Therapeutic efficacy of ferroptosis in the treatment of colorectal cancer (Review)

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Abstract. Colorectal cancer (CRC) is the third most common malignancy worldwide, and the second leading cause of cancer-associated mortality. The incidence and mortality rates of CRC remain high, posing a significant threat to humans and overall quality of life. Current therapeutic strategies, such as surgery and chemotherapy, are limited due to disease recurrence, chemotherapeutic drug resistance and toxicity. Thus, research is focused on the development of novel treatment approaches. In 2012, ferroptosis was identified as a form of regulated cell death that is iron-dependent and driven by lipid peroxidation. Notably, therapies targeting ferroptosis exhibit potential in the treatment of disease; however, their role in CRC treatment remains controversial. The present study aimed to systematically review the mechanisms and signaling pathways of ferroptosis in CRC, and the specific role within the tumor microenvironment. Moreover, the present study aimed to review the role of ferroptosis in drug resistance, offering novel perspectives for the diagnosis and treatment of CRC.

Contents

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1. Introduction

Colorectal cancer (CRC) is a prevalent malignancy of the gastrointestinal tract, with high rates of morbidity and mortality. In 2018, the GLOBOCAN database published an analysis of the incidence and mortality rates for 36 cancers across 185 countries, and the results revealed that CRC is the third most common cancer and the second leading cause of cancer-associated mortalities worldwide (1,2). The etiology of CRC is associated with various factors, including age, sex, inflammatory bowel disease, lifestyle and environmental factors (3-5). Current treatment options for CRC include surgery, chemotherapy, radiotherapy, immunotherapy and targeted biological therapies (6). However, the absence of highly specific biomarkers for the diagnosis of CRC and the development of chemoresistance in advanced stages of treatment may impact the quality of life of patients with late-stage disease (7). Thus, research is focused on the development of novel effective targeted therapies for CRC. Notably, ferroptosis may exhibit potential as an emerging strategy for CRC treatment.

Regulated cell death, including apoptosis, pyroptosis, necroptosis, ferroptosis, autophagy-dependent cell death and neoplastic cell death, is a crucial mechanism for maintaining the internal homeostasis of the human body and preserving tissue function and morphology (8,9). The primary method for distinguishing between different forms of cell death is based on the associated morphological characteristics (Table I).

Ferroptosis, initially described by Dixon in 2012, is a novel form of regulated cell death (9). It is distinct from other forms of regulated cell death in terms of morphology, biochemical features and gene expression (10). Notably, ferroptosis is characterized by unique morphological features, including mitochondrial shrinkage, increased mitochondrial membrane density, reduced or absent mitochondrial cristae, rupture of the outer mitochondrial membrane, and preservation of nuclear integrity (11,12). The main morphological characteristics of apoptosis include cell shrinkage, nuclear condensation and the maintenance of plasma membrane integrity, while its biochemical features are primarily DNA fragmentation and macromolecule synthesis (13). The key morphological traits of pyroptosis involve cell swelling, the formation of numerous bubbles on the pyroptotic cells, and chromatin degradation, leading to the formation of inflammasomes (14-16). The primary morphological characteristics of necroptosis include

increased cell membrane permeability, cell swelling and loss of organelle integrity, while its biochemical hallmark is a decrease in adenosine triphosphate levels (17,18). Autophagy is characterized by the formation of double-membraned autophagosomes, and its biochemical feature is an increase in lysosomal activity (19).

Ferroptosis has been investigated in a variety of diseases, including Parkinson's disease (20,21), Alzheimer's disease (22,23), liver injury (24,25), brain injury (26,27), spinal cord injury (28-30), kidney injury (31,32), cardiovascular disease (33-35) and gynecological disorders (36,37) (Fig. 1). At present, research is focused on the role of ferroptosis in the treatment of cancer. Yan *et al* (38) demonstrated that ferroptosis plays a key role in the development of CRC, breast cancer, ovarian cancer, renal cancer, lymphoma and melanoma (39). However, results of a previous study revealed that ferroptosis may also play a role in CRC progression and metastasis, through the activation of different signaling pathways (40). Thus, previous studies highlight that ferroptosis may exert contrasting effects in CRC, demonstrating the requirement for further investigations. In addition, the development of novel treatment approaches is required to mitigate the adverse effects of ferroptosis on CRC. This article systematically reviews the mechanisms and signaling pathways of ferroptosis in CRC, the role of ferroptosis within the tumor microenvironment, and the progress in research on ferroptosis in reducing drug resistance. It aims to provide new insights for the diagnosis and treatment of CRC.

2. Mechanism of action of ferroptosis

Ferroptosis is primarily characterized by the excessive accumulation of iron and lipid reactive oxygen species (10). Previous studies have identified mechanisms that may be involved with ferroptosis, including amino acid, lipid and iron metabolism (41). Key mechanisms involved in ferroptosis are displayed in Fig. 2.

