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REVIEW

Ferroptosis regulates key signaling pathways in gastrointestinal tumors: Underlying mechanisms and therapeutic strategies

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Abstract

Ferroptosis is an emerging novel form of non-apoptotic, regulated cell death that is heavily dependent on iron and characterized by rupture in plasma membrane. Ferroptosis is distinct from other regulated cell death modalities at the biochemical, morphological, and molecular levels. The ferroptotic signature includes high membrane density, cytoplasmic swelling, condensed mitochondrial membrane, and outer mitochondrial rupture with associated features of accumulation of reactive oxygen species and lipid peroxidation. The selenoenzyme glutathione peroxidase 4, a key regulator of ferroptosis, greatly reduces the lipid overload and protects the cell membrane against oxidative damage. Ferroptosis exerts a momentous role in regulating cancer signaling pathways and serves as a therapeutic target in cancers. Dysregulated ferroptosis orchestrates gastrointestinal (GI) cancer signaling pathways leading to GI tumors such as colonic cancer, pancreatic cancer, and hepatocellular carcinoma. Crosstalk exists between ferroptosis and other cell death modalities. While apoptosis and autophagy play a detrimental role in tumor progression, depending upon the factors associated with tumor microenvironment, ferroptosis plays a decisive role in either promoting tumor growth or suppressing it. Several transcription factors, such as TP53, activating transcription factors 3 and 4, are involved in influencing ferroptosis. Importantly, several molecular mediators of ferroptosis, such as p53, nuclear factor erythroid 2-related factor 2/heme oxygenase-1, hypoxia inducible factor 1, and sirtuins, coordinate with ferroptosis in GI cancers. In this review, we elaborated on key molecular mechanisms of ferroptosis and the signaling pathways that connect ferroptosis to GI tumors.

Key Words: Ferroptosis; Gastrointestinal cancers; Nuclear factor erythroid 2-related factor 2; Apoptosis; Autophagy

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Core Tip: Gastrointestinal tumors contribute to the majority of cancer-related deaths. Ferroptosis is a novel form of non-apoptotic cell death that plays a vital role in reducing the invasiveness and metastasis of gastrointestinal tumors. Herein, we discussed the regulatory mechanisms involved in ferroptosis through the hallmark pathways of glutathione peroxidase 4, iron metabolism, lipid peroxidation, and redox signaling that provide a novel therapeutic approach for gastrointestinal cancers.

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INTRODUCTION

Cancer is a notorious disease that causes numerous disorders and deaths worldwide, particularly gastrointestinal (GI) cancers comprising esophageal cancer, gastric cancer (GC), liver cancer, pancreatic cancer, and colorectal cancer[1]. A recent report stated that there are approximately 4 million new cases each year, which is far greater than breast and lung cancers combined; thus, there is a need to improve the therapeutics of GI cancers[2]. Although there has been an improvement in the prognosis of GI cancers in the last decade due to development of intensive therapies, such as incorporating cytotoxic drugs and targeted therapies, GI cancers are one of the leading causes of cancer deaths in developed and developing countries[3-5]. With varying risk factors, incidence, prevalence and prognosis, early diagnosis with increased screening may facilitate therapies to fight against GI cancers.

Biomarkers, including epigenetic markers, also play an effective role in decreasing the progression of GI cancers by early diagnosis and decreasing risk assessment by predicting the tumor response from specific therapies in patients[6]. Apart from internal stimulation, external exposures, such as dietary intake, tobacco use, alcohol consumption, obesity, and pathogens, are considered to increase the risk of GI tumors[7]. Various improvements in the therapeutic aspects to decrease the burden of GI cancer, including the chemoprevention of these cancers by using antioxidants, have drawn much attention[8]. Murphy *et al*[9] estimated that by 2025, the pervasiveness of obesity will be increased in men and women by 18% and 21%, respectively, which could escalate the encumbrance of GI cancers worldwide [9].

The induction of cell death by ferroptosis has increased in the recent past. Cell death is an endogenous mechanism that regulates homeostasis, and it is perceived as a requisite bodily process. As an imperative system, it exterminates useless or unwanted cells and bolsters the defense system of the body. Many forms of cell death have been observed in the recent past, particularly accidental cell death and regulated cell death (RCD)[10,11]. Accidental cell death occurs suddenly in response to stress, heat shock, or mechanical nature, while RCD is orchestrated by exhibiting a precise signaling cascade provided by a defined group of effector molecules. Many forms of RCD have been observed, such as apoptotic, autophagic, pyroptotic, necrotic, entotic, and ferroptotic cell death[12].

Investigating RCD introduces a new path for developing cancer therapeutics. Among the various forms of RCD, ferroptosis, an iron dependent, non-apoptotic RCD, is fascinating because of its ability to manage cancer cells that develop resistance to apoptosis and drugs. Although a link between iron and lipid peroxidation has been found in cancer research, this form of RCD has a peculiar combination of morphological, biochemical, and genetic characteristics distinct from necrosis, apoptosis, and autophagy [13]. Dixon *et al*[14] proposed the term ferroptosis in 2012, and its emerging role in several other disease settings was observed[14]. Ferroptotic cell death is characterized by the occurrence of oxidative stress and membrane lipid peroxidation, thereby causing mitochondrial atrophy, increased density of the mitochondrial membrane, and membrane damage[15]. Therefore, this review summarizes the role of ferroptosis in regulating key cancer signaling and cell death pathways in GI tumors for better prognosis.

GASTROINTESTINAL CANCERS: INCIDENCE AND MORTALITY

GI cancers contribute to significant morbidity and mortality rates worldwide[16] (Table 1), accounting for 26% of all cancer-related incidence and 35% of all cancer-related fatalities. It was noted that there is a two-fold increase in men compared to women. It has been reported that by 2040, there will be an increase in new cases and deaths from GI cancers by 58% and 73% to 7.5 million and 5.6 million, respectively[17]. Incidence and mortality rates of GI cancers worldwide is presented in Table 1[18-22].

Table 1 Incidence and mortality rates of gastrointestinal cancers worldwide								
No	Gastrointestinal cancers	Incidence	Mortality	Ref.				
1	Esophageal cancer	604100	544100	[18]				
2	Gastric cancer	1100000	770000	[19]				
3	Liver cancer	905700	830200	[20]				
4	Pancreatic cancer	495773	466003	[21]				
5	Colorectal cancer	1930000	900000	[22]				

While cell death modalities play a decisive role in eradication of tumor cells and maintenance of homeostasis, the role of RCD pathways, particularly ferroptosis, in tumor progression and metastasis of cancers has been the subject of interest for the last decade.

