ISSN 2218-4333 (online)

World Journal of *Clinical Oncology*

World J Clin Oncol 2024 March 24; 15(3): 360-463

Published by Baishideng Publishing Group Inc

World Journal of Clinical Oncology

Contents

Monthly Volume 15 Number 3 March 24, 2024

World Journal of Clinical Oncology

Monthly Volume 15 Number 3 March 24, 2024

Contents

World Journal of Clinical Oncology

Monthly Volume 15 Number 3 March 24, 2024

Contents

ABOUT COVER

Peer Reviewer of *World Journal of Clinical Oncology*, Alessandro Posa, MD, Department of Diagnostic Imaging, Oncologic Radiotherapy and Hematology, Fondazione Policlinico Universitario A. Gemelli - IRCCS, Rome 00168, RM, Italy. alessandro.posa@policlinicogemelli.it

AIMS AND SCOPE

The primary aim of *World Journal of Clinical Oncology* (*WJCO*, *World J Clin Oncol*) is to provide scholars and readers from various fields of oncology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJCO mainly publishes articles reporting research results and findings obtained in the field of oncology and covering a wide range of topics including art of oncology, biology of neoplasia, breast cancer, cancer prevention and control, cancer-related complications, diagnosis in oncology, gastrointestinal cancer, genetic testing for cancer, gynecologic cancer, head and neck cancer, hematologic malignancy, lung cancer, melanoma, molecular oncology, neurooncology, palliative and supportive care, pediatric oncology, surgical oncology, translational oncology, and urologic oncology.

INDEXING/ABSTRACTING

The *WJCO* is now abstracted and indexed in PubMed, PubMed Central, Emerging Sources Citation Index (Web of Science), Reference Citation Analysis, China Science and Technology Journal Database, and Superstar Journals Database. The 2023 Edition of Journal Citation Reports® cites the 2022 impact factor (IF) for *WJCO* as 2.8; IF without journal self cites: 2.8; 5-year IF: 3.0; Journal Citation Indicator: 0.36.

RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Clinical Oncology

ISSN
ISSN 2218-4333 (online)

LAUNCH DATE
November 10, 2010

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Hiten RH Patel, Stephen Safe, Jian-Hua Mao, Ken H Young

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2218-4333/editorialboard.htm

PUBLICATION DATE
March 24, 2024

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

World Journal of Clinical Oncology

Submit a Manuscript: https://www.f6publishing.com

World J Clin Oncol 2024 March 24; 15(3): 375-377

DOI: 10.5306/wjco.v15.i3.375

ISSN 2218-4333 (online)

EDITORIAL

Role of targeting ferroptosis as a component of combination therapy in combating drug resistance in colorectal cancer

Xiao-Ting Xie, Qiang-Hu Pang, Lian-Xiang Luo

Specialty type: Cell biology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Vynios D, Greece

Received: December 8, 2023
Peer-review started: December 8, 2023
First decision: December 18, 2023
Revised: December 27, 2023
Accepted: February 25, 2024
Article in press: February 25, 2024
Published online: March 24, 2024

Xiao-Ting Xie, Qiang-Hu Pang, The First Clinical College, Guangdong Medical University, Zhanjiang 524023, Guangdong Province, China

Lian-Xiang Luo, The Marine Biomedical Research Institute, Guangdong Medical University, Zhanjiang 524023, Guangdong Province, China

Corresponding author: Lian-Xiang Luo, PhD, Associate Professor, The Marine Biomedical Research Institute, Guangdong Medical University, No. 2 Wenming East Road, Xiashan District, Zhanjiang 524023, Guangdong Province, China. lulianxiang321@gdmu.edu.cn

Abstract

Colorectal cancer (CRC) is a form of cancer that is often resistant to chemotherapy, targeted therapy, radiotherapy, and immunotherapy due to its genomic instability and inflammatory tumor microenvironment. Ferroptosis, a type of non-apoptotic cell death, is characterized by the accumulation of iron and the oxidation of lipids. Studies have revealed that the levels of reactive oxygen species and glutathione in CRC cells are significantly lower than those in healthy colon cells. Erastin has emerged as a promising candidate for CRC treatment by diminishing stemness and chemoresistance. Moreover, the gut, responsible for regulating iron absorption and release, could influence CRC susceptibility through iron metabolism modulation. Investigation into ferroptosis offers new insights into CRC pathogenesis and clinical management, potentially revolutionizing treatment approaches for therapy-resistant cancers.