Induction of ferroptosis through inhibition of the cystine/glutamate antiporter system (System Xc-). System Xc- is a critical component of the cellular antioxidant system that is widely distributed in the phospholipid bilayer. System Xc- is a heterodimer composed of two subunits: Namely, solute carrier family 7 member 11 (SLC7A11) and SLC3A2. System Xc- facilitates the 1:1 exchange of cystine and glutamate across the cell membrane (9). Once inside the cell, cystine is utilized to synthesize glutathione, which, in the presence of glutathione peroxidase, reduces the production of lipid reactive oxygen species. Therefore, inhibition of System Xc- leads to reduced glutathione peroxidase activity, decreased cellular antioxidant capacity, accumulation of lipid reactive oxygen species and ferroptosis (9). A well-established oncogene, P53, may induce ferroptosis via downregulation of SLC7A11 expression, thereby inhibiting System Xc- activity (42,43). Moreover, sorafenib (44), sulfasalazine (45) and erastin (46) induce ferroptosis via inhibition of System Xc-.

Induction of ferroptosis through inhibition of glutathione peroxidase 4 (GPX4). GPX4 plays a critical role in the cellular peroxidase system, inhibiting the formation of peroxides and thus acting as a key regulator of ferroptosis. GPX4 catalyzes the conversion of glutathione to oxidized glutathione and reduces cytotoxic lipid peroxides to their corresponding alcohols (12). Yang *et al* (47) demonstrated that reduced GPX4 expression may lead to the induction of ferroptosis, whereas increased GPX4 expression may inhibit ferroptosis. RAS-selective lethal 3 (RSL3) is a widely established inhibitor of GPX4 and an inducer of ferroptosis. RSL3 directly targets GPX4, thereby inhibiting its activity and leading to reductions in cellular antioxidant capacity, the accumulation of lipid reactive oxygen species and the induction of ferroptosis (48). Costa *et al* (49) identified ML162 and ML210 as GPX4 inhibitors that induce ferroptosis, through a mechanism that is comparable with that of RSL3.

Lipid metabolism. Lipid peroxidation is critical in the induction of ferroptosis. Lipids are essential components of cell membranes, and lipid peroxidation disrupts these membranes, thereby triggering ferroptosis (50). Polyunsaturated fatty acids (PUFAs), such as arachidonic acid and adrenic acid, are long-chain fatty acids with multiple double bonds that are highly susceptible to lipid peroxidation. Phosphatidylethanolamine containing arachidonic and adrenic acids is a key phospholipid in the induction of cellular ferroptosis. There are two lipid-metabolizing enzymes associated with ferroptosis; namely, acyl-CoA synthetase long-chain family member 4 (ACSL4) and lysophosphatidylcholine acyltransferase 3, which are involved in the biosynthesis of phosphatidylethanolamine. These enzymes activate PUFAs and impact their transmembrane properties, leading to ferroptosis (51). In addition, cytochrome P450 oxidoreductase-mediated lipid peroxidation may play a key role in the induction of ferroptosis (52). Cytochrome P450 oxidoreductase transfers electrons from reduced nicotinamide adenine dinucleotide phosphate to oxygen, producing hydrogen peroxide. Hydrogen peroxide subsequently reacts with iron to generate reactive hydroxyl radicals, which peroxidize the polyunsaturated fatty acid chains of membrane phospholipids. This process disrupts the integrity of cellular membranes during iron accumulation, ultimately leading to ferroptosis (53,54).

Iron metabolism. Iron accumulation is closely associated with ferroptosis, and primarily involves iron absorption and reduction processes (55). Iron is a critical raw material for the production of hemoglobin and myoglobin. Moreover, iron plays a vital role in various cellular metabolic processes, such as oxygen storage and transport, DNA and RNA synthesis, cellular differentiation, and enzymatic reactions (56). Healthy individuals exhibit iron levels of 3-5 g, with >50% circulating in red blood cells as hemoglobin or stored as ferritin. In addition, small amounts of iron bind to transferrin in the plasma (57,58).

Intracellular iron homeostasis is maintained through a balance of iron absorption, utilization, storage and excretion. Fe^{3+} is absorbed in the duodenum and jejunum, and transported into cells via transferrin receptor 1, where it is reduced to Fe^{2+} by metal reductase in the endoplasmic reticulum. For biological activation, a small amount of Fe^{2+} is released into a labile iron pool in the cytoplasm via the divalent metal transporter 1, while the remainder is recycled or stored as ferritin (59,60). The results of a previous study revealed that cancer cells require higher levels of iron than healthy cells,

Table I. Characteristics of ferroptosis, apoptosis, pyroptosis, necroptosis and autophagy.

