


Ferroptosis: Reviewing CRC with the Third Eye

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Abstract: Colorectal cancer (CRC) has been one of the most common cancers and maintains the second-highest incidence and mortality rates among all cancers. The high risk of recurrence and metastasis and poor survival are still huge challenges in CRC therapy, in which the discovery of ferroptosis provides a novel perspective. It has been ten years since a unique type of regulated cell death driven by iron accumulation and lipid peroxidation was proposed and named ferroptosis. During the past decade, there have been multiple pieces of evidence suggesting that ferroptosis participates in the pathophysiological processes during disease progression. In this review, we describe ferroptosis as an imbalance of oxidant systems and anti-oxidants which results in lipid peroxidation, membrane damage, and finally cell death. We elaborate on the mechanisms of ferroptosis and systematically summarize recent studies on the regulatory pathways of ferroptosis in CRC from various perspectives, ranging from encoding genes, noncoding RNAs to regulatory proteins. Finally, we discuss the potential therapeutic role of ferroptosis in CRC treatments.

Keywords: ferroptosis, colorectal cancer, redox imbalance, regulatory pathways, therapeutic potential

Introduction

Colorectal cancer (CRC) is one of the most common cancers and it has become the second leading cause of cancer death which incidence increasing each year.¹ In addition to genetic risk and environmental factors, unhealthy diet and lifestyle factors may modify the risk of CRC.²⁻⁴ Although early screening and diagnosis have improved survival, side effects accompanying conventional treatment seriously affect the quality of life. Tumor recurrence and metastasis as well as drug resistance have become major challenges for CRC therapy, so new treatments are urgently needed to improve the survival and prognosis of CRC patients. Given that CRC is the only type of malignancy with two iron uptake pathways, from both the intestinal lumen and blood, we infer that focus on ferroptosis may become a breakthrough point for CRC treatments. So far, a series of studies have corroborated the relationship between CRC cells and ferroptosis.

Ferroptosis is a form of regulated cell death (RCD) that differs from other types of cell death in terms of morphology, biochemistry, and genetics. Ferroptosis was first proposed by Dixon and his colleagues in 2012.⁵ In 2018, the Nomenclature Committee on Cell Death (NCCD) added ferroptosis to the RCD family.⁶ Morphologically, ferroptosis is characterized by smaller mitochondria with condensed mitochondrial membrane densities, reduced or vanished mitochondrial cristae, and rupture of the outer mitochondrial membrane.

Ferroptosis is an emerging field that has quickly updated development, with the in-depth study of its mechanisms and regulation, there have been connections verified between ferroptosis and pathophysiologic phenomena. Over the past few years, we have found the trail of ferroptosis in a variety of malignancies, in which ferroptosis is involved in their progression and influenced therapeutic response.⁷ More and more drugs, chemicals, and bioactive products in the body or extracted from plants have shown a regulatory effect on ferroptosis. In this review, we summarize the progression of mechanisms and regulatory pathways of ferroptosis in CRC and elaborate on their associations under the corroboration of bioinformatics analysis and diverse experimental data. We also emphasize the potential of ferroptosis working as a novel strategy for therapy in CRC.

Mechanisms of Ferroptosis

Ferroptosis was originally defined as iron-dependent lipid peroxidation. For ferroptosis to occur, specific lipids must undergo oxidation. That is to say, the natural defenses that block the accumulation of oxidized lipids and repair the damaged membrane must become compromised. Ultimately, accumulated lipid peroxide stands out in the competition between the oxidative system and the reduction system, leading to plasma membrane damage and cell death. Figure 1 Iron and lipid peroxide released from ferroptotic cells also act as signals to wave-like propagation of ferroptosis in the cell population.⁸

Oxidative Damage

Iron Accumulation and ROS Production

Iron homeostasis is critical for ferroptosis regulation. Iron is an essential element for cellular homeostasis and organismal survival, and it is involved in a series of crucial physiological processes such as oxygen transport, oxidative phosphorylation, and enzymatic function. Ferritin is the major form of iron storage, which contains two components, including ferritin light chain (FTL) and ferritin heavy chain 1 (FTH1). Most of the iron in the systemic circulation is present as trivalent iron (Fe^{3+}) bound to transferrin (TF). Then, on the cell membrane, the transferrin receptor (TFRC) recognizes iron-containing TF and transports it into the cell via endosomes, where STEAP3 as a ferrireductase reduces Fe^{3+} to ferrous iron (Fe^{2+}). Then, with the assistance of SLC11A2 (also known as DMT1), Fe^{2+} is released from the endosome, and maintained in the form of labile iron pool (LIP) or transferred to the extracellular milieu through the iron-efflux protein solute carrier family 40 member 1 (SLC40A1/ferroportin1).⁹ Furthermore, the ferritin complex is transported to autophagosomes and undergoes degradation by nuclear receptor coactivator 4 (NCOA4), thus increasing cellular labile iron levels.¹⁰ Then, through the Fenton reaction, high levels of intracellular Fe^{2+} generate excess reactive oxygen species