DISTINCTIVE FEATURES OF FERROPTOSIS

The various features of ferroptosis include the morphological, biochemical, and epigenetic alterations that describe this novel form of cell death.

Morphological distortion of ferroptosis

Ferroptosis is a non-apoptotic form of cell death because it lacks the classical features of apoptosis, such as mitochondrial cytochrome-C release, caspase activation, and chromatin fragmentation^[23]. In contrast, ferroptosis induces mitochondrial membrane disintegration, which results in cell enlargement, plasma membrane rupture, volume reduction, increased density, and disappearance of cristae observed under the electron microscope. These changes are potentially caused by permeability loss due to increased lipid peroxidation[24].

Biochemical changes involved in ferroptosis

The main biochemical features of ferroptosis are iron accumulation, reactive oxygen species (ROS) production, and induction of lipid peroxidation. Iron is the most abundant metal and is essential to all life on earth. As an iron-dependent form of cell death, increased circulating iron leads to the Fenton reaction through activated iron-containing enzymes that act as biochemical markers of ferroptosis[25]. Intracellular iron and iron-containing enzymes are indispensable for the execution of ferroptosis. Molecular regulators associated with iron homeostasis, such as transferrin, lactotransferrin, transferrin receptor, nuclear receptor coactivator 4-dependent degradation of ferritin, iron regulatory protein, and iron responsive element regulatory network, facilitate ferroptotic cell death[26,27].

ROS are the major culprits in many disease settings. ROS can damage essential biomolecules such as DNA, protein, carbohydrates, and lipids, thereby causing denaturation, peptide s-s bond breaking, crosslinking, enzyme inhibition, and permeability changes in tissues and cells. Therefore, increased ROS promote several perturbances leading to altered cell death pathways as well as induction of ferroptosis [28].

Lipid peroxidation is a seminal process in which the generated free radicals (H2O2, super peroxides, peroxy radicals) target long-chain fatty acids[29]. Extensive lipid peroxidation affects the permeability, fluidity, and curvature of the membrane, thereby stimulating cell death by forming micelles and pores in the biological membrane. A close connection between lipid peroxidation and ferroptosis exists in cancers. Importantly, to overcome drug resistance in chemotherapy, ferroptosis plays a crucial role in tumor microenvironment, thereby controlling cell proliferation through redox signaling pathways[30].

Epigenetic alterations

Epigenetics is a genetic mechanism that can influence gene expression by DNA methylation, histone modifications, and the effects of noncoding RNA without altering the DNA sequence[31,32]. DNA methylation is an epigenetic modification process that uses DNA methyltransferases to covalently transfer the methyl group to the C-5 position in the cytosine ring of DNA[33]. It has been reported that hypermethylation of the CDH1 gene promoter could increase ferroptosis susceptibility in head and neck cancer cells[34]. Recently, epigenetic regulation through H2B monoubiquitination and p53 has been determined[35].

Histone acetylation is controlled by histone acetyltransferases, bromodomains (BRDs), and histone deacetylases (HDACs) to regulate ferroptosis. In the histone acetylation process, histone acetyltransferases play the writer role, BRDs the reader role, and HDACs the eraser role[36,37]. The tumor suppressive role of *Tp53* is well known. For p53-induced ferroptosis, acetylation plays a crucial role by regulating solute carrier family 7 member 11 (SLC7A11) expression[38]. Acetylated and mutant p53^{3KR}



suppresses SLC7A11 expression and inhibits cysteine uptake, which alleviates ferroptosis and lipid peroxidation by decreasing glutathione (GSH) synthesis[38,39]. BRD4 induces the expression of antiferroptotic genes, and it has been observed that the BRD4 inhibitor JQ1 induces ferroptosis by downregulating the expression of ferroptosis-related genes such as glutathione peroxidase 4 (GPX4), SLC7A11, and solute carrier family 3 member 2 in breast and lung cancer cells[40]. HDACs were initially identified as an eraser for removing acetyl groups from histones, but it was later discovered to be involved in many important biological functions. Recently, HDAC inhibitors have been endorsed as potential therapeutics for various cancers^[41].

As a multifarious group of noncoding transcripts, noncoding RNAs, microRNAs (miRNAs), long noncoding RNAs (lncRNAs), and circular RNAs were first considered nonfunctional junk, but they participate in a broad domain of gene-regulatory pathways^[42]. Beyond this, it has been suggested that circular RNAs play a role in ferroptosis by regulating multiple signaling pathways either directly or indirectly by acting on the key regulating factors and upstream targets of ferroptosis^[43]. miRNAs tend to act as stimulants in ferroptosis by targeting ferroptosis-associated factors by downregulating the expression of activating transcription factor 4 (ATF4), which is a stress signal that tends to inhibit ferroptosis by miR-214-3p in hepatocellular carcinoma (HCC) by inducing SLC7A11 and several other miRNAs, including miR-101-3p, at high expression levels. They profoundly enhance the activity of nuclear factor kappa B, which regulates ferroptosis via GPX4 and prostaglandin endoperoxide synthase 2 in lung cancer, and miR-324-3p at high expression levels induces ferroptosis in lung adenocarcinoma by targeting GPX4[44]. Furthermore, miRNAs have also been found to have inhibitory effects on ferroptosis; therefore, they play diverse roles in ferroptosis. The alterations they cause to ferroptosisassociated factors make them a potential target in cancer therapeutics.

FERROPTOSIS INDUCERS

Over the past few years, several small molecules and plant-based compounds that target transporters or enzymes involved in ferroptosis have been described.