Regulated form of cell death	Morphological characteristic	Biochemical characteristic	(Refs.)
Ferroptosis	Decreased mitochondrial volume, reduced number of cristae, increased mitochondrial membrane density and elevated rates of mitochondrial membrane rupture	Iron accumulation and lipid peroxidation	(8)
Apoptosis	Cell shrinkage, nuclear condensation and preservation of cytoplasmic membrane integrity	DNA fragmentation and macromolecular synthesis	(13)
Pyroptosis	Cell swelling and expansion, formation of numerous vesicles in necrotic cells, chromatin degradation, and the release of pro-inflammatory components	Inflammatory vesicle formation	(14-16)
Necroptosis	Plasma membrane permeabilization, cellular swelling and loss of organelle integrity	Decreased levels of adenosine triphosphate	(17,18)
Autophagy	Formation of autophagic lysosomes with double-membrane structures	Increased lysosomal activity	(19)

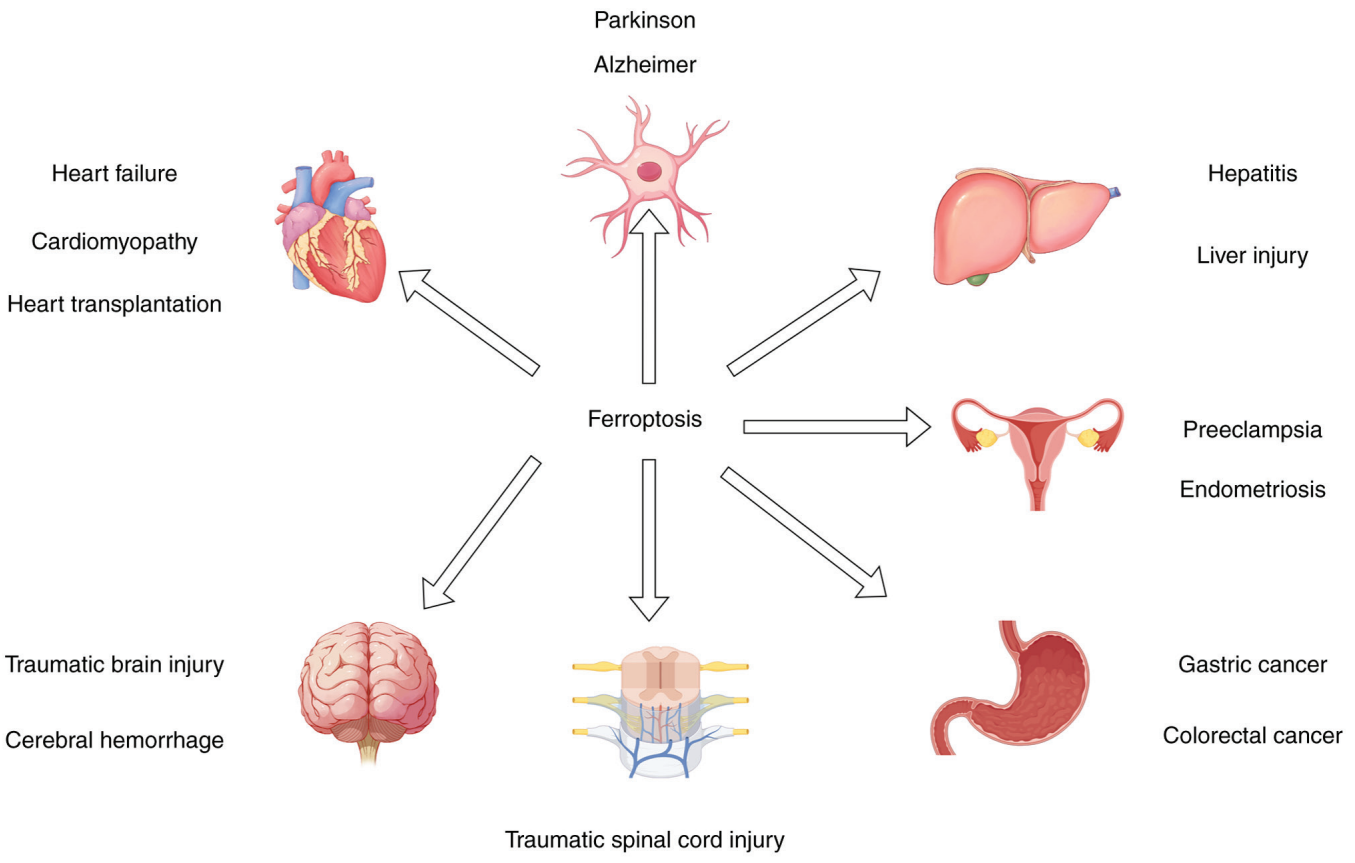

Figure 1. Ferroptosis is implicated in a wide range of diseases, including neurological, cardiac, cerebral, spinal cord, gastrointestinal, gynecological and hepatic disorders.

and are more susceptible to iron depletion, also known as iron addiction (61). Notably, in the presence of a large number of cancer cells, ferritin is degraded through autophagy. This process is carried out via autophagy-related proteins 5 and 7, and the nuclear receptor coactivator 4 (NCOA4) signaling pathways. NCOA4 binds to lysosomes, degrades ferritin and releases Fe^{2+}, leading to an abnormal increase in Fe^{2+} levels (62-64). Excessive Fe^{2+} accumulation triggers the Fenton reaction (Fig. 3), initiating ferroptosis and further contributing to the accumulation of reactive oxygen species (65).