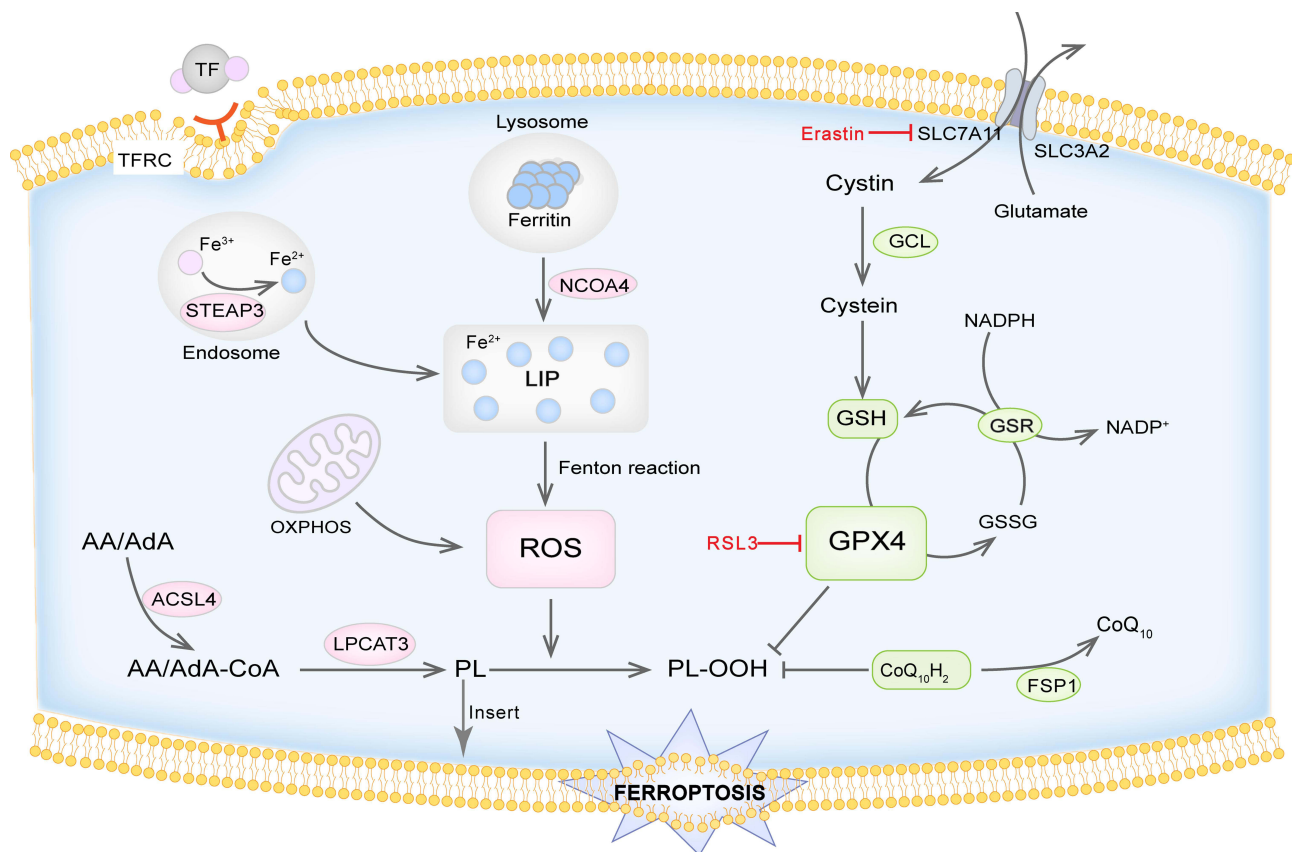


Figure 1 Schematic diagram of the mechanism of ferroptosis. Ferroptosis is a form of regulated cell death driven by iron-dependent lipid peroxidation. Ferroptosis is the result of imbalance in redox systems. The accumulation of ROS mainly mediated by iron overload is the key step which would lead to lipid peroxidation and destroy the cell membrane. GPX4 mediated enzymatic antioxidant process is a crucial defense mechanism against lipid peroxidation. The FSP1/CoQ10 axis also plays a role in negatively regulating ferroptosis.

