

80162_Auto_Edited.docx

Name of Journal: *World Journal of Gastrointestinal Oncology*

Manuscript NO: 80162

Manuscript Type: REVIEW

Role of Ferroptosis in Colorectal Cancer

Ferroptosis in colorectal cancer

Ya-qi Song, Xiao-dan Yan, Yi Wang, Zhen-Zhen Wang, Xin-Li Mao, Li-ping Ye, Shao-wei Li

Abstract

Colorectal cancer (CRC) is the second deadliest cancer and the third-most common malignancy in the world. Surgery, chemotherapy, and targeted therapy have been widely used to treat colorectal cancer, but some patients still develop resistance to these treatments. Ferroptosis is a novel non-apoptotic form of cell death. It is an iron-dependent non-apoptotic cell death characterized by the accumulation of lipid reactive oxygen species and has been suggested to play a role in reversing resistance to anticancer drugs. This review summarizes recent advances in the prognostic role of ferroptosis in CRC and the mechanism of action in CRC.

Key Words: Ferroptosis; Colorectal cancer; System Xc⁻; GSH; GPX4

Song YQ, Yan XD, Wang Y, Wang ZZ, Mao XL, Ye LP, Li SW. Role of Ferroptosis in Colorectal Cancer. *World J Gastrointest Oncol* 2022; In press

Core Tip: The prognosis of patients with advanced colorectal cancer is still poor, largely due to resistance to anticancer drugs. Ferroptosis is a novel form of non-apoptotic cell death, mainly characterized by abnormal iron metabolism and the excessive accumulation of lipid peroxidation. Studies have shown that ferroptosis can participate in the process of CRC through the accumulation of lipid peroxides, inhibition of the System Xc⁻, disruption of the GSH/GPX4 balance, imbalance of iron homeostasis, and mediation of the P53 pathway. Induction of ferroptosis can reverse the resistance of anticancer drugs and improve the prognosis of CRC patients.

INTRODUCTION

Colorectal cancer (CRC) is a common gastrointestinal malignancy and the second-most common cause of cancer death. During the last decade (2010-2019), CRC mortality declined by about 2% per year but increased among those under 50 years old^[1]. The

oncogenesis and development of CRC involve multiple genes and steps, which is an extremely complex process.

Studies have shown that CRC cells have characteristics of strong proliferation, easy recurrence and easy metastasis [2], but there are few effective therapeutic targets for CRC patients[3]. At present, the comprehensive treatment of CRC includes surgical resection, neoadjuvant chemoradiotherapy, postoperative chemoradiotherapy, targeted therapy, immunotherapy and other methods, but the prognosis of patients with advanced CRC is still poor.

Cell death is a basic life process and ³ can be divided into accidental cell death (ACD) and regulated cell death (RCD). Regulated cell death can be further divided into the category of apoptosis, pyroptosis, necroptosis and ferroptosis^[4]. Ferroptosis, first reported in 2012, is a newly defined form of RCD involving ⁴ iron-dependent, non-apoptotic cell death. The characterization methods included free iron and lipid reactive oxygen species (ROS), particularly lipid hydroperoxides [5], and by cytoplasmic and organelle swelling, chromatin condensation and mitochondrial disorder^[6, 7]. Studies have shown that the tumor cell survival is highly dependent on an abnormally activated antioxidant system.

Several therapeutic targets associated with ferroptosis have been identified in CRC (Figure 1). The induction of ferroptosis is also considered a promising research direction in cancer resistance.

FERROPTOSIS-RELATED INDICATORS CAN PREDICT THE PROGNOSIS OF CRC

Recently, a growing number of studies have shown that genes involved in ferroptosis are associated with the prognosis of CRC patients. CRC has a high recurrence rate and individual heterogeneity, so it is desirable to have good ¹¹ prognostic biomarkers that can be used to predict high-risk patients in order to help patients obtain appropriate treatment.