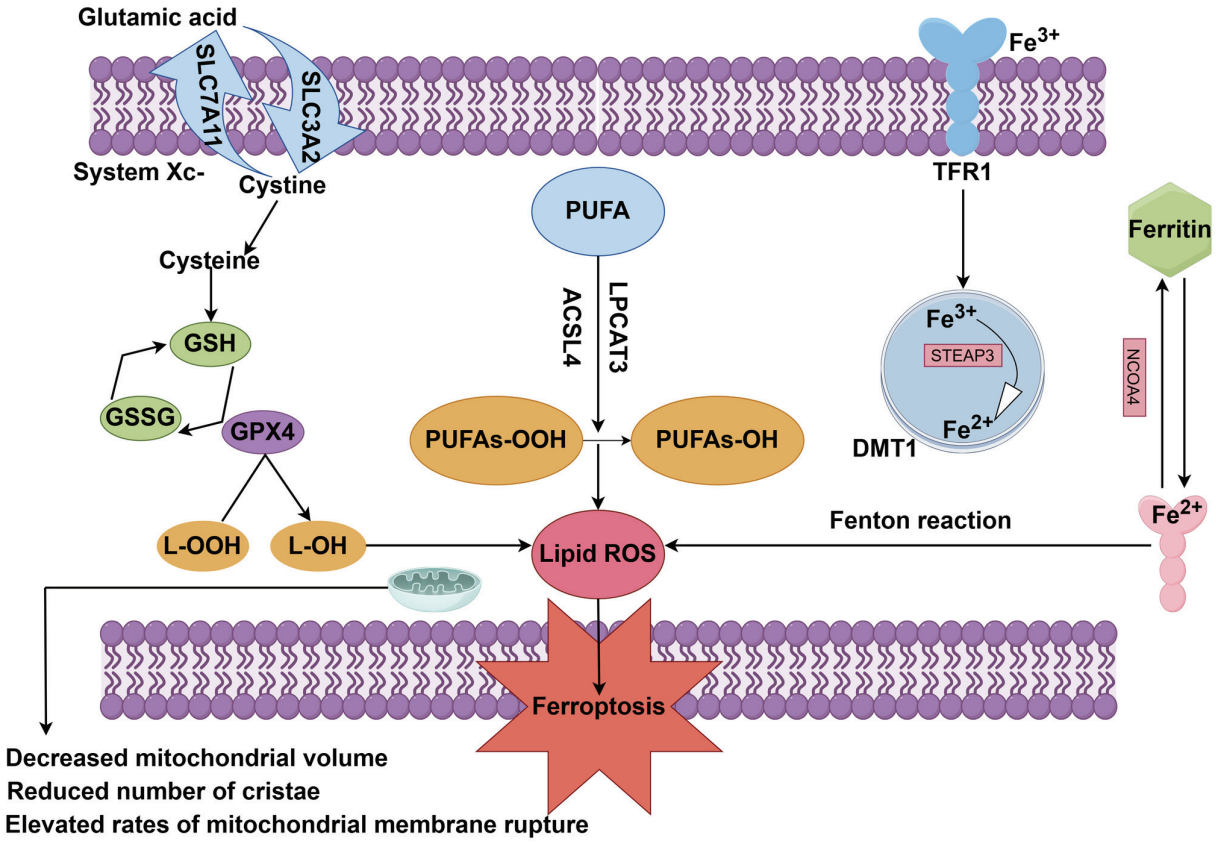

Figure 2. Regulatory mechanisms of ferroptosis. SLC7A11, solute carrier family 7 member 11; SLC3A2, solute carrier family 3 Member 2; System Xc-, cystine/glutamate antiporter system; GSH, glutathione; GSSG, oxidized glutathione; GPX4, glutathione peroxidase 4; PUFA, polyunsaturated fatty acid; ACSL4, acyl-CoA synthetase long-chain family member 4; LPCAT3, lysophosphatidylcholine acyltransferase 3; TFR1, transferrin receptor 1; STEAP3, six transmembrane epithelial antigen of the prostate 3; DMT1, divalent metal transporter 1; NCOA4, nuclear receptor coactivator 4; ROS, reactive oxygen species.