(ROS) which finally induce lipid peroxidation.¹¹ And naturally, iron chelators that bind free iron can protect against ferroptosis by reducing levels of intracellular Fe^{2+} .

ROS is a ubiquitous oxidation product of cellular metabolism that is primarily generated during oxidative phosphorylation in the mitochondria. It plays a pivotal role in stress response and acts as an important second messenger in signaling transduction. Under normal circumstances, intracellular ROS levels are maintained in a low physiological range. Mild elevation of ROS can promote tumor cell proliferation, invasion, and migration, and may also contribute to apoptosis evasion, thus leading to drug resistance.¹² While excess ROS initiates the production of lipid peroxides (LOOH) in the membrane phospholipids, leading to the damage of membrane structure and function. Above all, iron accumulation and ROS production are key steps to trigger ferroptosis.

Moreover, cancer cells, especially cancer stem cells, need a large amount of iron to sustain their rapid proliferation.¹³ They also have high basal levels of ROS as a result of their exuberant cell metabolism and proliferation. CRC is the only type of malignancy with two iron uptake resources, whose iron comes from the intestinal cavity and systemic circulation. And there have been reports suggesting that high dietary iron elevates the risk of CRC for humans.¹⁴ A recent study also shows that iron exposure could activate ROS and enhance the Warburg effect to protect CRC from ferroptosis.¹⁵ This evidence revealed a close link between ferroptosis and CRC and shed light on new therapeutic ideas.

Lipid Peroxidation

The accumulation of lipid peroxidation products is the central process of ferroptosis by which oxidants attack the carbon-carbon double bonds of lipids. The primary substrates of lipid peroxidation are polyunsaturated fatty acids (PUFAs).¹⁶ Several biological processes, for example, cellular growth, immunity regulation, and inflammation are regulated by PUFAs, which are components of the cell membrane. The unstable double bonds in the structure of PUFA make it sensitive to oxidation and their number largely determined the susceptibility. To drive ferroptosis, PUFAs need to be activated and inserted into membrane lipids.¹⁷ The two primary PUFAs that trigger ferroptosis are arachidonic acid (AA) and adrenic acid (AdA). Either enzyme catalysis or non-enzymatic-free radical-chain reaction can mediate PUFA oxidation. Free PUFAs are attached to CoA by Acyl-CoA Synthetase Long-Chain Family Member 4 (ACSL4), and then incorporated into membrane phospholipids by Lysophosphatidylcholine Acyltransferase 3 (LPCAT3).¹⁸ Some certain lipoxygenases (LOXs) can directly catalyze lipid peroxidation in the membrane.¹⁹ Lysophospholipids can be oxidized by prostaglandin-endoperoxide synthase 2/cyclooxygenase-2 (PTGS2/COX2), which is regarded as a biomarker of ferroptosis.²⁰ Extensive lipid peroxidation can destroy membrane structure and increase its permeability. It also causes the generation of numerous toxic byproducts including 4-hydroxynonenal (4-HNE) and malondialdehyde (MDA). They can produce extremely toxic cytotoxicity when they interact with proteins, DNA bases, and other nucleophilic molecules.²¹

Antioxidants and Oxidative Damage-Repairing Systems

GPX4 and GSH-Related Axis

An antioxidant enzyme, called glutathione peroxidase 4 (GPX4), mediates enzymatic antioxidant processes, which is a crucial defense mechanism against lipid peroxidation. By binding to reduced glutathione (GSH), it transforms toxic lipid peroxidation into harmless lipid alcohols, while producing oxidized glutathione (GSSG) to resist lipid peroxidation. GSH is a synthetic substrate and cofactor for GPX4. The cytosolic enzymes glutamate-cysteine ligase (GCL) and glutathione synthetase (GSS) catalyze the tripeptide's synthesis from glutamate, cysteine, and glycine. Glutamate-cysteine ligase catalytic subunit (GCLC) and glutamate-cysteine ligase modifying subunit (GCLM) make up GCL, which operates as a rate-limiting enzyme in the production of GSH. Cysteine is also considered a rate-limiting precursor of GSH synthesis due to its limited concentration. Cysteine is imported into the cell in its oxidized form via system xc-, which consists of two subunits including SLC7A11 and SLC3A2. The former mediates the antiporter activity and the latter maintains its protein stability and appropriate localization. And then, cystine is immediately reduced to cysteine. Erastin blocks SLC7A11 and causes GSH depletion, while RSL3 inactivates GPX4. Both of them are commonly used ferroptosis inducers in relevant experiments.^{20,22}