Key Words: Colorectal cancer; Ferroptosis; Immunotherapy; Drug resistance; Chemotherapy; Nanodrug delivery systems

Core Tip: Drug resistance poses a challenge to the treatment of colorectal cancer (CRC). In this paper, we offer novel perspectives on tackling this issue by focusing on ferroptosis in CRC cells. This approach holds promise in overcoming tumor cell resistance caused by CRC genome instability and changes in the tumor microenvironment, thereby providing innovative therapeutic strategies to break through the clinical drug resistance in CRC.

Citation: Xie XT, Pang QH, Luo LX. Role of targeting ferroptosis as a component of combination therapy in combating drug resistance in colorectal cancer. *World J Clin Oncol* 2024; 15(3): 375-377
URL: https://www.wjgnet.com/2218-4333/full/v15/i3/375.htm
DOI: https://dx.doi.org/10.5306/wjco.v15.i3.375

INTRODUCTION

Colorectal cancer (CRC) is a serious and aggressive form of cancer. Unfortunately, the majority of patients are diagnosed at advanced stages, with 50% of cases being prone to liver metastasis, leading to a poor prognosis and high mortality rate. The inflammatory tumor microenvironment (TME) and genomic instability in CRC make it resistant to existing treatments such as chemotherapy, targeted therapy, and immunotherapy. Ferroptosis emerges as a novel type of programmed cell death that is dependent on iron-induced lipid peroxidation. Cancer cells can evade ferroptosis signaling pathways, resulting in uncontrolled disease progression and drug resistance. Recently, ferroptosis has been proposed as a potential solution to the issue of cancer cells bypassing apoptosis and anti-apoptosis-induced drug resistance and metastasis[1].

The adenomatous polyposis coli (APC) tumor suppressor protein, forming a complex with GSK-3β and AXIN1, plays a significant role in the frequent mutation occurrence in CRC. Deactivation of this protein stands as a common CRC trigger. Studies indicate that pretreating HeLa cells with a GSK-3β inhibitor can thwart erastin-induced ferroptosis[2]. AMER1 is recognized as part of a complex that recruits AXIN1, β-TrCP, and APC to facilitate β-catenin ubiquitination and degradation. In CRC cells with wild-type status, AMER1 binds to SLC7A11 or FTL, recruiting β-TrCP1/2 to expedite FTL and SLC7A11 ubiquitination and degradation. This leads to an escalation in the labile free iron pool and a decline in cystine uptake, causing reactive oxygen species (ROS) overload and ferroptosis induction. However, AMER1 absence *in vivo* shields metastatic CRC cells from ferroptosis triggered by elevated blood oxygen levels, fostering CRC cell metastasis. This underscores a correlation between AMER1 mutations and CRC metastasis[3]. Studies have showed that KRAS mutations are one of the most common mutations in CRC. A recent study found that in male CRC patients, untargeted metabolomics data revealed that tumors with KRAS mutations have several pathways that inhibit ferroptosis. Furthermore, targeted metabonomics of RSL3 MC38 cells harboring KRAS mutations confirmed this finding by identifying iron metabolite precipitation. Inadequate administration of cetuximab to KRAS mutant cell lines can increase lipid peroxides or induce ferroptosis. Additionally, when used in combination with cetuximab and RSL3, cetuximab increases ROS production and the malondialdehyde enhanced RSL3 cytotoxic effect[4]. This suggests the clinical potential of ferroptosis inducers as a component of combination therapies to target tumor antioxidant status and treat CRC.