In an analytical study combining samples from eight CRC patients with the TCGA public database, changes in ferroptosis in CRC patients at various molecular levels, ranging from DNA, RNA and proteins to epigenetic modifications, were described, and four ferroptosis-related genes associated with the prognosis were identified: CDKN2A, GPX4, ALOXE3 and LINC00336^[8]. Another study constructed a clinical prediction model including GPX4, NOX1 and ACSL4 that effectively reflected the prognosis, tumor progression and ACT responsiveness of CRC patients. It is also worth noting that tumors with low ferroptosis scores may infiltrate more CD4+ and CD8+ T cells and fewer M1 macrophages^[9]. ALOX5 is considered a key ferroptosis-related gene associated with a poor prognosis in CRC patients, and it regulates ferroptosis in cancer cells through lipid peroxidation^[10, 11]. CRC patients with an increased NOX1 expression and decreased BRAF status have a higher survival rate than others, and genes positively correlated with NOX1 are also significantly correlated with the CRC survival rate. The mechanism underlying NOX1 and BRAF mutations needs to be further explored^[12]. A prognostic model combining genes related to oxidative stress and ferroptosis can distinguish colorectal cancer as hot and cold tumors. Patients in the low-risk group responded better to fluorouracil chemotherapy and immune checkpoint blocking therapy than those in the high-risk group.^[13]

¹⁶ Long non-coding RNA (lncRNA) is non-coding RNA longer than 200 nucleotides and refers to the major class of transcripts encoded by the genome but mostly not translated into proteins^[14]. LncRNA plays a key role in regulating cancer proliferation, the cell cycle, metastasis and programmed death^[15, 16]. The abnormal expression of lncRNA is associated with the risk of CRC, imbuing it with clinical potential as a stratification marker, diagnostic index and therapeutic target of CRC^[17-20]. A model containing only four lncRNAs was able to well predict the prognosis, vein invasion and lymphatic metastasis in CRC patients, and it was proven that AP003555.1 and AC005841.1 induced ferroptosis by regulating Erastin^[21]. The lncRNA model including AC016027.1, AC099850.3, ELFN1-AS1 and VPS9D1-AS1 was able to accurately predict the prognosis of CRC patients and showed great potential to guide individualized

treatment^[22]. Cai *et al* summarized the details of seven ferroptosis-related lncRNAs to predict the prognosis of CRC patients and found that these lncRNAs were mainly enriched in the MAPK signaling pathway, mTOR signaling pathway and glutathione (GSH) metabolism pathway^[23]. LINC00239 increased Nrf2 protein stability by inhibiting Nrf2 ubiquitination and decreased the antitumor activity of erastin and RSL3^[24]. Circular RNA (CircRNA) also plays an important role in ferroptosis. CircABC10 serves as a sponge of Mir-326 and eventually regulates ferroptosis of CRC by regulating CCL5.^[25]

In addition to being an independent clinical prognostic factor for CRC patients, genes associated with ferroptosis can also accurately predict the clinical status, including tumor occurrence and progression, drug resistance, somatic mutations and the immune function^[26, 27], which provides a new research direction for targeted therapy or immunotherapy.

MECHANISM OF ACTION OF FERROPTOSIS IN CRC

The accumulation of lipid peroxides is the core process of ferroptosis.

The process of lipid peroxide accumulation in cells is the crucial section of ferroptosis. Polyunsaturated fatty acids (PUFAs) containing diallyl matrigel are prone to hydrogen deprivation, causing the formation of lipid peroxides and inducing ferroptosis^[28]. When PUFAs are replaced by monounsaturated fatty acids (MUFAs) in the plasma membrane, lipid ROS accumulation is hindered, and ferroptosis is prevented^[29]. With the process of esterification into membrane phospholipids and oxidation into ferroptosis signals, free PUFAs then can be joined into the lipid signaling mediator syntheses^[30]. Several studies have shown that phosphatidylethanolamines (PEs), a key phospholipid containing arachidonic acid (AA) or its derivative epinephrine (AdA), are oxidized to oxophosphatidylethanolamines (ox-PEs) to induce ferroptosis^[31]. Elongation of very-long-chain fatty acid protein 5 (ELOVL5) and fatty acid desaturase 1 (FADS1) can participate in AA and AdA synthesis, which can effectively inhibit ferroptosis^[32]. Furthermore, regulatory enzymes involved in membrane phospholipid biosynthesis of

PUFAs, such as ACSL4^[33] and LPCAT3^[34], can also trigger or prevent ferroptosis. However, the effect of LPCAT3 on ferroptosis was mild compared to that of ACSL4^[34].

Bromelain, a pineapple stem extract, potently induces cell ferroptosis and inhibits the proliferation of Kras mutant CRC in Kras mutant cell lines by regulating ACSL-4 Levels compared to Kras wild-type cells^[35]. The behaviors of Emodin, inhibiting ACSL4 expression, which can inhibit the proliferation and invasion of CRC, bring new research directions for CRC^[36].