In principle, GSH synthesis and GPX4, a selenoenzyme, are the major regulators of ferroptosis. GSH is an important substrate for GPX4. Therefore, any depletion in GSH leads to substantial lipid peroxidation, leading to ferroptosis. By inhibiting GPX4, accumulation of lipid peroxidation takes place [45]. To produce GSH, system Xc⁻ regulated cysteine activity is needed. Certain compounds, such as sorafenib, glutamate, and erastin, induce ferroptosis through inhibition of system Xc⁻. Ras-selective lethal 3 (RSL3), a known GPX4 inhibitor and other compounds containing electrophilic chloroacetamides, covalently binds and restricts selenocysteine activity inside the active site of GPX4 to initiate ferroptosis[46]. Other nitrile oxide electrophiles include ML210, JKE-1674, and JKE-1716, which attach to selenocysteine and cause ferroptosis[46,47]. By directly oxidizing lipids and indirectly impairing GPX4 action, FINO2 causes ferroptosis, and FIN56 drives the destruction of GPX4 to induce ferroptosis[48]. To induce ferroptosis, FINO2 harnesses either a direct or indirect iron oxide to induce suppression of GPX4 activity. Organic peroxides are compounds with multiple O_2 bonds that are cleaved, resulting in the production of RO anions. These organic peroxides are often used as models to induce ROS. A commonly held view is that the lipid peroxide analogue tert-butyl hydroperoxide stimulates lipid peroxidation-dependent ferroptosis[49].

Excessive iron accumulation is a precursor of ferroptosis in a plethora of cell types. In vitro, hemoglobin causes ferroptosis, and *in vivo*, it causes intracerebral hemorrhage in other disease states [50-52]. Furthermore, the rise in cellular iron levels and consequent ferroptosis caused by pharmacological stimulation of selective autophagy through degradation of ferritin is known as ferritinophagy[53,54]. Apart from these, there are many other ferroptotic inducers; for example, in human pancreatic cancer cells, zalcitabine causes autophagy-dependent ferroptosis, pointing to a link between DNA sensor pathways, autophagy activation, and mitochondrial malfunction[55].

FERROPTOSIS INHIBITORS

The inhibition of ferroptosis by small molecular compounds takes place through the following mediators.

Iron chelators: The important role of iron is to promote lipid peroxidation by either activating ironcontaining lipid oxygenases (LOX) or nonenzymatic iron-mediated Fenton action [56-58]. Iron chelators like deferoxamine inhibit ferroptotic cell death. Iron chelators reduce H₂O₂-induced necrosis but not ferrostatin-1, suggesting that iron may be potentially involved in multiple cell death modalities[59,60].

Enzyme inhibitors: The enzyme inhibitor acyl-CoA synthetase long chain family member 4 (ACSL4) mediates addition of CoA to long-chain fatty acids, particularly arachidonic acid, and appears to be a crucial precursor to further arachidonate lipoxygenase-dependent lipid peroxidation[57]. ACSL4 and



arachidonate lipoxygenase inhibitors are known to inhibit the ferroptotic cell death process by preventing LOX accumulation[57,61]. In addition, NAD phosphate oxidase inhibitors comprising of diphenylene iodonium and GKT137831 prevent erastin-induced ferroptosis[62].

Protein degradation inhibitors: GPX4 may be degraded by a variety of ferroptosis activators, which results in lipid peroxidation. However, FIN56 and erastin-induced GPX4 breakdown is inhibited by the molecular chaperone heat shock protein 90, 5-(tetradecyloxy)-2-furoic acid, and dopamine[63-65].

Other inhibitors: The mitogen-activated protein kinase kinase inhibitor, U0162 is commonly used to reduce ferroptosis owing to its broad antioxidant activity[66]. The strong inhibitory effects of exogenous monounsaturated fatty acids (MUFAs) or deuterated polyunsaturated fatty acids (PUFAs) on ferroptosis may be attributed to their displacement of PUFAs from phospholipids, which lowers the accumulation of lipid peroxidation[67].

REGULATION OF FERROPTOSIS

A deeper knowledge of how ferroptosis is regulated by metabolic pathways, including iron, GSH, and lipid metabolism, has been the focus of research in proposing therapeutic drugs. In this context, several metabolic and cancer signaling pathways that connect ferroptosis have been described.

GPX4

Ferroptosis is primarily caused by the inactivation of the cellular antioxidant system, particularly the system that is dependent on the antioxidant defense Xc⁻ GSH-GPX4 that leads to toxic lipid ROS accumulation[68]. GSH peroxidases are pivotal enzymes that enable the reduction of peroxides *via* GSH. The system Xc⁻ family mediates transport of cysteine and glutamate, where glutamate is exported outside the cell and cysteine is imported inside the cell, which initiates the production of GSH, hence inhibiting ferroptosis in cancer cells[69] (Figure 1). The GPX protein comprises different types, among which GPX4, a selenoprotein, is an elemental antioxidant mediator known for its capability of reducing large peroxides such as PUFAs[68]. It is primarily involved in the maintenance of lipid metabolism and defense against the accumulation of toxic lipid ROS. Since GPX4 activity is directly impacted by conditions that reduce intracellular cysteine and subsequently GSH levels and because GSH is the dominant antioxidant in mammalian cells, these conditions trigger ferroptosis[70]. Small molecules such as erastin can block GSH or GPX4 expression to activate ferroptosis. In many cells, the rate at which GSH is synthesized is limited by the internal reduction of cystine to cysteine[71].

Lipid metabolism

The process in which free radicals and non-free radicals cleave the C-C double bonds in lipids such as PUFAs, phospholipids, glycolipids, and cholesterol is known as lipid peroxidation.

According to lipidomic research, arachidonic acid and adrenic acid are key driving factors in inducing ferroptosis. Elongation of very long-chain fatty acid protein 5 and fatty acid desaturase 1 are associated with the synthesis of fatty acids, where both enzymes are upregulated in mesenchymal GC cells, resulting in ferroptosis sensitivity, according to studies on the disease[72]. The process by which these PUFAs become coenzyme-A derivatives that are integrated into phospholipids triggers ferroptosis. Both autophagy and deubiquitylation can result in the reduction of intracellular GPX4[73]. Specialized sequences in GPX4 are distinctly recognized by heat shock protein 90 and facilitate the breakdown of GPX4 by chaperone-mediated autophagy[63]. On the other hand, the inhibition of chaperone-mediated autophagy by the mTOR pathway is relieved by its suppression, which may have caused GPX4 to degrade and cause ferroptosis[74].