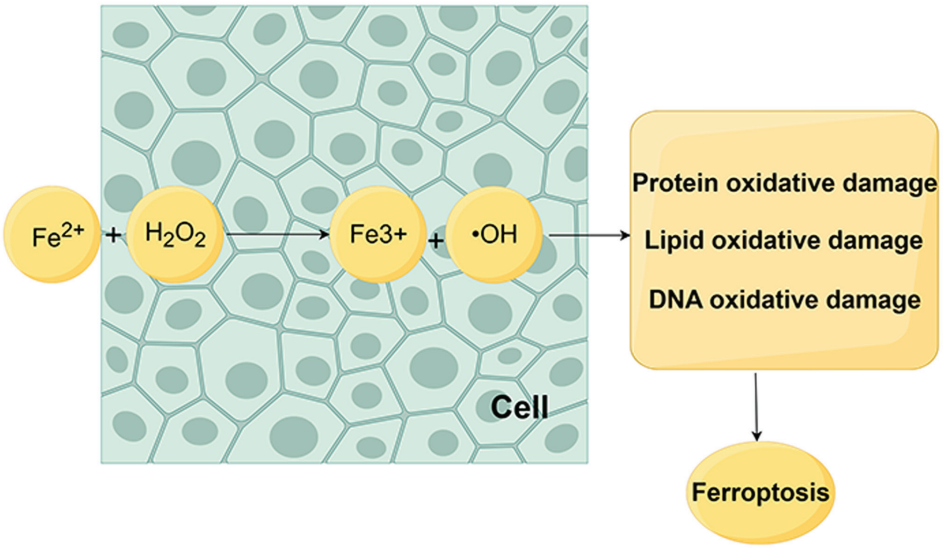

Figure 3. Fenton reaction.

3. Ferroptosis in CRC

At present, research is focused on the role of drug- (Table II), gene-, protein- (Table III), and RNA-induced ferroptosis (Table IV). Each of these mechanisms play distinct roles in CRC.

Drug-induced ferroptosis. In 2021, Yang *et al* (66) reported that cetuximab inhibits the progression of KRAS-mutant CRC through the promotion of RSL3-induced ferroptosis via inhibition of the Nrf2/heme oxygenase 1 (HO-1) signaling pathway. Results of a previous study demonstrated that apatinib promotes ferroptosis in CRC cells via the ELOVL6/ACSL4 signaling

Table II. Drug-induced ferroptosis may lead to inhibition of CRC development and progression.

Chemotherapeutic agent	Mechanism	(Refs.)
Cetuximab	Enhanced RSL3-induced ferroptosis through inhibition of the Nrf2/HO-1 signaling pathway	(66)
Apatinib	Promotion of ferroptosis through the ELOVL6/ACSL4 signaling pathway	(67)
Irrutinib	Enhanced sensitivity to ferroptosis in CRC cells via the BTK/nRF2 signaling pathway	(68)
Propofol	Downregulation of STAT3 expression	(69)
Aspirin	Enhanced RSL3-induced ferroptosis through inhibition of the mTOR/SREBP-1/SCD1 signaling pathway	(70)
Emodin	Induction of ferroptosis in CRC cells via NCOA4-mediated ferritin autophagy and the NF-κb pathway	(71)
Ginsenoside Rh3	Induction of ferroptosis in CRC cells via the Stat3/p53/NRF2 axis	(72)
Curcumin	Promotion of ferroptosis through regulation of the oncogene, P53, and the SLC7A11/glutathione/GPX4 axis	(73)
Curcumin in combination with Andrographis paniculata	Promotion of ferroptosis through downregulation of GPX4 and iron regulatory protein 1 expression levels	(74)
Esculin	Induction of endoplasmic reticulum stress via apoptosis and ferroptosis, through regulation of eIF2α/CHOP and Nrf2/HO-1 via the PERK signaling pathway	(75)
Baicalein	Promotion of ferroptosis through inhibition of the JAK2/STAT3/GPX4 signaling pathway	(76)

RSL3, RAS-selective lethal 3; Nrf2, nuclear factor erythroid 2-related factor 2; ELOVL6, elongation of very long chain fatty acids protein 6; ACSL4, Acyl-CoA synthetase long-chain family member 4; STAT3, signal transducer and activator of transcription 3; mTOR, mechanistic target of rapamycin; SREBP-1, sterol regulatory element-binding protein 1; SCD1, stearoyl-CoA desaturase 1; NCOA4, Nuclear receptor coactivator 4; SLC7A11, solute carrier family 7 member 11; GPX4, glutathione peroxidase 4; PERK, protein kinase R-like endoplasmic reticulum kinase; JAK2, Janus kinase 2; CRC, colorectal cancer.

pathway, highlighting the potential role of ferroptosis in CRC treatment (67). Ibrutinib enhances the sensitivity of CRC cells to ferroptosis through the BTK/nRF2 signaling pathway, thereby inhibiting CRC progression (68). In addition, Zhao *et al* (69) demonstrated that propofol induces ferroptosis in CRC cells via downregulation of STAT3 expression. The results of a previous study revealed that aspirin promotes RSL3-induced ferroptosis through inhibition of the mTOR/SREBP-1/SCD1 signaling pathway, highlighting the potential role of ferroptosis in the treatment of PIK3CA-mutant CRC (70).