Apatinib, also known as YN968D1, as a third-line therapy can effectively improve the prognosis of patients with metastatic CRC^[37]. ELOVL6 is a target of apatinib. By orienting the ELOVL6, Apatinib can promote ferroptosis with result of ACSL4 regulation, which has been verified by a co-IP assay. This suggests that apatinib inhibits CRC cell viability, at least in part, by targeting ELOVL6/ACSL4 signaling, thus providing novel mechanistic support for the use of apatinib in the clinical treatment of CRC patients^[38].

Inhibition of System X_c⁻ induces ferroptosis.

GSH has been known as a crucial antioxidant. It can bind toxic molecules, such as free radicals and heavy metals, and convert them into harmless substances that are excreted^[39]. GSH is also the first line of defense in the body to scavenge free radicals, which can effectively inhibit ferroptosis, and has a strong protective effect on the body^[40]. System X_c⁻ is a heterodimer, which was constructed by a heavy-chain subunit (SLC3A2) and a light-chain subunit (SLC7A11) that assists in the transmembrane transport of cystine and glutamate. Upon entry into the cell, cystine is reduced to cysteine^[41], and together with cysteine and glycine, GSH is synthesized intracellularly. Therefore, System X_c⁻ plays an important role in maintaining GSH homeostasis.

Studies have suggested that System X_c⁻ may mediate ferroptosis by affecting the glutamate uptake and GSH synthesis^[42, 43]. Erastin and sulfasalazine (SAS) are inhibitors of System X_c⁻ that can lead to intracellular GSH deficiency and ferroptosis by affecting intracellular GSH homeostasis^[44, 45]. By regulating the expression of SLC7A11, a

functional subunit of X_c^- , it can affect the activity of System X_c^- and the susceptibility to ferroptosis in cancer cells^[46-48].

Knockdown of SLC7A11 attenuates the viability of CRC stem cells by increasing ROS levels and decreasing cysteine and GSH levels^[49]. Talaroconvolutin A (TalaA) is a natural product, and studies have shown that, in addition to inducing ferroptosis by increasing ROS levels in cancer cells, this compound can also promote ferroptosis by down-regulating the SLC7A11 expression and up-regulating the arachidonic acid lipoxygenase 3 (ALOXE3) expression, becoming a new potentially powerful drug candidate for CRC therapy^[50]. Copper overload mediated by the copper chelator elesclomol inhibits CRC both *in vitro* and *in vivo*, and one of its pathways may induce ferroptosis by promoting the degradation of SLC7A11^[51].

5 The benzopyran derivative 2-imino-6-methoxy-2H-chromene-3-carbothioamide (IMCA) is considered to significantly inhibit the viability of CRC cells. IMCA can downregulate the expression of SLC7A11 and reduce cysteine and GSH glycine content, which leads to the accumulation of ROS and ferroptosis. In contrast, the overexpression of SLC7A11 was shown to attenuate ferroptosis induced by IMCA, which was confirmed to be involved in the AMPK/mTOR/p70S6k signaling pathway^[52].

18 Petunidin 3-O-[rhamnopyranosyl-(trans-p-coumaroyl)]-5-O-(β-D-glucopyranoside) (Pt3R5G) is a flavonoid compound. CRC cell proliferation can be inhibited by down-regulating SLC7A11 to reduce ferroptosis^[53].

Resveratrol (RSV) has been shown to promote ferroptosis by down-regulating the expression of SLC7A11 and GPX4. Combined with bionic nanocarriers, RSV's therapeutic potential as ferroptosis inducing anticancer agent has been developed. The bionic nanomaterial coated the RSV-supported 2 poly (ε-caprolactone) poly (ethylene glycol)(PCL-PEG) nanoparticles on the erythrocyte membrane to improve the transmission efficiency of RSV^[54].

Several ferroptosis-related genes are concentrated on System X_c^- . Activating transcription factor 3 (ATF3) promotes ferroptosis by inhibiting System X_c^- ^[55]. Deficiency of cyclin-dependent kinase inhibitor 2A (CDKN2A) and growth

differentiation factor 15 (GDF15) downregulates SLC7A11 expression, thereby sensitizing cells to ferroptosis^[56, 57].

Radiotherapy and poly-ADP-ribose polymerase inhibitors (PARPis) have been used in clinical trials in the treatment of CRC, the mechanism of which may be ionizing radiation (IR) activation of dsDNA that modulates ferroptosis through activation of the ATF3-SLC7A11 pathway. Triggers cGAS signaling mediated tumor control in cancer cell lines and mouse xenograft models^[58].

The transsulfuration pathway is a regulator of ferroptosis resistance.