Numerous investigations have revealed ACSL4 as a crucial sensitizer in ferroptosis machinery. ACSL4 mediates the esterification of PUFAs into phospholipids by adding CoA to the polyunsaturated bond of arachidonic acid[75] (Figure 1). Lysophosphatidylcholine acyltransferase 3, which is activated by ACSL4, contributes to ferroptotic lipid signaling by adding acyl groups to lysophospholipids, particularly to the phospholipids phosphatidylcholine and phosphatidylethanolamine[75]. Apart from PUFAs, MUFAs can promote ferroptosis resistance by initiating mutations in the PI3K-AKT-mTOR pathways, sterol regulatory element-binding protein 1 can mediate the production of MUFAs, which aids cancer cells in resisting ferroptosis[76]. MUFAs can modulate the hydroxycarboxylic acid receptor 1-sterol regulatory element-binding protein 1-stearyl-coenzyme A desaturase 1 pathway and lactate in the tumor microenvironment, which might increase the production of MUFAs and lower the expression of ACSL4 to avoid ferroptosis[77]. As functional lipids in ferroptosis, polyunsaturated ether phospholipids have a significant regulatory effect in changing cancer cells from a ferroptosis-sensitive state to a ferroptosis-resistant state[78]. Thus, lipid metabolism has a notable effect on the capability of cancer cells to induce ferroptosis.

Rabitha R et al. Role of ferroptosis in GI cancer



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Figure 1 Mechanistic insights of ferroptosis regulated pathways are represented. Glutathione peroxidase 4 (GPX4) is central in ferroptosis and works through the initiation of system Xc⁻, which mediates the export of glutamate and import of cystine. Cystine is required for the synthesis of glutathione (GSH). p53 induces the expression of p21 following oxidative stress and further induces GSH leading to GPX4 expression. Alternatively, p53 increases the expression of spermidine/spermine N1-acetyltransferase 1 (SAT1), which serves as the transcriptional target of p53. SAT1 joins ferroptotic pathway through induction of arachidonate lipoxygenase (ALOX) 15 leading to lipid peroxidation. In addition, p62 phosphorylation targets Kelch-like ECH-associated protein 1 (Keap1) leading to accumulation of nuclear factor erythroid 2–related factor 2 (Nrf2) in the nucleus to subscribe antioxidant enzymes during oxidative stress. Acyl-CoA synthetase long chain family member 4 (ACSL4) is an isozyme catalyzes polyunsaturated fatty acids (PUFAs) contributes to ferroptosis through induction of lipoxygenases. Ferritinophagy induction *via* ferritin contributes to the Fenton reaction leading to accumulation of reactive oxygen species (ROS) and lipid peroxidation. DMT1: Divalent metal transporter 1; GSSG: Glutathione disulfide; HO-1: Heme oxygenase-1; LOX: Lipid oxygenase; LPCAT3: Lysophosphatidylcholine acyltransferase 3; PUFA-PE: Polyunsaturated fatty acid-phosphatidylethanolamine; SLC3A2: Solute carrier family 3 member 2; SLC7A11: Solute carrier family 7 member 11; STEAP3: Six-transmembrane epithelial antigen of the prostate 3; TFR1: Transferrin receptor 1.

Iron metabolism

To carry out ferroptosis and allow lipid peroxides to build up, iron is particularly necessary. The capacity of iron to catalyze numerous metabolic events and flip between the various ionic states depends largely on how it can absorb and give electrons[79]. In the Fenton reaction, Fe^{2+} is converted to Fe^{3+} in the presence of H_2O_2 , and HO[•] is produced as a result of electron transfer to $H_2O_2[80]$. In contrast, the Haber-Weiss process could convert Fe^{3+} back to Fe^{2+} by reacting with O_2 , causing O_2 to lose one electron and become O^2 -[81].

The transfer of iron takes place in the following ways. Transferrin synthesized by the liver as a chelator of Fe³⁺ ions. In contrast to apo-transferrin, which is sans iron transferrin that is not recognized by transferrin receptor 1 (TfR1) and not internalized, transferrin recognizes and binds to TfR1 when it reaches the cell membrane, which is then internalized by clathrin-mediated endocytosis[82]. Accumulating evidence suggests the role of iron metabolism in ferroptosis[83,84]. Fe³⁺ is liberated from the transferrin TfR1 complex due to the acidic pH of endocytic vesicles and is converted to Fe²⁺ by the six-transmembrane epithelial antigen of the prostate (STEAP) family. STEAP1 and STEAP2 are implicated in multiple human malignancies, including Ewing sarcoma bladder, ovary, colon, breast, prostate, pancreatic, and cervical cancer[85-87]. Malignant gliomas have high levels of STEAP3, which triggers the cancer epithelial-mesenchymal transition[88]. Under hypoxic circumstances, STEAP4 is activated, resulting in an imbalance of mitochondrial iron and increased ROS generation[89].

The intracellular labile iron pool is subsequently created by divalent metal transporter 1, which mediates the release of Fe^{2+} into the cytoplasm[90]. Apo-transferrin is released back to the plasma membrane post recycling, while TfR1 and apo-transferrin remain linked[91]. Fe^{2+} is then directly transported into cells by divalent metal transporter 1 during the conversion of Fe^{3+} to Fe^{2+} (Figure 1). Another mechanism includes the absorption of porphyrin-bound Fe^{2+} that contains hemoglobin, particularly in macrophages, and involvement of cell membrane receptors of iron-storing protein ferritin, such as scavenger receptor class A member 5, as observed in kidney and embryonic development, which absorbs iron to regulate the ferroptosis mechanism[92,93].

Role of ferritin in Fe transport

Ferritin, an iron-sequestering protein with 4500 iron atoms, plays a crucial role in iron transport, cellular multiplication, angiogenesis, and immune suppression[94]. By using NCOA4, ferritin can also be split



up to liberate free iron, through "ferritinophagy" [95]. Ferroportin (FPN), recognized as the sole iron release pump that works with ceruloplasmin to export iron, is primarily in charge of moving Fe²⁺ out of cells[96]. Ceruloplasmin controls HepG2 and Hep3B cell iron regulation to prevent ferroptosis, and its loss causes a buildup of intracellular Fe²⁺ and lipid ROS and enhances ferroptotic death caused by erastin and RSL3[97]. Prominin-2 promotes the growth of multivesicular structures that comprise ferritin and exosomes that transfer iron from cells, enabling ferroptosis resistance in breast cancer[98]. FPN is severely reduced in many cancer types, suggesting that cancer cells may contain large amounts of iron^[99]. Decreased FPN levels promote proliferation and epithelial-mesenchymal transition in triplenegative breast cancer cells^[100]. Hepcidin, produced by tumors of the liver, promotes the breakdown of FPN and aids in the spread and development of cancer[101].