It is reported that colorectal cancer stem cells (CSCs) have lower levels of ROS and higher levels of cysteine, GSH, and SLC7A11 compared to normal CRC cells, and knockdown of SLC7A11 notably raise the ROS level and reduce

cysteine, GSH levels, and then attenuates the activity of CSCs. Erastin also has significantly stronger cytotoxic effects on CSCs that can be used to inhibit CRC progression and drug resistance.²³ RSL3 also showed its emerging role in CRC ferroptosis through GPX4 inactivation and ROS production.²⁴

GPX4-Independent Defense for Ferroptosis

Although GPX4 is the main defense against lipid peroxidation, ubiquinone (Coenzyme Q10, CoQ10) can directly scavenge lipid peroxy radicals and act as a secondary endogenous defense against lipid peroxidation.²⁵ And utilizing NAD(P)H, ferroptosis suppressor protein (FSP1) plays a role in catalyzing the regeneration of non-mitochondrial CoQ10.²⁶ Additionally, GCH1 (GTP cyclo- hydrolase 1) may also produce the metabolic byproducts tetrahydrobiopterin/dihydrobiopterin (BH4/BH2) and regulate the formation of CoQ10 to prevent ferroptosis.²⁷ Suppressing the GCH1/BH4 metabolism can activate NCOA4-mediated ferritinophagy to promote ferroptosis.²⁸ Besides, ESCRT-III is also a commonly accepted mechanism to repair membrane damage after different kinds of cell death, for example, necrosis and pyroptosis. It is also reported to protect tumor cells after being attacked by T cells. The increasing cytosolic Ca²⁺ appeared after lipid peroxidation and was also a hallmark of plasma membrane damage and ferroptosis. And the ESCRT-III complex will be activated by the increasing Ca²⁺ to mediate membrane repair.²⁹

Regulation of Ferroptosis in CRC

Gene

Genes encode and modulate the expression of proteins and are involved in various cellular activities. By integrating the clinical data of CRC patients and gene expression profiles from public databases, and verifying through gene technologies, a series of genes and signal pathways are proposed to engage in the regulation of ferroptosis in CRC and may be used to predict the prognosis of the disease. Inhibiting *SRSF9* can downregulate GPX4 levels and increase ferroptosis induced by erastin in CRC cells.³⁰ Liu et al performed both bioinformatics analysis and in vitro experiments to investigate the biological function and signal regulation pathway of Solute carrier family 2 member 1 (*SLC2A1*), which encodes a glucose transporter (GLUT) and is involved in multiple physiological and pathophysiological processes. They validated that *SLC2A1* was strongly expressed in CRC and connected to a series of regulatory networks for example ferroptosis, which makes it a potential diagnostic biomarker.³¹ Peng et al explored a ferroptosis-related gene (*FRG*), Metallothionein-1G (*MG1T*), and demonstrated that CRC patients' immune responses may be impacted by decreased levels of *MG1T*, which already showed a worse prognosis in CRC patients.³² There are also some other FRGs screened from databases that are closely related to ferroptosis in CRC, for example, *CYBB*, *YAPI*,³³ *NFS1*,³⁴ *TFAP2C*, *ALOX12*, *NOS2*,^{35–37} *NOX4*^{37,38} and so on. While these results may lack universality and need to be further verified.

One of the most thoroughly investigated traditional tumor suppressor genes is tumor protein 53 (*TP53*). About 60% of CRC patients had *P53* mutations. The mutant *P53* activates oncogenic and inflammatory pathways, giving tumor cells the capacity to invade and spread, thus accelerating the progression of advanced CRC. *P53* has a double-side ferroptosis regulation mode depending on different cancer types and intracellular metabolic states.^{39,40} *P53* blocks the transcription of *SLC7A11* to suppress cystine uptake and induce GSH depletion and ferroptosis in some types of human cancer cells.⁴¹ However, *TP53* was found to suppress ferroptosis in CRC cells by binding to dipeptidyl-peptidase 4 (*DPP4*). *DPP4* has peptidase activity and can mediate ROS production to regulate lipid metabolism and ferroptosis. Loss of *TP53* increased *DPP4* pathway activation, triggered lipid peroxidation, and made human CRC cells more susceptible to ferroptosis induced by erastin in vivo.⁴²

Noncoding RNA

Long Noncoding RNA

Transcripts with a length of more than 200 nucleotides that do not code for proteins are known as long non-coding RNA (lncRNA).⁴³ lncRNA regulates gene expression at epigenetic, post-transcriptional, and transcriptional levels.⁴⁴ It is an important factor in tumors' biological processes such as cell proliferation, differentiation, and migration.⁴⁵ Increasing studies have confirmed that lncRNA could regulate MicroRNA (miRNA) by acting as competing endogenous RNA (ceRNA) in cancer progression.⁴⁶ LNC01606 was frequently at a highly expressed level in CRC and closely linked to

a poor prognosis. Mechanically, LNC01606 served as a ceRNA to modulate the expression of miR-423-5p, which would enhance the stearoyl-CoA desaturase 1 (SCD1) expression and activate the classical Wnt/ β -catenin signaling, subsequently inhibiting ferroptosis and enhancing stemness.⁴⁷

Although there are no more reported mechanisms of specific lncRNA regulating ferroptosis in CRC, lncRNA can serve as valuable prognostic markers. Researchers analyzed lncRNA expression data profiles and integrated clinical data, thereby constructing CRC prognostic risk models based on ferroptosis-related lncRNAs.