More than 40% of the source of cysteine came from diet, and transfer to GSH via a biochemical process in body, which can combat the excessive deposition of peroxide. In addition to being transported into cells by System X_c⁻, cysteine can also be converted intracellularly by methionine *via* the transsulfuration pathway^[59].

¹³ Cystathionine-β-synthase (CBS), an enzymatic component of the transsulfuration pathway, is significantly increased in cells resistant to Erastin-induced ferroptosis^[60]. CBS has also been shown to be an independent regulator of ferroptosis^[61, 62]. Endogenous H₂S, a by-product of the transsulfuration pathway, is closely related to tumor cell physiology and is finely regulated in a variety of cancers^[63, 64]. xCT, a functional subunit of system X_c⁻, was shown to interfere with xCT in colon cancer cells, resulting in an increased expression of cystathionine-γ-lyase (CTH) and CBS, which are majority of the transsulfuration pathway. Additionally, the endogenous H₂S levels can be significantly decreased by interfering with xCT. The correlation of xCT and transsulfuration pathway has been investigated that is a makeable metabolic vulnerability.

Cysteinyl-tRNA synthetase, a genetic suppressor of ferroptosis, upturns the sulfur pathway and re-sensitizes cells to erastin, demonstrating a new mechanism for resistance to ferroptosis^[65]. This implies that the transsulfuration pathway is a regulator of ferroptosis resistance.

Zinc oxide has outstanding desulfurization ability, and VZnO can effectively reduce the content of H₂S in CRC, effectively deplete GSH in tumor cells and ultimately lead to ferroptosis in CRC cells, providing an effective strategy for CRC treatment^[66].

Disruption of the GSH/GPX4 Lipid repair system can promote the accumulation of lipid reactive oxygen species

ROS levels in the body are regulated by the antioxidant defense system, and oxidant/antioxidant imbalance may also contribute to ferroptosis^[67]. GPX4 is an important selenoprotein that belongs to the GPX antioxidant defense system and is a considerable enzyme to balance the concentration of GSH and GS-SG. GPX4 protects membrane lipid bilayers by transferring toxic lipid hydroperoxides (L-OOH) to nontoxic lipid alcohols (L-OH)^[68]. GPX4 has been literately proved as a factor of ferroptosis promotor and can be trigger by ferroptosis inducers, such as Erastin and RSL3. Likewise, direct knockdown of GPX4 leading to the excessive accumulation of intracellular lipid peroxidation and cell death^[69]. Thus, GPX4 is consider as a crucial target to trigger ferroptosis^[70, 71].

In experiments with three different CRC cells (HCT116, LoVo and HT29), RSL3 was found to trigger cellular ferroptosis in a dose- and time-dependent manner due to increased ROS levels and destabilization of the intracellular iron pool. In a further analysis, GPX4 inhibition was proven to be a key determinant of RSL3-induced ferroptosis, and overexpression of GPX4 rescued RSL3-induced ferroptosis^[72]. Aspirin has been reported to have therapeutic benefits for CRC carrying carcinogenic PIK3CA. The mechanism may be that aspirin inhibits protein kinase B (AKT)/mammalian target of rapamycin (mTOR) signaling. The expression of downstream sterol regulatory elm-binding protein 1 (SREBP-1) was inhibited, and the production of monounsaturated fatty acid fat by stearoyl-CoA desaturase-1 (SCD1) was reduced. Thus promoting RSL3-induced ferroptosis in colorectal cancer (CRC) cells^[73].

Serine- and arginine-rich splicing factor 9 (SRSF9) is frequently overexpressed in multiple tumor types and manifests as a proto-oncogene^[74-76]. SFRS9 upregulates GPX4

protein, which is an obstacle to ferroptosis^[77]. Knockdown of SFRS9 may be an effective treatment for CRC. In CRC tissues, the expression of SFRS9 mRNA and protein was significantly higher than that in adjacent tissues. Experiments in mice demonstrate that regulation of GPX4 by SRSF9 is an important ² mechanism driving CRC tumorigenesis and resistance to Erastin-induced ferroptosis. This molecular mechanism may provide a novel approach to improving the sensitivity of CRC to Erastin^[78].

ACADSB is a member of the Acyl-CoA dehydrogenase family, and its overexpression inhibits the migration, invasion and proliferation of CRC cells. Studies have shown that ACADSB negatively regulates the expression of GSH reductase and GPX4 while increasing the concentrations of malondialdehyde, Fe ions and superoxide dismutase. This suggests that ACADSB may affect CRC cell migration, invasion and proliferation by regulating CRC cell ferroptosis^[79].