In addition, herbs and plant extracts may induce ferroptosis. Emodin, a natural anthraquinone derivative extracted from various herbs, may induce ferroptosis in CRC cells through NCOA4-mediated ferritin autophagy and NF-κB pathways, thereby inhibiting CRC progression (71). Ginsenoside Rh3, a semi-natural product isolated from Panax ginseng, may induce ferroptosis in CRC cells via the Stat3/p53/NRF2 axis, demonstrating potential in the treatment of cancer (72). Moreover, curcumin may inhibit CRC through the induction of ferroptosis. Results of a previous study demonstrated that curcumin played a role in the regulation of oncogenes, such as P53, and the SLC7A11/glutathione/GPX4 axis (73). The combination of curcumin and *Andrographis paniculata* may induce ferroptosis in CRC, through the downregulation of GPX4 and iron regulatory protein 1 (74). In addition, esculin induces endoplasmic reticulum stress through the regulation of eukaryotic translation initiation factor 2α/CHOP and Nrf2/HO-1 pathways via the PERK signaling pathway; thus, promoting apoptosis and ferroptosis in CRC cells, ultimately inhibiting CRC occurrence and progression (75). Results of a previous study revealed that baicalein promotes ferroptosis through inhibition of the JAK2/STAT3/GPX4 signaling pathway; thus, exerting an inhibitory effect on CRC (76).

Gene- and protein-induced ferroptosis. Kruppel-like factor 2 (KLF2) is an oncogene that may also inhibit CRC progression. Notably, KLF2 suppresses the PI3K/AKT signaling pathway, thereby inducing ferroptosis (77). Results of a previous study demonstrated that bromelain inhibits the proliferation of KRAS-mutant CRC cells and induces ferroptosis via ACSL4 (78). Wei *et al* (79) revealed that Tagitinin C, a novel inducer of ferroptosis, acts as a potent chemosensitizer that enhances the efficacy of chemotherapeutic agents. Notably, Tagitinin C induces ferroptosis through the PERK/Nrf2/HO-1 signaling pathway. TIGAR, a TP53-induced regulator of glycolysis and apoptosis, plays a crucial role in energy metabolism, autophagy, stem cell differentiation and cell survival (80). Liu *et al* (81) demonstrated that TIGAR inhibits CRC progression through increasing the sensitivity of CRC cells to ferroptosis via the ROS/AMPK/SCD1 signaling pathway. Chaudhary *et al* (82) revealed that lipid carrier protein 2 inhibits ferroptosis through upregulation of GPX4 expression and the cystine/glutamate antiporter component, xCT; thus, promoting CRC progression. Moreover, increased expression of lipid carrier protein 2 may lead to resistance to 5-fluorouracil in CRC cells, further contributing to chemotherapeutic resistance. In a recent study, it has been reported that TRIM36-mediated FOXA2 promotes colorectal

Table III. Gene- and protein-induced ferroptosis in CRC.

A, Inhibition of CRC development and progression

Gene or protein	Mechanism	(Refs.)
Kruppel-like factor 2	Induction of ferroptosis through inhibition of the PI3K/AKT signaling pathway	(77)
Bromelain	Inhibition of proliferation and induction of ferroptosis in KRAS-mutant CRC cells through ACSL4	(78)
Tagitinin C	Induction of ferroptosis through the PERK/Nrf2/HO-1 signaling pathway	(79)
TIGAR	Increased sensitivity of CRC cells to ferroptosis via the ROS/AMPK/SCD1 signaling pathway	(80,81)

B, Promotion of colorectal carcinogenesis and progression

Gene or protein	Mechanism	(Refs.)
Lipid transport protein 2	Induction of ferroptosis through increased expression of glutathione peroxidase 4 and the cystine/glutamate antiporter component, xCT	(82)
FOXA2	Inhibition of ferroptosis through inhibition of the Nrf2/GPX4 signaling pathway	(83)
Uridine cytidine kinase-like 1	Inhibition of ferroptosis through the UCKL1/Nrf2/SLC7A11 axis	(84)

PI3K, phosphoinositide 3-kinase; KRAS-mutant, Kirsten rat sarcoma viral oncogene homolog; ACSL4, acyl-CoA synthetase long-chain family member 4; ROS, reactive oxygen species; AMPK, AMP-activated protein kinase; SCD1, stearoyl-CoA desaturase 1; xCT, cystine/glutamate transporter; Nrf2, nuclear factor erythroid 2-related factor 2; GPX4, glutathione peroxidase 4; UCKL1, uridine-cytidine kinase-like 1; SLC7A11, solute carrier family 7 member 11; CRC, colorectal cancer.

Table IV. RNA-regulated ferroptosis in CRC.