TRANSCRIPTION FACTORS

Activating transcription factor 3 and activating transcription factor 4

The unfolded protein response is activated in mammalian cells due to endoplasmic stress and has a twodimensional functional role in cell survival and death[102]. Activating transcription factor 3 (ATF3) is a member of the ATF/cAMP-responsive element-binding protein family of transcription factors. It binds to the ATF/cAMP-responsive element-binding protein cis-regulatory element and coordinates gene expression. ATF3 has tumor suppressive roles and inhibits cancer malignancy in GI cancers [103]. The context-dependent role that ATF3 plays in cancer is likely due to complex protein-protein interaction networks in which ATF3 is involved.

Indeed, in addition to transcriptional regulation, ATF3 has been found to interact with many critical cellular proteins and regulate their functions. One of the well-characterized ATF3-binding proteins is wild-type p53, and ROS signals are necessary for this aberrant production of endoplasmic reticulum stress markers; however, the antioxidant N-acetyl L-cysteine prevents overexpression and consequent ferroptotic cellular death. Although the ATF3-TP53 complex helps to initiate DNA damage, TP53 is not necessary for ATF3-regulated suppression of SLC7A11 transcription[104]. Nuclear factor erythroid 2related factor 2 (Nrf2) can, in contrast, regulate the expression of ATF3 by creating complex feedback loops for the activation of a number of transcription factors in coordinating the ferroptotic response [105].

ATF4 is a double-sided sword that plays a dual role in ferroptosis. In numerous cancer cells, including human glioblastoma as well as pancreatic cancer cell lines, the depletion of ATF4 increases erastin-induced or RSL3-induced ferroptosis, and the inhibition of ATF4 increases artesunate-induced ferroptosis in the DAUDI cell line[106,107]. The classes of genes targeted by ATF4, such as SLC7A11, heat shock protein 5 (HSPA5), and tribbles pseudokinase 3, may have an impact on this ATF4dependent mediation of ferroptosis in various cancer types. ATF4 is inhibited by the erastin-induced overexpression of HSPA5, which results in the sequential breakdown of GPX4 and lipid peroxidation [108-112]. Thus, ATF3-dependent and/or ATF4-dependent pathway dysregulation might influence ferroptosis in a tumor-specific phenotype.

Nrf2

Binding to antioxidant response elements, Nrf2, a transcription factor from the Cap-N-Collar family, is essential in regulating antioxidant genes and maintaining redox homeostasis[113]. Nrf2 transcriptional activity is normally attached to Kelch-like ECH-associated protein 1 (Keap1), retaining it in the cytoplasm. Nrf2 separates from Keap1 during environmental conditions (such as oxidative stress) and subsequently translocates into the nucleus, where it stimulates the expression of ARE-dependent target genes[113]. Nrf2, however, depends on the expression of the target genes that are involved in the control of cell proliferation, migration, and death to have a double impact on carcinogenesis and tumor treatment[114].

Initially, researchers showed that ferroptosis resistance may be promoted by activating the Nrf2 pathway using a model of HCC. In human HCC cell lines, ferroptosis activators like erastin and sorafenib boost Nrf2 stability by inhibiting the development of the Nrf2-Keap1 complex. The autophagy receptor SQSTM1/p62 elevates Nrf2 expression by inactivating Keap1, which is another regulator of this process[115]. By boosting GSH production and function, Nrf2-dependent genes such as glutathione synthetase, GPX4, and SLC7A11 contribute to ferroptosis inhibition[115]. Control of NADPH synthesis, a vital electron donor required for reduction of oxidized substrates[116], which is also a ferroptosis sensitivity biomarker[117], is another way that Nrf2 intermediate metabolism is connected to the regulation of ferroptosis. Overall, Nrf2 is an important transcription factor that regulates ferroptosis.

TP53

p53, a tumor suppressor encoded by the TP53 gene, is involved in the mediation of DNA damage, oncogene activation, and hypoxia. p53 promotes ferroptosis by transcriptional or posttranscriptional pathways in addition to its impacts on apoptosis, autophagy, and cell cycle. p53 can both induce and inhibit ferroptosis in a context dependent manner. To cause ferroptotic cell death, p53 increases the



production of spermidine/spermine N1-acetyltransferase 1, which sequentially causes increased 15-LOX expression responsible for oxidation of PUFAs (Figure 1)[118]. Simultaneously, p53 decreases the expression of ELAV-like RNA-binding protein and its action with LINC00336, by limiting the capability of cells to fight ferroptosis by increasing the activity of cystathionine β synthase (CBS)[119]. Additionally, p53 interaction with ubiquitin-specific protease 7, a deubiquitinating enzyme, facilitates its nuclear translocation by altering histones, favorably controlling ferroptosis[120]. Human colon cancer cells, such as HCT116 and SW48, are inhibited against ferroptosis by p53 in a transcription-independent manner^[121] The p53-p21 axis prevents ferroptosis, allowing cancer cells to withstand stressful metabolic situations. Thus, this dual role of p53 in ferroptosis can be explored for therapeutic treatment of cancers.

Heme oxygenase-1

Heme oxygenase-1 (HO-1) is a significant redox-mediating enzyme that is activated in reaction to oxidative stress, cellular stress, neurodegeneration, and other diseases. HO-1 has a dual personality. The use of HO-1 antagonist zinc protoporphyrin IX and HO-1 knockdown animals demonstrated that HO-1 increases erastin-induced ferroptosis[121]. Conversely, because HO-1 expression is knocked down, erastin and sorafenib more effectively limit cell proliferation in HCC caused by these drugs[121]. In addition, HO-1 mediates iron and ROS levels where Nrf2-derived HO-1 provides a cytoprotective effect by scavenging ROS when HO-1 is moderately active[121]. In contrast, given that cancer cells produce more HO-1 than normal cells, a high level of HO-1 activation may increase fragile Fe²⁺, resulting in an excess of ROS and eventual oxidative cell death[121]. Hence, the employment of ferroptosis by HO-1 activation can define the fate of cancer cells.