ROS causes GSH accumulation through nuclear factor erythroid 2-related factor .

Antioxidant proteins, such as Nrf2, are major antioxidant transcription factors that help prevent the accumulation of excess ROS and maintain redox homeostasis. Downregulation of Nrf2 enhances the sensitivity of cancer cells to ferroptosis promoters^[80].

The Warburg effect is thought to be a characteristic of cancer cells, that is, cancer cells will undergo glycolysis beyond very high levels under aerobic conditions ^[81]. Inhibition of the Warburg effect reduces the ability of cells to proliferate. Therefore, inhibiting the Warburg effect may be a therapeutic strategy for cancer. *In vivo* and *in vitro* experiments in CRC showed that iron-induced ROS activated the expression of Nrf2 in the nucleus has the positive correlation with Warburg enzymes expression and CRC cell proliferation by enhancing the Warburg effect.

Heme oxygenase 1 (HO-1) is a downstream gene of Nrf2, and NGF2 protects against lipid peroxidation^[80] and ferroptosis through the transcription of enzymes such as HO-1^[82]. Ferroptosis can be effectively alleviated by the elimination of lipid oxidation through the Nrf2/HO-1 axis activation^[83, 84].

Tagitin C, a sesquiterpene lactone^[85], can induce ferroptosis in HCT116 cells and inhibit the growth of CRC cells. Mechanistically, Tagitin C induces endoplasmic reticulum stress and oxidative stress as well as nuclear translocation of Nrf2. As a downstream gene of Nrf2, HO-1 was significantly increased with Tagitin C treatment^[86].

Tagitin C-induced ferroptosis was accompanied by a decrease in GSH levels and an increase in lipid peroxidation. Cetuximab combined with chemotherapy has made great progress in the treatment of metastatic CRC^[87], but cetuximab is not effective in CRC patients with KRAS mutations^[88, 89].

Lysionotin (Lys), a flavonoid, has been demonstrated to successfully inhibit ² cell proliferation, migration and invasion of HCT116 and SW480 CRC cells in vitro. Lys treatment worked by increasing Nrf2 cells' degradation rate to reduce the concentration of Nrf2 protein, inducing ferroptosis and reactive oxygen species (ROS) accumulation in CRC cells^[90].

P38MAPK has been investigated that participate in the regulation of Nrf2/HO-1^[91, 92]. It has been shown that cetuximab can significantly inhibit ¹ Nrf2/HO-1 signaling through p38 MAPK activation in KRAS-mutant CRC cell lines, thereby promoting RSL3-induced ferroptosis. This provides a research direction for cetuximab in the treatment of KRAS-mutant CRC^[93].

Oxaliplatin is the first-line chemotherapy drug for CRC. By inhibiting the Nrf2 signaling pathway, the sensitivity of CRC cells to oxaliplatin can be enhanced ^[94, 95]. Furthermore, the study found that oxaliplatin significantly inhibited the protein expression of Nrf2, HO-1 and NQ in the Nrf2 signaling pathway in a dose-dependent manner. Therefore, the anticancer effect of oxaliplatin may be enhanced by inhibiting the Nrf2 signaling pathway, leading to ferroptosis and oxidative stress in CRC cells^[96].

Cellular iron homeostasis is a key factor in ferroptosis

The primary condition for the initiation of ferroptosis pathway is the need of iron ion. Dietary iron is absorbed primarily in the gut as ferric ion and delivered to the blood by

transferrin. In general, extracellular iron transport into the cell through the sequence of complexing with circulating transferrin (TF), then binds to membrane transferrin receptor protein-1 (TFR1), finally to the cytoplasmic unstable iron pool. Excess cellular iron is stored as ferritin or transported extracellularly by ferritin^[97, 98]. Maintenance of cellular iron homeostasis prevents oxidative damage, cytotoxicity and death.

Lipid reactions can be divided into enzymatic and non-enzymatic reactions. Iron can promote the production of ROS through the Fenton reaction, leading to enzymatic lipid peroxidation^[99, 100], and also acts in a non-enzymatic manner as a cofactor for lipid-oxidizing lipoxygenase (LOX). Supplementation of exogenous iron ions can accelerate erastin-induced ferroptosis^[5]. Knockout the gene encoding the transferrin receptor or upregulate the expression of iron storage proteins can inhibit iron overload and ferroptosis. Iron metabolism can be regulated by inhibition of the major transcription factors, like iron regulatory protein 2, significantly upregulates the expression of iron metabolism-related genes, such as FTH1 and FTL, thereby inhibiting erastin-induced ferroptosis^[101]. Iron chelators can prevent the transfer of electrons from iron to oxides, thus inhibiting the production of oxygen free radicals and inhibiting lipid peroxidation to prevent ferroptosis. Therefore, the regulation of iron metabolism and ferritin phagocytosis may become new targets and new pathways for regulating ferroptosis.