A, Inhibition of CRC development and progression

RNA	Mechanism	(Refs.)
miR-148a-3p	Activation of ferroptosis via targeting of SLC7A11	(85)
miR-509-5p	Promotion of ferroptosis via targeting of SLC7A1	(86)
miR-15a-3p	Activation of ferroptosis via direct targeting of GPX4	(87)

B, Promotion of colorectal carcinogenesis and progression

RNA	Mechanism	(Refs.)
miR-19a	Inhibition of ferroptosis via targeting of IREB2	(88)
miR-545	Inhibition of ferroptosis through inhibition of transferrin	(89)
lncRNA LINC00239	Inhibition of ferroptosis through interaction with Kelch-like ECH-related protein 1	(90)

SLC7A11, solute carrier family 7 member 11; GPX4, glutathione peroxidase 4; IREB2, iron-responsive element binding protein 2; miR, microRNA; CRC, colorectal cancer.

cancer by inhibiting the Nrf2/GPX4 signaling pathway and suppressing ferroptosis. However, the specific mechanism by which FOXA2 regulates Nrf2, whether directly or indirectly, remains unclear (83). Results of a previous study demonstrated that uridine-cytidine kinase-like 1 (UCKL1) enhances the proliferation and metastasis of CRC cells via the UCKL1/Nrf2/SLC7A11 axis, ultimately inhibiting ferroptosis and promoting CRC development and progression (84). These findings suggest that reduced lipid carrier protein 2, FOXA2 and UCKL1 expression levels may promote ferroptosis; thus, acting as an effective strategy for the treatment of CRC.

RNA-regulated ferroptosis. MicroRNAs (miRNAs/miRs) may play a role in the regulation of ferroptosis. Results of a previous study have revealed that miR-148a-3p acts as a tumor suppressor in CRC through targeting SLC7A11 and

Table V. Attenuating chemotherapeutic resistance to oxaliplatin and 5-fluorouracil through ferroptosis in colorectal cancer.

A, Direct attenuation of chemotherapeutic resistance

Drug	Mechanism	(Refs.)
Oxaliplatin	Induction of ferroptosis through inhibition of the KIF20A/NUAK1/Nrf2/GPX4 signaling pathway	(100)
	Increased intracellular reactive oxygen species levels and promotion of ferroptosis through inhibition of cysteine desulfurase expression levels	(101)

B, Indirect attenuation of chemotherapeutic resistance

Drug	Mechanism	(Refs.)
Oxaliplatin	Promotion of ferroptosis through inhibition of RNA-binding motif single-stranded interacting protein 1 expression	(102)
	Promotion of ferroptosis in *Candida nucleatum*	(103)
	Promotion of ferroptosis through inhibition of cyclin-dependent kinase 1 expression	(104)
5-Fluorouracil	Promotion of ferroptosis through inhibition of lipid transport protein 2 expression	(82)
	Promotion of ferroptosis through inhibition of serine protease 1 expression	(105)

KIF20A, kinesin family member 20A; NUAK1, NUAK family kinase 1; Nrf2, nuclear factor erythroid 2-related factor 2; GPX4, glutathione peroxidase 4.

activating ferroptosis (85). In addition, miR-509-5p promotes ferroptosis through targeting SLC7A1 (86), while miR-15a-3p induces ferroptosis through the direct targeting of GPX4 (87). The oncogenic miRNA, miR-19a, promotes the proliferation, migration and invasion of CRC cells. Iron-responsive element binding protein 2 (IREB2) is a direct target of miR-19a. Thus, targeting IREB2 may lead to the inhibition of ferroptosis via miR-19a, exhibiting potential as a novel target for CRC treatment (88). In addition, results of a previous study have revealed that miR-545 suppresses transferrin, promoting CRC cell survival through the inhibition of ferroptosis (89).

Long non-coding RNAs (lncRNAs) may also regulate ferroptosis. The results of a previous study have revealed that LINC00239 may act as a ferroptosis inhibitor in CRC, through interaction with Kelch-like ECH-associated protein 1. This leads to a reduction in the antitumor activity of Erastin and RSL3, and the promotion of CRC progression (90).

4. Ferroptosis and the tumor microenvironment (TME)

Ferroptotic damage induces the activation of immune responses within the TME (45). Thus, further investigations into the interaction between ferroptosis and the TME may provide a basis for the development of effective strategies for CRC treatment (91).

The TME is a complex environment containing tumor cells, stromal cells, immune cells, adipocytes, endothelial cells and the extracellular matrix (92). Dai *et al* (93) revealed that autophagic degradation-mediated ferroptosis leads to the release of cancer cell components into the TME and tumor-associated macrophage polarization. Moreover, Ma *et al* (94) revealed that CD36 mediates fatty acid uptake via CD^{8+} T cells within the TME induced ferroptosis, leading to a reduction in CD^{8+} T cell effector function and antitumor activity. In addition, cancer-associated fibroblasts in the TME may impair the antitumor capacity of natural killer cells through the induction of ferroptosis (95).

Notably, CD^{8+} T cells resist tumor growth and metastasis via multiple mechanisms (96-98). The results of a previous study have demonstrated that CD^{8+} T cell-derived IFN-γ promotes ferroptosis in cancer cells. This process leads to the release of a variety of tumor antigens into the TME, and antigen-presenting cell-mediated activation of CD^{8+} T cells, thereby enhancing anticancer immunity. However, CD^{8+} T cells in tumors exhibit increased levels of sensitivity to ferroptosis compared with cancer cells, which may limit the use of ferroptosis inducers in the treatment of cancer (99).