To assess the prognosis of patients suffering from colon adenocarcinoma (COAD), Zeng et al created a differentially expressed lncRNA signature and found that four lncRNAs (LINC01555, RP11-610P16.1, RP11-108K3.1, and LINC01207) were identified to possess the most remarkable correlation with survival in COAD.⁴⁸ Zhang et al developed a nomogram including age, T stage, pathologic stage, and risk score that has great predictive power. They also developed a ferroptosis-related lncRNA prognosis signature in CRC that consists of VPS9D1-AS1, ELFN1-AS1, AC099850.3, and AC016027.1.⁴⁹ These researches filtered out some ferroptosis-related lncRNAs that were highly related to CRC prognosis and revealed potential signal pathways among them. These models not only present individualized predictions for prognosis but also provide promising targets for exploring the mechanisms of ferroptosis and CRC.

MiRNA

MiRNAs are a series of tiny single-stranded RNA molecules of 18–25 nucleotides, which are highly conserved yet do not have an encoding function. They repress translation and regulate gene expression levels by binding the sequences in the 3'-untranslated region of messenger RNAs (mRNAs). And by binding with various mRNAs and blocking post-transcriptional expression of specific genes, miRNAs play different roles in regulating ferroptosis.

MiR-15a-3p could directly target GPX4 and result in sensitivity to ferroptosis in CRC cells.⁵⁰ MiR-539 can stimulate the SAPK/JAK axis, which will promote ferroptosis in vitro and inhibit tumor growth in vivo.⁵¹ On the contrary, miR-545 targets the TF genes to suppress ferroptosis and play an oncogenic role in CRC cells. Nude mice with implanted miR-545 knocked down CRC cells were found with decreased tumor size after erastin treatment.⁵²

Using whole-transcriptome profiling and anti-correlation analysis, Angius et al thoroughly analyzed the miRNA expression profiles of CRC and healthy colon tissue to determine the genes that each deregulated miRNA was targeting. Their research characterized numerous pathways involved in the development of CRC and discovered an integrated signature of 20 deregulated miRNAs in CRC.⁵³

CircRNA

Circular RNAs (circRNAs) are covalently closed loops that are generated by the back splicing of pre-mRNAs. CircRNAs can function as sponges of miRNAs to regulate gene expression and then the pathogenesis of tumors.⁵⁴ Their abundant presence, relatively high stability, and widespread expression make them potential diagnostic and prognostic biomarkers for cancers.⁵⁵

Circ_0007142 was found as a sponge of miR-874-3p, which directly repressed glycerophosphodiester phosphodiesterase domain containing 5 (GDPD5) expression and acted as a ferroptosis promoter and a tumor inhibitor in CRC.⁵⁶ Circular ATP binding cassette subfamily B member 10 (circABCB10) serves as a sponge of miR-326 to regulate C-C motif chemokine ligand 5 (CCL5) expression in CRC cells. CircABCB10 and CCL5 were highly expressed in CRC. CircABCB10 knockdown promoted ferroptosis in vitro and suppressed tumor growth in vivo, indicating its potential as a therapeutic target for CRC therapy.⁵⁷

Nrf2

The transcription factor nuclear factor-erythroid 2-related factor 2 (Nrf2) is considered a pivotal mechanism in regulating redox balance. Normally, Nrf2 binds primarily to Kelch-like ECH-associated protein 1 (KEAP1), inhibits its activation, and undergoes constant ubiquitination proteasome and degradation, which maintains Nrf2 at a basally low level.⁵⁸ When cells are under stress conditions induced by ROS or electrophilic substances, Nrf2 is activated after dissociating from KEAP1. Then, Nrf2 enters the nucleus and binds to the antioxidant response element (ARE) sequence, leading to the production of cellular defense-related proteins and enzymes.⁵⁹ Nrf2 protects cells from ferroptosis by regulating relative

genes. NRF2 positively regulates xCT, GCLC, and GCLM, three genes involved in the synthesis of GSH.^{60–62} NRF2 also promotes the expression of FTH1 and FTL.⁶³ A vital NRF2-controlled enzyme is called heme oxygenase-1 (HO-1), which can catalyze the degradation of heme into iron, biliverdin, and carbon monoxide (CO). The first two products are strong antioxidants to protect against ferroptosis, while the latter promotes ferroptosis. HO-1 has been confirmed to be a double-edged sword in regulating ferroptosis.^{63,64}