HIF-2 α is a master transcriptional regulator of cellular iron levels^[102]. Activation of HIF-2 α increases cellular iron in CRC, leading to an increase in lipid ROS and a decrease in GSH production, thus enhancing cellular sensitivity to ferroptosis^[103].

There is a conserved miR-545 binding site in the 3' untranslated region (UTR) of TF, and the overexpression of TF in CRC cells was found to induce increased levels of ROS, MDA and Fe²⁺, thereby promoting CRC cell death. This suggests that miR-545 may play an oncogenic role in CRC by regulating the iron accumulation in cells^[104].

Dichloroacetate (DCA) attenuates the stemness of CRC cells by chelating iron in lysosomes, leading to the up-regulation of iron concentrations and lipid peroxide levels, thus triggering ferroptosis^[105].

OTUD1 is a deubiquitinase of iron-responsive element-binding protein 2 (IREB2), which is mainly expressed in intestinal epithelial cells. OTUD1 promotes TFR1-mediated iron transport through deubiquitination and stabilization of IREB2, leading to increased ROS production and ferroptosis, which is highly associated with a poor prognosis in CRC^[106].

Dual role of p53 in mediating tumor ferroptosis

The tumor suppressor gene p53 plays a dual role in mediating ferroptosis in a variety of cancers^[99]. Studies have found that p53 can enhance ROS-mediated ferroptosis by inhibiting SLC7A11 protein expression, resulting in decreased cystine import and thus reduced GSH production^[46, 107]. However, unlike in CRC, p53 can protect CRC cells from ferroptosis by stirring SLC7A11^[108]. In addition, p53 can also inhibit CRC cell ferroptosis by blocking dipeptidyl peptidase 4 (DPP4) activity ^[97, 109].

Cytoglobin (CYGB) is a regulator of ROS that plays an important role in oxygen homeostasis and acts as a tumor suppressor^[110]. Yes-associated protein 1 (YAP1) is a key downstream target of CYGB. CYGB modulates cellular ferroptosis through p53-YAP1 signaling in CRC cells^[111]. A novel antitumor compound optimized from the natural saponin biocide A has also been shown to trigger ferroptosis by activating p53 ^[112].

Ginsenoside Rh4 can increase ROS accumulation, lead to the activation of ROS/p53 signaling pathway, and induce ferroptosis to inhibit the proliferation of cancer cells^[113]. Cullin-9 can bind p53 to ubiquitinated heteroribonucleoprotein C for degradation through whole genome sequencing and external differential expression analysis. Cullin-9 overexpression increases resistance to erastin-induced ferroptosis and is a novel and important regulator of CRC ferroptosis^[114].

INDUCTION OF FERROPTOSIS REVERSES RESISTANCE TO ANTICANCER DRUGS

⁸ Oxaliplatin prolongs the median disease-free survival (DFS) and overall survival (OS) in patients with advanced CRC, but clinical data suggest that <40% of patients with advanced CRC benefit from it^[115, 116]. This may be related to oxaliplatin resistance, and recent studies have shown that induction of ferroptosis can significantly reverse oxaliplatin resistance in CRC cells.

Ferroptosis in CRC cells may be inhibited through the KIF20A/NUAK1/PP1 β /GPX4 pathway, which may underlie CRC resistance to oxaliplatin^[117]. Deletion of cysteine desulfurase (NFS1) can significantly enhance the sensitivity of CRC cells to oxaliplatin. The mechanism may involve ¹² NFS1 deficiency synergizing with oxaliplatin to induce PANoptosis (apoptosis, necroptosis, pyroptosis and ferroptosis), thus increasing the intracellular ROS levels. This also demonstrated that ferroptosis is involved in the oxaliplatin resistance pathway^[118]. Obesity is strongly associated with a poor prognosis in patients with advanced CRC, and adipose-derived exosomes reduce susceptibility to ferroptosis in CRC, thereby promoting chemoresistance to oxaliplatin ^[119].