Chemotherapy is widely used in the clinical treatment of CRC. Oxaliplatin (OXA), as a chemotherapeutic drug, is frequently used in the treatment of CRC, but patients frequently develop drug resistance, which limits its therapeutic effect. Some studies have found that cyclin dependent kinase 1 (CDK1) may be a key factor in OXA resistance. The mRNA and protein levels of CDK1 were significantly up-regulated in OXA-resistant CRC tissues, while the number of clones formed by CDK1 knockout cells treated with OXA was decreased, indicating that the depletion of CDK1 could overcome OXA resistance in CRC patients. Moreover, the physical interaction of CDK1 with ACSL4 led to ACSL4 degradation in OXA-resistant CRC cells, thwarting tumor cell ferroptosis. Thus, inhibiting ACSL4 lipid peroxidation and promoting ferroptosis through CDK1 inhibition create essential conditions for managing OXA-resistant CRC patients. CDK1 inhibitors synergistically enhance the anti-tumor effect of OXA in OXA-resistant CRC[5]. Additionally, research has unveiled that the ferrophilic short-chain fatty acid butyrate can enhance the ferrophilic ability of OXA and induce ferroptosis in CRC. Butyrate can also inhibit xCT mediated ferroptosis resistance by inducing c-Fos expression, reverse the resistance of cancer stem cells to ferroptosis, and promote the occurrence of ferroptosis[6].

The conventional treatment of metastatic CRC, however, is still limited by the adverse reactions associated with chemotherapy drugs and the biological characteristics of tumors. Immune checkpoint blockade holds considerable promise in malignancy treatment. Regrettably, immunotherapy achieves notable curative outcomes only in a minority of patients with high microsatellite instability, with most patients displaying a certain level of resistance. Research indicates that CYP1B1 enhances tumor cell resistance to ferroptosis by increasing ACSL4 ubiquitination and promoting its degradation, and the therapeutic effect of anti-PD-1 therapy may be enhanced by inhibiting CYP1B1[7]. Moreover, through *in vivo* analysis, some researchers have identified the role of the APOL3-LDHA axis in promoting CRC cell ferroptosis and enhancing CD8+ T cell cytotoxicity by increasing IFNγ levels and reducing lactate concentration in the TME[8]. These findings suggest that targeting ferroptosis in CRC cells might effectively combat immune checkpoint blockade resistance.

Because targeting ferroptosis has shown great potential in CRC treatment, enhancing the selectivity of ferroptosis inducers and mitigating unnecessary side effects emerge as pressing concerns in clinical transformation. In this regard, the development of nanotechnology provides new possibilities for ferroptosis induction in cancer treatment. Nanodrug delivery systems (nano-DDSs) leverage the unique physical and chemical properties of nanomaterials for efficient targeted drug delivery to achieve more precise therapeutic effects[9]. Zhang *et al*[10] coordinated and assembled ions with 6-[2-(3-methyl)-naphthoquinyl]-hexanoic acid (NQA), a derivative of vitamin K3, to obtain multifunctional Fe-NQA nanopolymer particles, which reduced Fe^{3+} to Fe^{2+} while producing a large amount of ROS. In addition, the Fenton reaction occurred and ferroptosis was induced. The nano-DDS exhibited remarkable tumor inhibitory effect and inhibited tumor metastasis in the CT26 mouse tumor model. Most importantly, some studies have suggested that nano-DDSs may improve the multidrug resistance of CRC cells and the treatment effect in CRC patients[11]. These findings proved that

nano-therapy has great potential in targeting ferroptosis in CRC cells. However, since nano-DDSs are still in the emerging stage of research, more clinical studies are needed to further explore their efficacy.

CONCLUSION

This editorial emphasizes the potential of targeting ferroptosis in CRC cells to reduce the drug resistance of tumor cells due to CRC genomic instability and inflammatory TME, and presents a potential new approach for the treatment of this malignancy by combining ferroptosis targeting with chemotherapy, targeted therapy, radiotherapy, and immunotherapy.

FOOTNOTES

Author contributions: Xie XT, Pang QH, and Luo LX wrote the editorial; Luo LX conceived and designed the editorial, reviewed the paper, and provided comments; all authors read and approved the final manuscript.

Conflict-of-interest statement: All authors declare no conflicts of interest for this article.

Country/Territory of origin: China

ORCID number: Lian-Xiang Luo 0000-0002-3391-9713.