Cetuximab inhibits the Nrf2/HO-1 axis thus enhancing RSL3-induced ferroptosis.⁶⁵ However, Tagitinin C, a sesquiterpene lactone, induces oxidative stress and activates the Nrf2/HO-1 pathway. The increased HO-1 expression leads to the increased LIP and promotes lipid peroxidation, ultimately inducing ferroptosis in CRC cells.⁶⁶ Likewise, the *B. etnensis* Raf. extract promotes the oxidation degree of the cellular redox environment, stimulates ferroptosis, and causes CRC cell death by increasing HO-1 expression.⁶⁷

Other Signaling Regulatory Pathways

The activation of transcription factors hypoxia-inducible factor 2 α (HIF-2 α) can upregulate cellular iron levels and enhance irreversible cysteine oxidation, thereby inducing ferroptosis in CRC cells. Knockdown or inhibition of HIF-2 α leads to reduced ROS and tolerance to ferroptosis *in vivo* and *in vitro*, which can be used for CRC therapy.⁶⁸

OTUD1 was found to be the deubiquitinase of iron-responsive element-binding protein 2 (IREB2). OTUD1 stimulates ROS generation and ferroptosis by deubiquitinating and stabilizing IREB2 and promoting iron transportation. Downregulation of OTUD1 limits the accumulation of tumor-reactive T cells, which also makes it correlated with poor outcomes of CRC.⁶⁹

Additionally, ferroptosis has some links with other types of regulated cell death. Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) and ferroptosis inducers like erastin and artesunate (ART) exerted synergic action in CRC cell death. Erastin and ART can stimulate the C/EBP-homologous protein (CHOP), leading to endoplasmic reticulum stress and the expression of p53 upregulated modulator of apoptosis (PUMA), which is a potent pro-apoptosis factor. The lack of CHOP and PUMA, but not p53 downstream eliminates the synergism of ferroptosis inducers, indicating that the CHOP/PUMA axis also affects the function of ferroptosis inducers.⁷⁰ These findings remind us of a new angle to implore the crosswalk between ferroptosis and other forms of RCD.

Bright Future of CRC Therapy

Ferroptosis and Tumor Drug Resistance

Drug resistance and cancer metastasis are major obstacles in CRC treatment and profoundly influence the therapeutic efficiency and prognosis. A better understanding of the mechanisms and regulation of ferroptosis in CRC cells not only helps to uncover the mechanisms of drug resistance but also provides useful guidance for improving therapeutic strategies.

The inhibition of cellular ferroptosis in CRC cells may be one of the basics of drug resistance. Lipocalin 2 (LCN2) is an iron-trafficking protein that can decrease intracellular iron levels. Meanwhile, LCN2 stimulates the expression of xCT and GPX4. It has been found that LCN2 is highly expressed in various kinds of cancers including CRC, and leads to resistance to 5-fluorouracil (5-FU) *in vitro* and *in vivo* by inhibiting ferroptosis.⁷¹ Andrographis mitigates resistance to 5FU-based chemotherapy by stimulating ferroptosis and downregulating the β -catenin/Wnt-signaling pathway.⁷² It was found that KIF20A is overexpressed in oxaliplatin-resistant cell lines and is closely related to patient survival. Silencing KIF20A promotes the ferroptosis process in CRC cells via the KIF20A/NUAK1/PP1 β /GPX4 pathway and enhances cellular sensitivity to oxaliplatin.⁷³

RAS mutation is known to be a mechanism of resistance to anti-EGFR antibody therapy in CRC.⁷⁴ In KRAS mutant CRC cell lines, cetuximab promotes RSL3-induced ferroptosis by activating p38 MAPK and blocking the Nrf2/HO-1 axis.⁶⁵ β -elemene is extracted from the Chinese herb *Curcumae Rhizoma* and is known as a bioactive component with broad-spectrum anticancer effects. It was found to induce ferroptosis in CRC cells. By triggering ferroptosis and preventing epithelial–mesenchymal transition, cetuximab and β -elemene together increase the sensitivity of KRAS mutant CRC cells.⁷⁵ Vitamin C (VitC) could disrupt iron homeostasis and induce ROS-mediated stress ultimately leading to ferroptosis. The combination of VitC and Cetuximab inhibits the growth of CRC cells and prevents the development of acquired resistance to anti-EGFR targeted therapy *in vitro*.⁷⁶