5. Inducing ferroptosis may attenuate drug resistance in CRC

Mitigating CRC-associated drug resistance to chemotherapy. Chemotherapy is the most common post-operative treatment for patients with CRC. The results of our previous study demonstrated that oxaliplatin and 5-fluorouracil are highly associated with ferroptosis in CRC (82,100) (Table V).

The results of a previous study revealed that the induction of ferroptosis through the inhibition of the KIF20A/NUAK1/Nrf2/GPX4 signaling pathway enhances sensitivity to oxaliplatin, thereby improving the quality of life of patients with CRC (100). In addition, inhibition of cysteine desulfurase expression leads to increased intracellular reactive oxygen species levels, the promotion of ferroptosis and reduced levels of resistance to oxaliplatin (101). Overexpression of RNA-binding motif single-stranded interacting protein 1 (RBMS1) inhibits ferroptosis; therefore, suppressing RBMS1 expression may increase the sensitivity of CRC cells to oxaliplatin (102). Inhibition of *Candida nucleata* also promotes

ferroptosis and decreases CRC cell resistance to oxaliplatin (103). The results of a previous study also demonstrated that oxaliplatin resistance is reversed following inhibition of cyclin-dependent kinase 1 expression (104).

Overexpression of lipid transport protein 2 leads to inhibition of ferroptosis, which ultimately increases the resistance to 5-fluorouracil. Therefore, targeting lipid transport protein 2 levels may attenuate resistance to 5-fluorouracil (82). In addition, serine protease 1 is associated with chemotherapeutic resistance in CRC. This protein is highly expressed in CRC cells and is negatively associated with the prognosis of patients. Moreover, Liu *et al* (105) demonstrated that serine protease 1 interacts with SLC7A11 to increase expression levels, ultimately inhibiting ferroptosis, leading to increased resistance to 5-fluorouracil. Thus, targeting serine protease 1 may exhibit potential in the treatment of CRC.

Mitigating CRC-associated drug resistance to targeted therapies. When targeting cancer cells, chemotherapy may also target healthy cells. Thus, targeted therapy is considered an alternative treatment option to chemotherapy. Mu *et al* (106) demonstrated that 3-bromopyruvic acid and cetuximab may induce ferroptosis; thus, exhibiting potential in mitigating cetuximab resistance in CRC. In addition, the combination of β-elemene, a natural product derived from turmeric, and cetuximab may exert effects on metastatic CRC cells with Kras mutations, inducing ferroptosis and reducing cetuximab resistance (107).

6. Conclusions

At present, research is focused on the role of ferroptosis in the physiological and pathological processes of numerous diseases, leading to the development of novel treatment approaches. The present study aimed to review the specific mechanisms underlying ferroptosis in CRC, including drug-, gene-, protein- and RNA-induced ferroptosis. The aforementioned forms of ferroptosis play distinct roles in CRC. For example, various signaling pathways directly facilitate drug-induced ferroptosis, thereby impeding CRC onset and progression. By contrast, gene-, protein- and RNA-induced ferroptosis involve specific signaling pathways and mechanisms that may exhibit potential as effective strategies for targeted CRC treatment. Notably, mechanisms may include targeting of GPX4 expression and xCT, the Nrf2/GPX4 signaling pathway, the UCKL1/Nrf2/SLC7A11 signaling pathway, miR-19a, miR-545, and lncRNA LINC00239. In addition, the association between ferroptosis and the TME further highlighted that induction of ferroptosis may attenuate drug resistance in CRC.

Results of the present study demonstrated that induction of ferroptosis may inhibit CRC progression. In addition, genes, proteins and RNAs that inhibit ferroptosis may promote CRC development and progression. However, the clinical application of ferroptosis is limited at present, as the specific mechanisms and signaling pathways through which ferroptosis promotes or inhibits CRC development are yet to be fully elucidated. Thus, further investigations into the specific role of ferroptosis in CRC are required for the development of effective targeted therapies.

In conclusion, ferroptosis may exhibit potential in the treatment of CRC. Further investigations are required to elucidate the signaling pathways involved in ferroptosis, and to identify the genes, proteins and signaling pathways that inhibit ferroptosis in CRC. Moreover, further investigations should focus on determining alternative therapeutic modalities that may increase the therapeutic effects of ferroptosis, and on assessing the specific anti-tumor effects of ferroptosis in CRC progression. An increased understanding of ferroptosis in CRC may lead to the effective implementation of treatment in clinical practice.

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Authors' contributions

ZG, HZ and XS contributed to the conception and the main idea of the work. ZG and HZ drafted the manuscript, figures and tables. XS reviewed and modified the manuscript. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

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Competing interests

All authors declare that they have no competing interests.

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