¹⁴ Combination with chemotherapy with monoclonal antibodies against anti-epidermal growth factor receptor (EGFR) or vascular endothelial growth factor (VEGF) has advanced in the treatment of metastatic CRC (mCRC). However, inherent resistance to downstream KRAS mutations, so the effect of combination chemotherapy is often less optimistic. β -elemene has broad-spectrum anticancer effects, and it has been demonstrated that combined treatment of β -elemene and cetuximab can induce ferroptosis and inhibit epithelial-mesenchymal transition, thereby improving resistance to KRAS-mutated CRC cells^[120].

²⁰ FAM98A is a microtubule-associated protein involved in cell proliferation and migration. Increased expression of FAM98A can inhibit ferroptosis and promote CRC resistance to 5-fluorouracil^[121]. Similarly, PYCR is an oncogene that desensitizes colorectal cancer cells to 5-FU cytotoxicity by promoting ferroptosis in CRC cells^[122].

In addition, *Andrographis Paniculata* may also exert a sensitizing effect on CRC treatment by activating ferroptosis^[123, 124]. *Andrographis Paniculata*-mediated

sensitivity to 5FU-based chemotherapy in CRC is primarily mediated through activation of ferroptosis and inhibition of the β -catenin/Wnt signaling pathway^[123].

NANOTECHNOLOGY PROMOTES FERROPTOSIS IN CRC CELLS

Although increasing iron concentration promotes ferroptosis in tumor cells has been demonstrated experimentally, direct administration of Fe²⁺ is not feasible in the clinic due to the protective effect of cell membranes and the defense mechanism of the tumor immune microenvironment (TME). Nano-drug delivery system (nano-DDSs) has unique physical and chemical properties of nanomaterials, which can not only enhance drug solubility and improve drug circulation time in the body, but also achieve targeted delivery and controlled release of drugs^[125]. Therefore, the use of novel nanodelivery systems to improve the efficiency of iron release has great prospects in CRC targeted therapy.

Nano DDS can directly drive the death of iron in tumor cells, and iron-based nanoparticles can be catabolized by acid lysosomes of tumor cells to release Fe²⁺ and iron 3⁺^[126]. Iron-based nanoparticles induce ferroptosis by catalyzing the Fenton reaction, but because of their low reactive oxygen production, they are often used in conjunction with other treatments. Huan Liang *et al* synthesized ultra-small single crystal Fe nanoparticles (bcc-USINPs) that are highly active in the tumor microenvironment and can effectively induce tumor cell ferroptosis and immunogenetic cell death at very low concentrations^[127].

In addition to acting directly on cancer cells, nanotechnology also works by acting on key components of TME. Due to TME's weak acidity, abundant angiogenesis and hypoxia conditions, the effectiveness of conventional cytotoxic therapy delivery is limited, while active targeting of nanoparticles may be more useful^[128].

Sodium persulfate (NaSO) is a novel chemodynamic therapy (CDT) that can produce •SO and Na, which can cause ferroptosis in cells. Ir780-iodide (IR780) is a phototherapy agent that produces ROS in conjunction with NaSO's CDT to overcome CRC chemotherapeutic resistance. Co-assembly of NaSO and IR780 on the nano

platform improved the stability of NaSO and solubility of IR780, significantly enhancing the anti-tumor effect on CRC cell lines^[129]. A novel composite nanomaterial PPy@Fe₃O₄ has been demonstrated to regulate the NF- κ B signaling pathway and then inhibit the proliferation, migration and invasion of CRC cells in vitro. Interestingly, Fer-1, an ferroptosis inhibitor, reversed changes in transfer-related proteins induced by nanoparticle therapy^[130].

CONCLUSION

Ferroptosis, a newly discovered type of RCD mediated by iron-dependent lipid ROS accumulation, plays a role in a variety of diseases of the gastrointestinal tract. Many ferroptosis-related genes have been confirmed to be associated with the prognosis of CRC, and various models have been confirmed to be able to stratify CRC patients well and facilitate the early identification of high-risk patients. Iron metabolism and the accumulation of lipid peroxides are the core processes in ferroptosis. As mentioned above, GPX4, SLC7A11, ACSL4 and p53 act as key regulators in ferroptosis-related CRC mediation (Table 1). Induction of ferroptosis can reverse the resistance of anticancer drugs or exert a synergistic effect with other anticancer drugs to enhance the sensitivity of antitumor drugs and improve the prognosis of CRC patients. Furthermore, in colon cancer, copper chelators have also been shown to facilitate CRC cell death by promoting the degradation of SLC7A11. The mechanism underlying ferroptosis and the relationship between key regulators and other RCDs, such as autophagy and apoptosis, should be explored in future research.

