

Name of journal: World Journal of Gastrointestinal Oncology

Manuscript NO: 80162

Title: Role of Ferroptosis in Colorectal Cancer

Responses for reviewer's comments

Reviewer's code: 03259131

Comment:

It is my great honour and pleasure to review such an interesting manuscript. The authors review that ferroptosis (an iron-dependent non-apoptotic cell death) is characterized by the accumulation of lipid reactive oxygen species and plays a role in reversing resistance to anticancer drugs.

This study is a narrative review.

Major points,

1. There is a big discrepancy between the experimental models and real clinical circumstances. The authors must comment it and disclose the data concerning an iron accumulation, uptake, in/out imbalance, etc.
Academically, it is very important to compare the experimental study and the clinical phenomenon, the concentration, oxidation, dynamics, etc.
2. Above all, this study is well-designed. I agree the authors' insistence. This manuscript is well-written and illustrated. On the other hand, as a review article, the collected literatures are a little older. There have been already issued many similar reports. At least, the authors should discuss by referring the newest trials and reports. Also, the authors must show the priority and the superiority of this manuscript. This is important.
3. The figure should include some ferroptosis pathway. It is my recommendation.

Minor points,

Figure and figure legends should be arranged separately.

Of course, this review is interesting and important. However, the present manuscript needs some revisions for the publication of "World Journal of Gastroenterology" .

Author's response:

We appreciate for the thorough review and positive comments on our manuscript.

Major points,

1.Regarding the differences between experimental studies and clinical practice of iron metabolism, the manuscript complements the processes of iron absorption and excretion. The differences between iron metabolism in vitro and in clinical practice and its possible causes are added in the second paragraph of the conclusion. And it complements the current new technology, namely the application of nanomedical drug delivery systems.

2.In the introduction of each mechanism, the manuscript is supplemented with the latest literature. In addition to targeting drug resistance, it also complements the application of nanomedical drug delivery systems. Compared with previous literatures, the mechanism of ferroptosis in colorectal cancer, the improvement of drug resistance and the application of treatment were summarized.

3. The P53-YAP1 and ATF3-SLC7A11 pathways are added in the figure, and the attached figure description is detailed. Please check the revised manuscript.

Minor points,

We have arranged the figure and figure legends separately according to reviewer' s comments. Please check the revised manuscript.

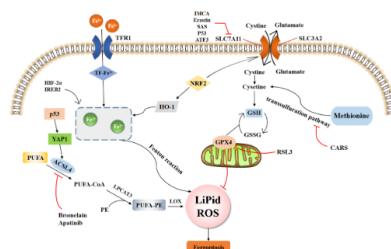


Figure 1 Mechanisms of ferroptosis in CRC.

Figure Legends

Figure 1. The diagram shows several potential regulatory pathways for ferroptosis. Including Xc^- system, lipid peroxide accumulation, sulfur transfer pathway, GSH /GPX4 lipid repair system, Nrf2-HO-1, cellular iron homeostasis, p53, etc. TFR1 transferrin receptor 1, TF transferrin, IREB2 iron response element-binding protein 2, PUFA polyunsaturated fatty acid, ACSL4 acyl-CoA synthetase long-chain family member 4, LPCAT3 lysophosphatidylcholine acyltransferase 3, PE phosphatidylethanolamine, LOX lipoxygenase, NRF2 nuclear factor erythroid 2-related factor, HO-1 hemo oxygenase 1, SLC7A11 solute carrier family 7 member 11, IMCA-benzoxazin derivative 2-imino-6-methoxy-2H-chromene-3-carbothioamide, SAS sulphasalazine, GSH glutathione, GSSG oxidized glutathione, GPX4 glutathione peroxidase 4, RSL3 Ras-selective lethal 3, CARS cysteinyl-tRNA synthetase, ATF3 activating transcription factor 3, YAP1 Yes-associated protein 1.

Reviewer' s code: 05837732

Comment: This manuscript by Ya-qi Song et al. highlights the prognostic role of ferroptosis and deciphers its mechanistics in colorectal cancer (CRC). In general, this review adequately reports on the current state of knowledge of ferroptosis in CRC. It is coherently organized with an appropriate bibliography. Minor concern: Line 134: please define CircRNA. Figure 1: The authors should implement the figure legend with a very brief description of the scheme. Abbreviations are not self-explanatory. The P53-YAP1 pathway should also be added in the figure.

Author's response:

CircRNA has been defined, the P53-YAP1 pathway has been added to the figure, and a short description of each mechanism has been added to the accompanying illustration.