussion: I am not familiar the hypothesis proposed in this study. The authors should clarify this concern for discussion.

Responses: We deeply appreciate the reviewer's professional suggestion. According to the reviewer's comment, we first made a

comprehensive review of the context of the article and added subheadings to each part to enhance the logic of the article. Secondly, we supplemented the framework and content of the paper by adding "Morphological changes of ferroptosis" (Page 12-13) and "Ferroptosis related genes predict prognosis of colon cancer patients" (Page 23-24), making the paper clearer and more comprehensive in content. Finally, this review article mainly elaborates and summarizes the development, molecular mechanism, key links, influencing factors, clinical application and prognosis of ferroptosis, and focuses on the role of ferroptosis in colorectal cancer.

8 Illustrations and tables: I am not familiar in vivo model. Please introduce commonly used illustrations and tables for predictive model. Does any vitro model involve the similar topic?

Responses: We feel great thanks for your professional review work on our article. According to your nice and valuable suggestions, we have made extensive corrections to our previous manuscript. We have added necessary predictive models to supplement our review. In previous manuscripts, we have summarized in vitro models of other research, including drug-induced experiments on ferroptosis inducers and inhibitors. In response to your valuable suggestions to us, we have added the table entitled "Prognostic Model of Colon Cancer Associated with Iron Death Genes" (Page 24, Table 1).

9 Biostatistics: Not applicable.

10 Units: Does the manuscript meet the requirements of use of international system of units?

Responses: Thanks for your reminder. There is no data involved in this paper and no international system of units involved.

11 References: Please cite appropriately the latest, important and authoritative references in the introduction and discussion sections.

Responses: Thank you for your professional comments. We revised the whole manuscript and cited associated references, especially in the introduction and discussion.

12 Quality of manuscript organization and presentation: Please provide English editing certificate.

Responses: Thank you for your valuable suggestions. The revised manuscript has been polished by a native English-speaker with biological background. The certificate was attached in the submission system.

13 Research methods and reporting: Please provide appropriate research methods and reporting. Authors should have prepared their manuscripts according to manuscript type and the appropriate categories, as follows: (1) CARE Checklist (2013) - Case report; (2) CONSORT 2010 Statement - Clinical Trials study, Prospective study, Randomized Controlled trial, Randomized Clinical trial; (3) PRISMA 2009 Checklist - Evidence-Based Medicine, Systematic review, Meta-Analysis; (4) STROBE Statement - Case Control study, Observational study, Retrospective Cohort study; and (5) The ARRIVE Guidelines - Basic study.

Responses: Thank you for your review. Since this is a review article, there is no reports for the research methods and reporting.

14 Ethics statements: Please provide appropriate ethics approval.

Responses: Thank you for your review. This review did not cover any animal or clinical trials. So no ethics approval was attached with this manuscript.

To Reviewer #3:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: It is my honor to be invited by your journal to be the reviewer of this review. I have carefully read the manuscript. It is a topic of interest to researchers in the related areas because of the popularity of ferroptosis recently. The expression of this whole review is comprehensive, but the paper still needs some improvements before acceptance for publication.

Responses: Thank you for your positive comments and valuable suggestions to improve our manuscript. We have revised the manuscript according to your valuable comments and suggestions. The revised manuscript has been polished by an English-native speaker with biological background. All the revision was highlight with yellow for tracking.

My detailed comments are as follows:

1. In this article, the author discussed the mechanism of ferroptosis and its signaling pathway. However, the relevant information we see in the article is complex and cluttered. And the organization of the article needs to be adjusted. In addition, it is suggested to add the correlation with colorectal cancer.

Responses: Thanks for your critical comments and valuable suggestions to improve the quality of our manuscript. According to your suggestions, we have carefully sorted out the article, adjusted and supplemented the structure and content of the article (Page 12-13, Page 23-24), and focused on describing and expanding the

colorectal cancer part (Page 24, Table 1). We hope this version will be improved and benefit the readers.

2. The title of the author revolves around friends or enemies, but the explanation in the article is insufficient. It is suggested to add relevant content.

Responses: We deeply appreciate your suggestions. This article summarizes the relevant research on ferroptosis in the past decades, and explains the dual role of ferroptosis in colon cancer. According to the current findings, ferroptosis plays a different role in colon cancer, and its effect on colon cancer is still debated. In response to your comments, we have revised the title with its type and mentioned the main mechanism of ferroptosis in CRC (Page 23-24).

3. At the end of the article, the practical clinical significance of inducing ferroptosis was described, it is suggested to supplement other aspect that inhibit the effect of ferroptosis on tumor, so as to better respond to the enemy in title.

Responses: We feel great thanks for your professional review work on our article. While explaining the positive significance of inducing ferroptosis in the treatment of colon cancer, this paper also expounds the negative effect of inhibiting ferroptosis on the treatment of colon cancer. Based on your opinion, we tried to separate the effects of inducing and inhibiting ferroptosis on colon cancer, but we found that the connection between the two is too close and inseparable, so we have divided this paragraph into subheadings (Page 20-24).

To EDITORIAL OFFICE'S COMMENTS

(1) Science editor:

The manuscript has been peer-reviewed, and it' s ready for the first decision.

Language Quality: Grade B (Minor language polishing)

Scientific Quality: Grade C (Good)

Responses: Thank you for the editor's and reviewers' positive comments and valuable suggestions to improve our manuscript. We have revised the manuscript according to the valuable comments and suggestions. The revised manuscript has been polished by an English-native speaker with biological background. All the revision was highlight with yellow for tracking.

(2) Company editor-in-chief:

I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Gastroenterology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. Before final acceptance, the author(s) 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. Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file. Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is 'original', the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2022. If an author of a submission is re-using a figure or figures published elsewhere, or that is copyrighted, the author must provide documentation that the previous

publisher or copyright holder has given permission for the figure to be re-published; and correctly indicating the reference source and copyrights. For example, “Figure 1 Histopathological examination by hematoxylin-eosin staining (200 ×). A: Control group; B: Model group; C: Pioglitazone hydrochloride group; D: Chinese herbal medicine group. Citation: Yang JM, Sun Y, Wang M, Zhang XL, Zhang SJ, Gao YS, Chen L, Wu MY, Zhou L, Zhou YM, Wang Y, Zheng FJ, Li YH. Regulatory effect of a Chinese herbal medicine formula on non-alcoholic fatty liver disease. World J Gastroenterol 2019; 25(34): 5105-5119. Copyright ©The Author(s) 2019. Published by Baishideng Publishing Group Inc[6]”. And please cite the reference source in the references list. If the author fails to properly cite the published or copyrighted picture(s) or table(s) as described above, he/she will be subject to withdrawal of the article from BPG publications and may even be held liable. Before final acceptance, when revising the manuscript, the author must supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript. To this end, authors are advised to apply a new tool, the Reference Citation Analysis (RCA). RCA is an artificial intelligence technology-based open multidisciplinary citation analysis database. In it, upon obtaining search results from the keywords entered by the author, "Impact Index Per Article" under "Ranked by" should be selected to find the latest highlight articles, which can then be used to further improve an article under preparation/peer-review/revision. Please visit our RCA database for more information at: https://www.referencecitationanalysis.com/.

Responses: Thank you for the editor’s and reviewers’ positive comments and valuable suggestions to improve our manuscript. We have revised the manuscript according to the valuable comments and suggestions. The revised manuscript has been polished by an English-native speaker with biological background. All the revision was highlight with yellow for tracking. The Figure is