In animal studies, the underlying mechanism of ferroptosis is complex, involving multiple targeted enzyme systems and metabolic networks. However, the actual clinical situation is more complicated, which requires the combination of gene mutation, epigenetic modification, metabolomics, *etc.* The absorption, transport, storage and metabolism of iron in the body is a very complex process, and how to define the therapeutic iron concentration needs to be carefully considered. In practice, increasing iron concentration to promote ferroptosis in tumor cells seems difficult to achieve due

to the presence of defense mechanisms in the tumor immune microenvironment. At present, many studies have mentioned the promotion of ferroptosis in CRC cells through nanotechnology, and nano-DDSs seems to be able to effectively help solve this problem due to the advantages of targeted delivery and controlled release. In fact, ferroptosis seems to be a double-edged sword in the treatment of gastrointestinal diseases. The role of ferroptosis in different gastrointestinal diseases is different, and the pros and cons of ferroptosis treatment need to be evaluated more carefully.

15 At present, research on the mechanism underlying ferroptosis in the colorectum is still in its infancy, and other ferroptosis pathways or related targets, such as the FSP1/CoQ/NADPH pathway, still need to be further explored. In the future, ferroptosis genes related to the prognosis of CRC also need to be verified. The mechanism underlying ferroptosis and tumor escape in CRC is also worth further in-depth study in order to promote the development of new and effective therapeutic strategies.

9%

SIMILARITY INDEX

PRIMARY SOURCES

1	www.ncbi.nlm.nih.gov Internet	65 words — 1%
2	www.researchgate.net Internet	47 words — 1%
3	www.frontiersin.org Internet	44 words — 1%
4	pdfs.semanticscholar.org Internet	42 words — 1%
5	www.omicsdi.org Internet	31 words — 1%
6	f6publishing.blob.core.windows.net Internet	26 words — 1%
7	academic.oup.com Internet	19 words — < 1%
8	aging-us.com Internet	17 words — < 1%
9	spiral.imperial.ac.uk Internet	17 words — < 1%

10 Shazhou Ye, Mingjun Xu, Tingwei Zhu, Jiayi Chen, Shanping Shi, Haizhong Jiang, Qingfang Zheng, Qi Liao, Xiaoyun Ding, Yang Xi. "Cytoglobin promotes sensitivity to ferroptosis by regulating p53 - YAP1 axis in colon cancer cells", Journal of Cellular and Molecular Medicine, 2021

Crossref

11 Yafang Zhong, Wei Zhang, Haiyan Yu, Liewen Lin et al. "Multi-platform-based characterization of ferroptosis in human colorectal cancer", iScience, 2022

Crossref

12 Jin-Fei Lin, Pei-Shan Hu, Yi-Yu Wang, Yue-Tao Tan et al. "Phosphorylated NFS1 weakens oxaliplatin-based chemosensitivity of colorectal cancer by preventing PANoptosis", Signal Transduction and Targeted Therapy, 2022

Crossref

13 Shanwen Chen, Dingfang Bu, Jing Zhu, Taohua Yue, Shihao Guo, Xin Wang, Yisheng Pan, Yucun Liu, Pengyuan Wang. "Endogenous hydrogen sulfide regulates xCT stability through persulfidation of OTUB1 at cysteine 91 in colon cancer cells", Neoplasia, 2021

Crossref

14 studymoose.com 14 words — < 1%

Internet

15 Liu Yang, Yewei Zhang, Yingyi Zhang, Zhe Fan. "Mechanism and application of ferroptosis in colorectal cancer", Biomedicine & Pharmacotherapy, 2023

Crossref

16 jeccr.biomedcentral.com 13 words — < 1%

Internet

17 nutritionandmetabolism.biomedcentral.com

13 words — < 1%

18 pubmed.ncbi.nlm.nih.gov
Internet

13 words — < 1%

19 Sixin Zheng, Lingling Hu, Qingwen Song, Yuqiang Shan, Guang Yin, Hanzhang Zhu, Wencheng Kong, Chunhua Zhou. "miR-545 promotes colorectal cancer by inhibiting transferring in the non-normal ferroptosis signaling", Aging, 2021
Crossref

12 words — < 1%

20 pubag.nal.usda.gov
Internet

12 words — < 1%

21 www.scilit.net
Internet

12 words — < 1%

EXCLUDE QUOTES ON
EXCLUDE BIBLIOGRAPHY ON

EXCLUDE SOURCES < 12 WORDS
EXCLUDE MATCHES < 12 WORDS