Sirtuins

Sirtuins are NAD⁺-dependent deacetylases that are involved in DNA repair, cellular metabolism, and cancer development. As a key oxidizing agent, sirtuins tend to play a crucial role in regulating redox signaling pathways[122]. Seven sirtuins have been identified in mammals so far, and each family has been found to regulate cellular homeostasis. SIRT1 activation increases the antioxidant activity mediated by oxidative stress-related transcription factors[122]. Studies have found that increased expression of SIRT1 induces Nrf2-mediated antioxidant activity, thereby increasing GPX4 and GSH levels in HCC. Conversely, their downregulation by protocadherin 20 mediates ferroptotic cell death by lowering the expression of GPX4 and GSH and increasing intracellular iron levels and ROS[123]. SIRT6 promotes ferroptosis in pancreatic cells through upregulation of the ROS levels[124], and its downregulation causes GC cells to resist sorafenib-induced ferroptosis[125].

Hypoxia inducible factor

Hypoxia is a prominent factor involved in the progression and metastasis of numerous cancers. Prolyl hydroxylase hydroxylates the hypoxia inducible factor (HIF)-a subunits HIF-1α and HIF-2α under normoxic circumstances; subsequently, they are subjected to ubiquitin-mediated proteolysis and destruction. HIF target genes are activated in hypoxia as a result of HIF-1 α and HIF-2 α failing to hydroxylate and translocate into the nucleus[126]. Our laboratory's previous studies found that under hypoxic conditions, hypoxia-inducible factors such as HIF-1a and HIF-2a are activated and stimulate the activation of matrix metalloproteinases 2 and 9, thereby increasing tumorigenesis[127]. Singhal et al[128] demonstrated the mechanism by which activation of HIF-2a raises cellular iron to accelerate ferroptosis or irreversible cysteine oxidation that causes cell death.

FERROPTOSIS AS A NOVEL TARGET FOR GI CANCER RESEARCH

The leading cause of cancer deaths and incidence from GI tumors has become the most essential health concern, so improving the therapeutic aspects provides an important way to decrease the burden of GI cancers. Several studies have used ferroptotic cell death as a key modulator to inhibit the growth of GI cancers such as colorectal cancer, liver cancer, pancreatic cancer, GC, and esophageal cancer.

Ferroptosis in colorectal cancer

Recent studies by Wang et al[129] suggested that ferroptosis can have a potential modulatory role in the targeted killing of chemoresistant colon cancer cells, and ferroptosis-related genes could also be harnessed as biomarkers in colorectal cancer therapeutics. Genes involved in the colorectal cancer tumor microenvironment are intricately linked to ferroptosis, and some of them are involved in the lipid peroxidase and GPX/GSH enzyme system. Iron metabolism genes are also powerful prognostic markers in colorectal cancer; for example, elevated expression of thio-redoxin tumor suppressing protein is closely concomitant with iron accumulation in mitochondria[130]. The above findings clearly state that targeting ferroptosis-inducing genes could provide a novel avenue for treating colorectal cancer. p53 tumor-suppressing protein and heme oxygenase have been implicated as key factors in regulating ferroptosis in colorectal cancer.



Ferroptosis in liver cancer

HCC is the most prevalent type of liver cancer, accounting for approximately 90% of cases[131]. Multiple studies have reported that ferroptosis plays a role in ameliorating the burden of HCC progression. Sorafenib, an anticancer agent that is used for the treatment of advanced HCC, has been found to induce ferroptosis by initiating the translation of rapamycin kinase signaling pathway, thereby initiating ferroptosis. Iron chelators such as deferoxamine inhibit sorafenib-induced ferroptosis by reducing the oxidative stress created by sorafenib in HCC cells[132].

The finding of a potent inhibitor of CBS, which is the main source of cystathionine gamma lyase by metabolizing homocysteine to cystathionine to increase intracellular L-cysteine, called CH004, selectively inhibits CBS but not human cystathionine gamma lyase in both in vivo and in vitro experiments, thereby increasing lipid ROS and decreasing the viability of HepG2 cells, indicating their role in ferroptosis[133].

Modulating the function of key regulators of ferroptosis also plays a significant role in the induction of ferroptotic cell death in HCC cells. Nrf2 is a key regulator of the antioxidant response. It plays a negative regulatory role in ferroptosis by actuating p62-Keap1-Nrf2 pathway, which upregulates the expression of quinone oxidoreductase 1, HO-1, and ferritin heavy chain 1. Therefore, inhibiting the p62-Keap1-Nrf2 pathways by erastin and sorafenib significantly enhances the ferroptosis-mediated cell death of liver cancer cells[134].

The mitochondrial membrane protein CDGSH iron sulfur domain 1 serves as a target to treat diabetes using glitazone, but it acts as a negative regulator of ferroptosis by modulating mitochondrial iron uptake; therefore, the pharmacological or genetic inhibition of CDGSH iron sulfur domain 1 enhanced mitochondrial lipid peroxidation, increasing erastin-induced ferroptosis in liver cancer cells[135].

The highly reactive metabolite NAPQ1 from acetaminophen, an analgesic and antipyretic agent, is involved in the ferroptotic cell death of HepG2 cells by decreasing their viability through GSH depletion and GPX inhibition[136]. The expression of retinoblastoma protein (Rb) in HCC cells determines the susceptibility of cancer cells to sorafenib treatment and regulates ferroptosis. Louandre et al[137] showed that the decrease in the levels of Rb protein exhibits an increase in cell death when cells were treated with sorafenib compared with controls; thus, determining the Rb status of HCC patients treated with sorafenib will provide novel insight into the HCC treatment.

LncRNAs represent a vital class of molecules that have regulatory effects in both physiological and abnormal conditions, but lncRNA GABPB1-AS1 has a role in regulating oxidative stress, confirming its involvement in the ferroptosis-mediated cell death of HCC cells. The expression of this lncRNA was upregulated by erastin to inhibit the translation of GA binding protein transcription factor subunit beta 1, resulting in the rapid accumulation of ROS in HepG2 cells by decreasing the expression of the PRDX5 peroxidase gene[138].