S-Editor: Zhang H
L-Editor: Wang TQ
P-Editor: Zhao S

REFERENCES

1 **Yan H**, Talty R, Aladelokun O, Bosenberg M, Johnson CH. Ferroptosis in colorectal cancer: a future target? *Br J Cancer* 2023; **128**: 1439-1451 [PMID: 36703079 DOI: 10.1038/s41416-023-02149-6]
2 **Wang L**, Ouyang S, Li B, Wu H, Wang F. GSK-3β manipulates ferroptosis sensitivity by dominating iron homeostasis. *Cell Death Discov* 2021; **7**: 334 [PMID: 34732689 DOI: 10.1038/s41420-021-00726-3]
3 **Lei S**, Chen C, Han F, Deng J, Huang D, Qian L, Zhu M, Ma X, Lai M, Xu E, Zhang H. AMER1 deficiency promotes the distant metastasis of colorectal cancer by inhibiting SLC7A11- and FTL-mediated ferroptosis. *Cell Rep* 2023; **42**: 113110 [PMID: 37682704 DOI: 10.1016/j.celrep.2023.113110]
4 **Yang J**, Mo J, Dai J, Ye C, Cen W, Zheng X, Jiang L, Ye L. Cetuximab promotes RSL3-induced ferroptosis by suppressing the Nrf2/HO-1 signalling pathway in KRAS mutant colorectal cancer. *Cell Death Dis* 2021; **12**: 1079 [PMID: 34775496 DOI: 10.1038/s41419-021-04367-3]
5 **Zeng K**, Li W, Wang Y, Zhang Z, Zhang L, Zhang W, Xing Y, Zhou C. Inhibition of CDK1 Overcomes Oxaliplatin Resistance by Regulating ACSL4-mediated Ferroptosis in Colorectal Cancer. *Adv Sci (Weinh)* 2023; **10**: e2301088 [PMID: 37428466 DOI: 10.1002/advs.202301088]
6 **He Y**, Ling Y, Zhang Z, Mertens RT, Cao Q, Xu X, Guo K, Shi Q, Zhang X, Huo L, Wang K, Guo H, Shen W, Shen M, Feng W, Xiao P. Butyrate reverses ferroptosis resistance in colorectal cancer by inducing c-Fos-dependent xCT suppression. *Redox Biol* 2023; **65**: 102822 [PMID: 37494767 DOI: 10.1016/j.redox.2023.102822]
7 **Chen C**, Yang Y, Guo Y, He J, Chen Z, Qiu S, Zhang Y, Ding H, Pan J, Pan Y. CYP1B1 inhibits ferroptosis and induces anti-PD-1 resistance by degrading ACSL4 in colorectal cancer. *Cell Death Dis* 2023; **14**: 271 [PMID: 37059712 DOI: 10.1038/s41419-023-05803-2]
8 **Lv Y**, Tang W, Xu Y, Chang W, Zhang Z, Lin Q, Ji M, Feng Q, He G, Xu J. Apolipoprotein L3 enhances CD8+ T cell antitumor immunity of colorectal cancer by promoting LDHA-mediated ferroptosis. *Int J Biol Sci* 2023; **19**: 1284-1298 [PMID: 36923931 DOI: 10.7150/ijbs.74985]
9 **Qiao C**, Wang H, Guan Q, Wei M, Li Z. Ferroptosis-based nano delivery systems targeted therapy for colorectal cancer: Insights and future perspectives. *Asian J Pharm Sci* 2022; **17**: 613-629 [PMID: 36382305 DOI: 10.1016/j.ajps.2022.09.002]
10 **Zhang Z**, Ding Y, Li J, Wang L, Xin X, Yan J, Wu J, Yuan A, Hu Y. Versatile iron-vitamin K3 derivative-based nanoscale coordination polymer augments tumor ferroptotic therapy. *Nano Res* 2021; **14**: 2398-2409 [DOI: 10.1007/s12274-020-3241-7]
11 **Kang XJ**, Wang HY, Peng HG, Chen BF, Zhang WY, Wu AH, Xu Q, Huang YZ. Codelivery of dihydroartemisinin and doxorubicin in mannosylated liposomes for drug-resistant colon cancer therapy. *Acta Pharmacol Sin* 2017; **38**: 885-896 [PMID: 28479604 DOI: 10.1038/aps.2017.10]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: office@baishideng.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com