Novel Ferroptosis Inducers with Anti-Tumor Activity

Except for the commonly used ferroptosis inducers such as erastin and RSL3, more chemicals and synthesized drugs were found to induce ferroptosis. Cisplatin was reported to trigger ferroptosis in CRC cells achieved by decreasing reduced glutathione as well as guiding the inactivation of glutathione peroxidase. And it can cooperate with erastin to play a synergistic anti-tumor effect.⁷⁷ Tian et al proved that apatinib stimulated ferroptosis in CRC cells by targeting the elongation of very long-chain fatty acids family member 6 (ELOVL6) and subsequently up-regulating ACSL4 and down-regulating GPX4 and FTH1.⁷⁸ Dichloroacetate (DCA) can sequester iron in lysosomes, thereby triggering ferroptosis and reducing the stemness of CRC cells.⁷⁹ 2-Imino-6-methoxy-2H-chromene-3-carbothioamide (IMCA) is a benzopyran derivative with broad biological activities and was revealed to induce CRC cells' ferroptosis *in vivo* and *in vitro*. By activating the AMPK/mTOR/p70S6k signaling pathway, IMCA reduces the expression of SLC7A11 and causes ferroptosis.⁸⁰

Currently, bioactive ingredients from plants and other organisms have attracted wide interest and concern. In addition to the Andrographis mentioned above, bromelain derived from pineapple stem was reported to effectively induce ferroptosis in Kras-mutant CRC cells by regulating ACSL4 levels.⁸¹ Punicic acid (PunA, C18:3 c9t11c13) which is present at up to 83% in pomegranate seed oil was known to exert a strong anti-cancer activity. Recent work has presented that PunA triggered intense lipid peroxidation leading to ferroptosis in CRC cells.⁸² Talaroconvolutin A (talaA) is a natural product isolated from the *Talaromyces purpureogenus*. It was found to trigger ferroptosis more effectively than erastin by raising ROS levels and decreasing the expression of SLC7A11. Experiments showed that TalaA could significantly inhibit the growth of CRC cells while it did not cause obvious liver and kidney toxicities, which made it a promising drug for CRC therapy.⁸³ Similarly, Auricularin, a polyphenolic flavonoid isolated from *Flemingia philippinensis*, promotes ferroptosis, apoptosis, and oxeiptosis in CRC cells by stimulating ROS production, thus inhibiting cell viability, colony formation, and invasion.⁸⁴

Combination of Ferroptosis Inducers and CRC Treatment

For better therapeutic effects, we highlight the importance of combining ferroptosis with other knowledge areas and techniques. The tumor microenvironment (TME) has significant implications for tumor development, invasion, metastasis, and immune evasion. Immune cells in TME may act as promoting or suppressing factors in tumor growth.⁸⁵ Ferroptosis also interacts with TME and plays a dual role in cancer immunity.⁸⁶ Iron and immunity are also closely related. Nowadays, immunotherapy that targets immunological checkpoints and immune microenvironment control has exhibited substantial efficiency in the treatment of cancer.⁸⁷ Besides, nano-technology is playing a significant role in precision therapy, and various nanomaterials and nanomedicines have been used for the detection and treatment of diseases.

A study by Zhu et al found that myeloid-derived suppressor cells (MDSCs) from colon cancer patients overexpressed asah2, which protected MDSCs from ferroptosis by repressing the p53–Hmox1 axis. And they developed an Asah2-selective small molecular inhibitor, NC06, which can suppress MDSCs accumulation by inducing ferroptosis and activating T cell infiltration to suppress tumor growth *in vivo*. NC06 has been shown to suppress CRC and some other cancers in preclinical mouse models and may provide greater value in cancer immunotherapy.⁸⁸

BEBT-908, a dual inhibitor that targets both PI3K and HDAC signaling pathways, effectively induces immunogenic cellular ferroptosis and suppresses tumor growth, thus enhancing immune checkpoint blockade therapy.⁸⁹

Dihydroartemisinin (DHA) has shown cytotoxicity in various cancers by inducing ferroptosis and would induce more ROS production to cause tumor inhibition in cooperating with an exogenous iron delivery. ZnP@DHA/Pyro-Fe core-shell nanoparticles stabilize DHA against hydrolysis and enhance uptake in tumors, the combination also sensitizes non-immunogenic colorectal tumors to anti-programmed cell death-Ligand 1 (anti-PD-L1) checkpoint blockade immunotherapy.⁹⁰ The combination of glycyrrhetic acid-based nanomaterials and ferumoxytol could synergistically increase Fe-dependent cytotoxicity via the Fenton reaction and could synergize PD-L1 blockade to enhance the T-cell immune response against CRC.⁹¹

Moreover, conventional treatment of SN38 in combination with electroporation therapy showed better efficacy in CRC therapy. SN38 is the active metabolite of irinotecan, which has become one of the most widely used strategies in first- and second-line treatment of advanced CRC. Such combination changed the redox homeostasis, causing increased

generation of intracellular superoxide and depletion of GSH, which may lead to cell death by ferroptosis.⁹² Electro-assisted sensitization of CRC cells to SN38 opens a new door for innovative CRC treatment.