Ferroptosis in pancreatic cancer

Several molecules were demonstrated to induce ferroptosis in pancreatic cancer cells in which the firstline drug gemcitabine is used to treat advanced pancreatic cancer, but HSPA5 causes resistance to gemcitabine treatment by inhibiting ferroptosis. Therefore, genetically or pharmacologically inhibiting HSPA5 enhanced the sensitivity of gemcitabine to pancreatic ductal adenocarcinoma cells by inducing ferroptosis[139]. Inhibiting cytosolic aspartate aminotransferase, which is predominant for redox balance, represses the growth of pancreatic cancer cells by enhancing labile iron release, thereby inducing sensitivity to ferroptosis[140].

Several studies have shown that certain natural plant extracts possess potential anticancer effects by inducing ferroptosis in pancreatic cancer cells. A saponin called ruscogenin represses cell viability and induces ferroptotic cell death in a pancreatic cancer cell line by increasing the concentration of intracellular ferrous iron and ROS production; it also exerts anti-tumor effects in in vivo experiments with less toxicity[141].

The combinatorial regimen using plant derivatives also expresses effective anticancer effects in pancreatic cancer cells by inducing ferroptosis; cotylenin A (a plant growth regulator) in combination with phenethyl isothiocyanate, an anti-carcinogenic compound, stimulated ferroptotic cell death in PANC-1 cells (Figure 2)[142]. Artesunate, an antimalarial agent, induced ferroptosis in Kras-activated pancreatic ductal adenocarcinoma cell lines driven by ROS generation and lysosomal iron-dependent cell death without affecting normal pancreatic cell lines[143]. Piperlongumine alone, as well as in combination with cotylenin A and sulfasalazine, generates ferroptotic death of pancreatic cancer cells [144].

Ferroptosis in GC

GC is a heterogeneous disease among GI cancers, with over 1 million new cases worldwide where surgery is the primary treatment to prevent progression[145]. The factors involved in PUFA biosynthesis play an essential role in inducing ferroptosis sensitivity in GC[72]. Apatinib, an anti-tumor agent, decreases the expression of GPX4 and results in apatinib-mediated ferroptotic cell death in GC cells [146]. GC cells resistant to sorafenib-induced ferroptosis treatment by silencing SIRT6, one of the sirtuin proteins that plays a vital role in the regulation of metabolism, DNA repair, and cancer development





Figure 2 Regulation of ferroptosis in gastrointestinal tumors is schematically illustrated. The factors cotylenin A, phenethyl isothiocyanate, artesunate, and piperlongumine induce lipid peroxidation and thereby ferroptosis. Small molecules such as erastin, sorafenib, and sulfasalazine inhibit system Xc⁻ thereby inducing ferroptosis through glutathione peroxidase 4 (GPX4). Cisplatin, curcumin, and apatinib inhibit GPX4 thereby attenuating reactive oxygen species. Several inducers of ferroptosis such as RAS-selective lethal 3, FINO2, and FIN56 inhibit GPX4. Several synthetic and natural compounds regulate ferroptosis through hemoxygenase leading to iron overload. Transferrin receptor 1 mediates endocytosis of iron particles and facilitates ferroptosis. CDGSH iron sulfur domain 1, an iron chelator, blocks iron production and inhibits ferroptosis. Several compounds mediate ferritin degradation via ferritinophagy and modulate ferroptosis. CAPE: Caffeic acid phenethyl ester; CISD1: CDGSH iron sulfur domain 1; GSH: Glutathione; GSSG: Glutathione disulfide; HO-1: Heme oxygenase-1; PEITC: Phenethyl isothiocyanate; RSL3: Ras-selective lethal 3; ROS: Reactive oxygen species; SLC3A2: Solute carrier family 3 member 2; SLC7A11: Solute carrier family 7 member 11; TFR1: Transferrin receptor 1.

> and is primarily located in the cell nucleus. SIRT6 sensitizes GC cells to sorafenib-induced ferroptosis by the Keap1/Nrf2/GPX4 signaling pathway[125,147]. The ingredient from the Chinese medicine tanshinone IIA, isolated from the rhizome of Saliva miltiorrhiza Bunge, exhibits an anticancer effect on GC cells by inducing ferroptosis and downregulating p53-mediated SLC7A11[148].

Ferroptosis in esophageal cancer

Targeting ferroptosis will provide new avenues for esophageal cancer diagnostics and treatment strategies. Sulfasalazine, a ferroptotic inducer, inhibits the progression of esophageal cancer, and plantderived compounds such as oridonin, a diterpenoid, have also been reported to stimulate ferroptotic cell death in esophageal cancer cells[149].

FERROPTOSIS AND LINK TO OTHER RCD PATHWAYS

Ferroptosis is intricately intertwined with other forms of cell death through various iron and lipid peroxidation proteins and several transcription factors. However, molecular mechanisms underlying the role of other forms of RCD remain poorly understood. For example, TP53, a critical mediator of tumor suppressive response involved in apoptosis, ferroptosis, and antioxidant response machinery like Nrf2, has a significant role in ferroptosis as well as autophagy. The molecular mechanisms associated with other forms of RCD pathways and ferroptosis are discussed herein.

Apoptosis and ferroptosis: Molecular switch

Numerous studies have reported the interconnection between apoptosis and ferroptosis. Apoptosis, typically through p53, induces cell cycle arrest, thereby preventing tumorigenesis; likewise, TP53 is known to sensitize cells to ferroptosis, leading to a reduced tumor burden[150]. The widely known ferroptosis inducer erastin has the potential to induce the unfolded protein response and promote p53 expression through apoptotic markers PUMA, CHOP, and TRAIL, and TRAIL-dependent apoptosis implies an augmented link between apoptosis and ferroptosis[151]. A similar study on a metal-



encapsulated p53 plasmid construct by Zheng et al[152] was found to release ions of iron, instigating the Fenton reaction and leading to ROS oxyradical overload, thereby leading to ferroptosis-dependent apoptosis in the liver. This consequently reduced the tumor burden and prevented metastasis in mice. An imbalance in the ferroptotic process is implicated in severely hindering apoptosis induction; for example, cancer cells subjected to ferroptosis by cysteine starvation were found to have reduced GSH levels but failed to induce caspase activation, which is seminal in apoptosis[153].

