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Role of targeted ferroptosis and its combination strategy in combating drug resistance in colorectal cancer

Xie XT *et al*. Targeting ferroptosis in CRC

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Abstract

Colorectal cancer (CRC) is a severe 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 been found to reduce the stemness and chemoresistance of CRC cells, making it a potential target for treating CRC. Furthermore, the gut, which plays a role in regulating iron absorption and output, may make CRC more susceptible to the regulation of iron metabolism. 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.

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

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Core Tip: The drug resistance of colorectal cancer (CRC)is a challenge in its treatment strategy. Here, we provide unique insights that targeting ferroptosis in CRC cells can improve tumor cell resistance caused by CRC genome instability and tumor microenvironment alterations and provide new therapeutic strategies to break through the clinical drug resistance of CRC.

INTRODUCTION

Colorectal cancer (CRC) is a serious and aggressive form of cancer. Unfortunately, the majority of patients are not diagnosed until the later stages, and 50% are prone to liver metastasis, leading to a poor prognosis and high mortality rate. Its inflammatory tumor microenvironment (TME) and genomic instability make it resistant to existing treatments such as chemotherapy, targeted therapy, and immunotherapy. Ferroptosis is a novel type of programmed cell death that is dependent on iron-induced lipid peroxidation. Cancer cells are able to 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 gene, which includes GSK-3β and AXIN1, is a major contributor to the high frequency mutation of CRC. Deactivation of this gene is a common cause of CRC. Research has shown that pre-treatment of HeLa cells with GSK-3β inhibitor can prevent erastin-induced ferroptosis[2]. 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. In wild-type CRC cells, AMER1 binds to SLC7A11 or FTL and recruits β-TrCP1/2 to promote the ubiquitination and degradation of FTL and SLC7A11, resulting in an increase in the labile free iron pool and a decrease in cysteinyl uptake. This leads to an overload of reactive oxygen species (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. This implies a link between AMER1 mutations and CRC metastasis[3]. Studies have shown 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 handling KRAS mutations identified the precipitation of iron metabolites, confirming this same result. It has also been found that 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, it increases ROS production and the malondialdehyde enhanced RSL3 cytotoxic effect[4]. This suggests the clinical potential of ferroptosis inducers as 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 used in the treatment of CRC, but patients are prone to develop drug resistance, which limits the therapeutic effect. Some studies have found that protein 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 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[5]. It has also been found 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, destroy 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 is considered to have great potential in the treatment of malignant tumors. Unfortunately, immunotherapy for only a minority of patients with high microsatellite instability plays a significant curative effect, and most patients will have certain resistance. Some studies have found that CYP1B1 increases the resistance of tumor cells to ferroptosis by increasing ACSL4 ubiquitination and promoting its degradation, and the therapeutic effect of anti-PD-1 may be enhanced by

inhibiting CYP1B1[7]. 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 IFNγ and reducing lactate concentration in TME[8]. These results imply that targeting ferroptosis in CRC cells may be effective against ICB resistance.

Because targeted ferroptosis has shown great potential in the treatment of CRC, improving the selectivity of ferroptosis inducers and avoiding unnecessary side effects have become an urgent problem in clinical transformation. In this regard, the development of nanotechnology provides new possibilities for ferroptosis 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 iron 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 using NQA. In addition, the Fenton reaction occurred and ferroptosis was induced. The nano-DDS showed excellent tumor inhibitory effect and inhibited tumor metastasis in CT26 mouse model. In addition, some studies have suggested that nano-DDSs may improve the multidrug resistance of CRC and improve the treatment effect of patients[11]. These findings suggest that nano-therapy has great potential in targeting ferroptosis in CRC cells. However, since nano-DDSs is still in the emerging stage of research, more clinical studies are needed to further explore.

CONCLUSION

This editorial highlight 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.

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