Conclusion

During the past ten years since ferroptosis was found, there has been remarkable progress in the study of ferroptosis. We gradually shed light on the mechanisms and signal pathways involved in ferroptosis and try to link it with diverse diseases to overcome the therapeutic obstacles. As for CRC, considerable progress has been made but what we saw is just the tip of the iceberg. There are still continuous explorations to reveal the underlying mechanisms and the whole signal pathways. The term that specific lipids undergo oxidation drives the cell death process and results in ferroptosis can be summarized as an imbalance of intracellular oxidative and antioxidant systems. The treatment of cancer has always been regarded as a major challenge in the medical field. As one of the cancers with the greatest incidence and highest mortality rate, CRC urgently needs more effective treatment approaches to improve the prognosis of patients. The particular access by which CRC cells acquire iron from the intestinal lumen and the growth-promoting role of iron in cancer provide more possibilities for the connection between CRC and ferroptosis. Following this way, we have found that specific genes, noncoding RNAs, and proteins showed their potential in regulating ferroptosis in CRC cells and can be developed as therapeutic targets. We give a brief overview of the regulators of ferroptosis and their mechanisms in CRC. **Table 1** Regulators of ferroptosis and brief mechanisms in CRC. Recent studies have also shown the great therapeutic potential of ferroptosis combined with conventional treatments such as radiotherapy, chemotherapy, and immunotherapy. The development of new drugs, the application of nanotechnology, and the

Table 1 Regulators of Ferroptosis and Brief Mechanisms in CRC

Category	Molecular/Drug	Target Molecular/Regulatory Pathway	Function	Reference
Gene	<i>SRSF9</i>	GPX4	–	[30]
	<i>TP53</i>	DPP4	–	[42]
lncRNA	LNC01616	miR-423-5p/SCD1/Wnt/ β -catenin	–	[47]
miRNA	miR-15a-3p	GPX4	+	[50]
	miR-539	SAPK/JAK	+	[51]
	miR-545	TF	–	[52]
circRNA	Circ_0007124	miR-874-3p/GDPD5	+	[56]
	CircABCBI0	MiR-326/CCL5	–	[57]
Other	HIF-2 α	Iron	+	[68]
	OTUD1	IREB2	+	[69]
	LCN2	Iron	–	[71]
	KIF20A	NUAK1/PP1 β /GPX4	–	[73]
	VitC	ROS	+	[76]
Drug	Erastin	SLC7A11	+	[23]
	RSL3	GPX4	+	[24]
	Cetuximab	Nrf2/HO-1	+	[65]
	Tagitinin C	Nrf2/HO-1	+	[66]

(Continued)

Table I (Continued).

Category	Molecular/Drug	Target Molecular/Regulatory Pathway	Function	Reference
	B. etnensis Raf.	HO-1	+	[67]
	Apatinib	ELOVL6/ACSL4, GPX4, FTH1	+	[78]
	DCA	Iron	+	[79]
	IMCA	AMOK/Mtor/p70S6k/SLC7A11	+	[80]
	Bromelain	ACSL4	+	[81]
	PunA		+	[82]
	talaA	SLC7A11, ROS	+	[83]
	Auricularin	ROS	+	[84]
	NC06	Asah2/P53/HMOX1	+	[88]
	BEBT-908	PI3K/HDAC	+	[89]
	DHA	ROS	+	[90]

assistance of bioinformatics also provide more power for the treatment of CRC. As a relatively young field, the mechanisms of ferroptosis also intersect with other cell death forms such as apoptosis and autophagy. Iron as well as ferroptotic cells may also have impacts on the tumor microenvironment and, ultimately, on the tumor behavior.⁹³ In the future, the execution mechanisms and diverse triggers of ferroptosis need to be identified to selectively and more effectively control ferroptosis and translate it into therapies. We also attach importance to the potential connections with other cell death forms and tumor microenvironment, and the complex network may be a key point to fight against cancer. Above all, the discovery of ferroptosis blaze a new trial for CRC therapy.

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Disclosure

The authors report no conflicts of interest in this work.

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