Autophagy-dependent ferroptosis

Autophagy-dependent ferroptosis is putatively ferritinophagy; under an excessive Fe²⁺ milieu, ferritin degradation is mediated by Atg5, an autophagy regulator protein. Ferritin is a seminal protein complex with light and heavy chain polypeptides (ferritin light chain 1 and ferritin heavy chain 2) predominantly controlling iron metabolism. Atg5 and Atg7 knockdown is implicated in preventing erastin-induced ferroptosis, facilitating tumorigenesis[154]. Similarly, BECN1 or Atg6 is known to induce ferroptosis by regulating glutamine and cysteine and inhibiting system Xc⁻ through the BECN1-SLC7A11 complex in cancer cells. Additionally, studies have reported BECN1 facilitates lipid peroxidation through malondialdehyde (MDA) stress modulation[155]. Observations from our laboratory demonstrated that Eupatilin exhibits anticancer effects in part through regulation of autophagy-mediated ferroptosis (data not shown).

In summary, while apoptosis, ferroptosis, and autophagy are all different cellular pathways, they can be linked in the sense that autophagy can play dual roles by promoting apoptosis and protecting against ferroptosis. In contrast, both apoptosis and ferroptosis are forms of RCD mediated by different enzymes and signals that manifest different morphological outcomes.

THERAPEUTIC ASPECTS OF FERROPTOSIS

The listed drugs have potential therapeutic applications and have been reported to regulate ferroptosis (Table 2)[156-164].

Although conventional drugs are implicated in inducing or modulating ferroptosis, resistance to these drugs supersedes the benefits. Therefore, the identification of compounds with neutral toxicity profiles and natural origins has garnered tremendous attention in ferroptosis and iron metabolism. The section below briefly discussed the role of natural compounds in ferroptosis.

Formasanin C (FC) is known to induce ferroptosis in p53-null and p53 wildtype cellular phenotypes of HCC, and FC treatment increases the mitochondrial morphology and membrane potential in HepG2 cells, as a hallmark of cells undergoing ferroptosis[165]. FC and cisplatin synergistic treatment is known to induce ferritinophagy and enhance therapeutic potential of cisplatin. Similarly, gallic acid (GA) is known to prompt lipid peroxidation and ferroptosis. Upon exposure to an Fe²⁺ chelator, GA activity is suppressed, which in part signifies its role in ferroptosis. GA exhibited anti-tumor effects in colorectal cancer by deterring GPX4 and elevating MDA expression[166]. Celastrol, a tri-terpenoid is reported to induce ROS production, thereby promoting ferroptosis in liver cancer cells. Structural protein activity revealed that celastrol directly binds to multiple orthologues of PDXs. PDX knockdown in turn elevates ROS production, ensuing ferroptosis[167]. Chen et al[168] reported that curcumin could induce ferroptosis in colorectal cancer by modulating expression of key ferroptotic markers Fer1, SLC7A11, GSH, MDA, and ROS through PI3K/mTOR pathway.

The mechanisms orchestrating ferroptosis has been the subject of interest in several cancers. Many investigators have contributed to identifying key molecules that regulate ferroptosis in GI tumors[169]. The above findings are helpful in understanding the mechanism of many synthetic and natural compounds in inducing iron-dependent cell death in GI cancers. There are ample avenues to further elucidate the mode of action and mechanistic aspects of how natural compounds could be synergistically used to induce ferroptosis.

CONCLUSION

The increasing incidence and mortality imposed by GI cancers, a dangerous malignancy, warrants novel therapeutic strategies. Ferroptosis, a form of non-apoptotic RCD, has been found to play a significant role in regulating the progression of GI cancers. This review delineated the major regulatory mechanisms involved in ferroptosis for better understanding to create a new opportunity for diagnosis and therapeutic intervention. The involvement of ferroptosis-associated factors and the effect of several drugs, including the first discovered ferroptotic inducers erastin, sorafenib, cisplatin, artesunate, piperlongumine, haloperidol, baicalein, bromelain, and saponins have been found to induce ferroptotic cancer cell death in GI cancers. Ferroptotic inducers synergized with various anticancer drugs in clinical trials have demonstrated effective therapeutic results in GI cancers. Thus, inducing ferroptosis may have significant potential for treating GI cancers and related malignancies. Overall, this review provides insights into the regulatory mechanisms involved in ferroptotic cell death for development of novel



Table 2 Conventional drugs and their mode of action in ferroptosis								
GI cancer	Drugs	Pathway involved	Mode of action	Ref.				
Colorectal cancer	Paclitaxel	p53, SLC7A11	Lipid peroxidation by suppressing GPX4 expression	[156]				
	5-fluorouracil	Lipocalin2 (LCN2), xCT	Stimulates GPX4 expression by diminishing circulating iron levels	[157]				
	Cisplatin	Ferrostatin-1	Conjugates with GPX and GSH modulation	[158]				
	Cetuximab	GSH, GPX4 HO-1, <i>SLC7A11,</i> KRAS, RSL3	Through β-elemene synergism by inducing iron dependent ROS, GSH accumulation, and EMT regulation	[159]				
	Dihydro-artemisinin (DAT)	Iron metabolism, GPX4	Sensitizes cells to ferroptosis by iron overload and lysosomal degradation	[160]				
Hepatocellular carcinoma	Artesunate	Ferritin	Elevates lysosomal degradation partially through autophagy along with sorafenib; it induces cathepsin activation	[161]				
	Sorafenib	Nrf2	Through metallothionein-1 activation (MT- 1G-Nrf2) axis	[162,125]				
	Deferoxamine	Iron metabolism	Through peroxidation and iron storage depletion	[163]				
Gastric cancer	Cisplatin	Nrf2/Keap1-xCT	Through transcription factor ATF3 overexpression	[164]				

ATF3: Activating transcription factor 3; EMT: Epithelial-mesenchymal transition; GI: Gastrointestinal; GPX4: Glutathione peroxidase 4; GSH: Glutathione; HO-1: Heme oxygenase-1; Keap1: Kelch-like ECH-associated protein 1; Nrf2: Nuclear factor erythroid 2-related factor 2; ROS: Reactive oxygen species; RSL3: Ras-selective lethal 3; SLC7A11: Solute carrier family 7 member 11.

> therapeutic strategies. The mechanism of ferroptosis with other RCD, such as autophagy and apoptosis, to induce cancer cell death may also provide new development in the therapeutic aspects of treating GI tumors. Therefore, further investigation of ferroptosis in GI cancers will improve the prognosis and therapeutic aspects of GI cancers.

FOOTNOTES

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