

Dear Editors and Reviewers:

Thank you for giving us the opportunity to submit a revised draft of the manuscript **“The role of targeted ferroptosis and its combination strategy in combating drug resistance in colorectal cancer”** for publication in *World Journal of Clinical Oncology*. We appreciate the time and effort that you and the reviewers dedicated to providing feedback on our manuscript and are grateful for the insightful comments on and valuable improvements to our editorial.

We have carefully considered all the suggestions of the reviewer. We have tried our best to revise the manuscript, and in the latest manuscript, the revision is highlighted in yellow. Please see below, for a point-by-point response to the reviewers’ comments and concerns.

Responses to reviewer’s comments:

Reviewer:

1.

Lines 84-85: Revise the sentence.

Response: We are grateful for the suggestion. We carefully revised and polished the sentence, and marked it in yellow.

Sentence: The conventional treatment of metastatic CRC, however, is still limited by the adverse reactions associated with chemotherapy drugs and the biological characteristics of tumors.

2.

Delete the commas (lines 22; 31; 55; 126).

Response: Thank you for your advice. We corrected comma usage in the relevant sentences and marked it in yellow.

Sentence:

Research into ferroptosis offers new insights into the pathogenesis and clinical treatment of CRC and may provide new treatments for cancers that are resistant to traditional therapies. (lines 22)

Here, we provide unique insights that targeting ferroptosis in CRC cells can improve tumor cell resistance caused by CRC genome instability and TME alterations and provide new therapeutic strategies to break through the clinical drug resistance of CRC. (lines 31)

However, the absence of AMER1 *in vivo* protects metastatic CRC cells from ferroptosis caused by high oxygen levels in the blood and promotes the metastasis of CRC cells. (lines 55)

This editorial highlights how targeting ferroptosis in CRC cells can help to reduce the resistance of tumor cells due to CRC genomic instability and TME and presents a potential new approach for combining ferroptosis targeting with chemotherapy, targeted therapy, radiotherapy, and immunotherapy. (lines 126)

3.

Add a comma (line 76, after “Thus”).

Response: Thank you for your advice. We corrected comma usage in the relevant sentences and marked it in yellow.

Sentence:

Thus, inhibiting the lipid peroxidation of ACSL4 drive and ferroptosis is CDK1 promote CRC patients with drug-resistant OXA into the necessary conditions.

4.

Insert space (lines 48; 76).

Response: Thank you for your advice. We corrected and insert space in the relevant sentences and marked it in yellow.

Sentence:

Research has shown that pre-treatment of HeLa cells with GSK-3 β inhibitor can prevent erastin-induced ferroptosis. AMER1 has been identified as a component of a complex which recruits AXIN1, β -TrCP and APC to facilitate the ubiquitination and degradation of β -catenin.(lines 48)

In addition, the physical binding of CDK1 to ACSL4 facilitated the degradation of ACSL4 in OXA-resistant CRC cells, thereby resisting ferroptosis of tumor cells. Thus, inhibiting the lipid peroxidation of ACSL4 drive and ferroptosis is CDK1 promote CRC patients with drug-resistant OXA into the necessary conditions. CDK1 inhibitors

synergistically enhance the anti-tumor effect of OXA in OXA-resistant CRC. (lines 76)

5.

“in vivo” should be written in italics (lines 53; 92)

Response: Thank you for your advice. We modified the font format of each “*in vivo*” and marked it in yellow.

Sentence: This leads to an overload of ROS and induces ferroptosis. However, the absence of AMER1 *in vivo* protects metastatic CRC cells from ferroptosis caused by high oxygen levels in the blood and promotes the metastasis of CRC cells.(lines 53) Moreover, through *in vivo* analysis and tumor samples, some researchers have found that APOL3-LDHA axis can promote ferroptosis of CRC cells and the cytotoxic ability of CD8⁺ T cells by increasing IFN γ and reducing lactate concentration in TME. (lines 92)

6.

A dot is missing (line 66).

Response: Thank you for your advice. We added a dot at the end of the sentence and marked it in yellow.

Sentence: This suggests the clinical potential of ferroptosis inducers as combination therapies to target tumor antioxidant status and treat CRC.

7.

Delete space after “OXA” (lines 71; 75; 79) and in “6-[2-(3-methyl) -naphthoquinyl]-hexanoic” (line 104).

Response: Thank you for your advice. We removed the spaces as requested and marked it in yellow.

Sentence: The mRNA and protein levels of CDK1 were significantly up-regulated in OXA-resistant CRC tissues, while the number of clones formed by OXA and CDK1 knockout cells was down-regulated, indicating that the depletion of CDK1 could overcome OXA resistance in CRC patients. In addition, the physical binding of CDK1 to ACSL4 facilitated the degradation of ACSL4 in OXA-resistant CRC cells, thereby resisting ferroptosis of tumor cells. Thus, inhibiting the lipid peroxidation of ACSL4 drive and ferroptosis is CDK1 promote CRC patients with drug-resistant OXA into the necessary conditions. CDK1 inhibitors synergistically enhance the anti-tumor effect of OXA in OXA-resistant CRC. (lines 71; 75; 79)

Xu et al. coordinated and assembled iron ions with 6-[2-(3-methyl) -naphthoquinyl]-hexanoic acid (NQA), a derivative of vitamin K3, to obtain multifunctional Fe-NQA

nanopolymer particles (Fe-NQA NPs), which reduced Fe³⁺ to Fe²⁺ while producing a large amount of ROS using NQA. (line 104)

8.

Replace “play” with “plays” (line 88).

Response: Thank you for your advice. We replaced “play” with “plays” and marked it in yellow.

Sentence: Unfortunately, immunotherapy for only a minority of patients with high microsatellite instability plays a significant curative effect, and most patients will have certain resistance.

9.

Change the capital letter in “Through” with small (line 92).

Response: Thank you for your advice. We Changed the capital letter in “Through” with small and marked it in yellow.

Sentence: Moreover, through *in vivo* analysis and tumor samples, some researchers have found that APOL3-LDHA axis can promote ferroptosis of CRC cells and the cytotoxic ability of CD8⁺ T cells by increasing IFN γ and reducing lactate concentration in TME.

10.

Add a reference after Xu et al. (line 103).

Response: Thank you for your advice. We Added a reference after *Xu et al.* and marked it in yellow.

Sentence: Xu et al. [10] coordinated and assembled iron ions with 6-[2-(3-methyl) - naphthoquinyl]-hexanoic acid (NQA), a derivative of vitamin K3, to obtain multifunctional Fe-NQA nanopolymer particles (Fe-NQA NPs), which reduced Fe³⁺ to Fe²⁺ while producing a large amount of ROS using NQA.

11.

Correctly write the chemical formulae of the ions (line 106).

Response: Thank you for your advice. We corrected the chemical formulae of the ions and marked it in yellow.

Sentence: Xu et al. [10] coordinated and assembled iron ions with 6-[2-(3-methyl) -

naphthoquinyl]-hexanoic acid (NQA), a derivative of vitamin K3, to obtain multifunctional Fe-NQA nanopolymer particles (Fe-NQA NPs), which reduced Fe^{3+} to Fe^{2+} while producing a large amount of ROS using NQA.

We sincerely hope that this revised manuscript has addressed all your comments and suggestions. We appreciated for reviewer's warm work earnestly, and hope that the correction will meet with approval. Once again, thank you very much for your comments and suggestions.