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Review Article

Ferroptosis and its role in gastric and colorectal cancers

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ABSTRACT Ferroptosis is a novel mechanism of programmed cell death, characterized by intracellular iron overload, intensified lipid peroxidation, and abnormal accumulation of reactive oxygen species, which ultimately resulting in cell membrane impairment and demise. Research has revealed that cancer cells exhibit a greater demand for iron compared to normal cells, indicating a potential susceptibility of cancer cells to ferroptosis. Stomach and colorectal cancers are common gastrointestinal malignancies, and their elevated occurrence and mortality rates render them a global health concern. Despite significant advancements in medical treatments, certain unfavorable consequences and drug resistance persist. Consequently, directing attention towards the phenomenon of ferroptosis in gastric and colorectal cancers holds promise for enhancing therapeutic efficacy. This review aims to elucidate the intricate cellular metabolism associated with ferroptosis, encompassing lipid and amino acid metabolism, as well as iron metabolic processes. Furthermore, the significance of ferroptosis in the context of gastric and colorectal cancer is thoroughly examined and discussed.

INTRODUCTION

Ferroptosis is a novel form of programmed cell death, proposed by Dixon *et al*. [1] in 2012, which is distinct from apoptosis. This phenomenon is characterized by excessive accumulation of iron in cells, heightened lipid peroxidation, and abnormal accumulation of reactive oxygen species (ROS), which plays a significant role in the pathogenesis of a variety of diseases.

Morphologically, ferroptosis is characterised by intact nuclei, shrunken mitochondria, reduced cristae and increased mitochondrial membrane density [2]. Dysregulation of iron metabolism, lipid peroxidation and the antioxidant systems are significant factors implicated in iron-induced cell death [3]. This process plays a crucial role in regulation of signaling pathways in malignancies, including gastric cancers (GCs) and colorectal cancers (CRCs), making it an attractive target for tumor therapy [4]. In addition, the prevalence of GCs and CRCs globally underscores the urgent need to address their impact on human health. Despite advancements in surgery, cytotoxic drugs, and targeted therapies, GCs and CRCs continue to be a significant contributor to cancer-related mortality in both developed and developing nations [5,6]. Previous articles have shown that ferroptosis plays an important role in GC, and the importance of iron metabolism and ferroptosis in GC was emphasized in the review of Gu *et al*. [7]. However, the metabolic mode and the metabolic process of ferroptosis in rectal cancer have not been discussed in detail. This review aims to comprehensively examine the intricate mechanisms through which lipid, amino acid, and iron metabolism influence ferroptosis, as well as the molecular proteins associated with GCs and CRCs that regulate this process. The ultimate objective is to establish a solid theoretical foundation for the development of targeted cancer therapies.

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FATTY ACIDS (FAs)

FAs are categorized as saturated fatty acids (SFAs), polyunsaturated fatty acids (PUFAs) and monounsaturated fatty acids (MUFAs), which are involved in constituting the sn1 and sn2 sites of the phospholipid (PL) fatty acyl tail. The sn1 position can be occupied by either SFA or MUFA, while the sn2 position can be occupied by SFA, MUFA or PUFA [8]. FA content in PLs is regulated by a variety of mechanisms, including FA synthesis, storage, release and β-oxidation, as well as PL synthesis and PL remodelling [9]. The content of FAs in PL is regulated through various mechanisms, including FA synthesis, storage, release, β-oxidation, as well as PL synthesis and PL reconstruction [9].

FA BIOSYNTHESIS

Mammalian cells lack the ability to internally synthesize PUFA. Arachidonic acid (AA) can be produced in occur through two pathways: direct synthesis from dietary meat or ingestion of linoleic acid (LA) from plant-based diets. This process involves the elongation and desaturation reactions of LA. Specifically, LA can be elongated from an 18-carbon FA to a 20-carbon long-chain FA by the ELOVL5 enzyme, which is responsible for long-chain FA elongation. Subsequently, the addition of an additional double bond is facilitated by the enzyme FADS1/29, leading to the conversion of the elongated FA to AA [10]. We found that up-regulated expression of FADS1 and ELOVL5 expression in GC cells has been observed to enhance their susceptibility to iron-induced cell death [11]. However, the inhibition of FADS2 has been shown to impede the dissemination of tumor cells [12]. Thus, FADS1, FADS2 and ELOVL5 may have a close relationship with ferroptosis.

Endogenous synthesis of SFA and MUFA can occur within mammalian cells. The process involves the conversion of acetyl coenzyme A (CoA) to malonyl CoA through the carboxylation mediated by acetyl coenzyme A carboxylase (ACC). Subsequently, malonyl CoA is further converted to SFA palmitate by FA synthase. In addition, stearoyl coenzyme A desaturase 1 (SCD1) plays a role in the desaturation of SFAs to MUFAs [13]. It has been found that energy stress can inhibit ferroptosis by activating the energy receptor AMPK, which subsequently inactivates ACC1, thereby impeding FA synthesis and thereby inhibiting ferroptosis [14]. The mechanism by which exogenous MUFAs inhibit ferroptosis is controversial, potentially involving competition with PUFA in PLs or the redistribution of intracellular lipids and storage of excess lipids as triacylglycerols in specialized intracellular lipid droplets [15]. Thus, it is clear that each FA biosynthesis process is closely related to ferroptosis.

FA CONVERSION-β-Oxidation

FAs exhibit various metabolic pathways within the vivo, such as FA β-oxidation, triglyceride synthesis and storage in lipid droplets, and involvement in PL synthesis. The traditional mode of FA β-oxidation involves the breaking down of medium-long chain FAs into acetyl-CoA through mitochondrial beta oxidation, followed by entry into the tricarboxylic acid (TCA) cycle to generate ATP [16]. This process is facilitated by carnitine palmitoyl transferase 1, which catalyzes the attachment of acyl-CoA to carnitine, enabling its transport into the mitochondria *via* carnitine acyl-carnitine translocase. Carnitine palmitoyl transferase 2 located in the mitochondria facilitates the release of acyl-CoA from carnitine, thereby enabling its entry into the β-oxidation cycle. The inhibition of β-oxidation and induction of iron-mediated cell death in prostate cancer cells can be observed upon knockdown of diene-coenzyme A reductase 1, the enzyme responsible for rate-limiting reduction of PUFAs [17]. In contrast, the production of hydrogen peroxide (H_2O_2) by very long chain FAs is almost dependent on peroxisomal β-oxidation. The rate-limiting step in peroxisomal β-oxidation relies on the activity of acyl coenzyme A oxidase 1, which catalyzes the desaturation of acyl CoA to 2-trans-enolyl CoA, ultimately leading to produce H_2O_2. In order to effectively mitigate the oxidative stress induced by heightened peroxisomal β-oxidation, the peroxisome introduces catalase (CAT) into the substrate, thereby converting H_2O_2 to H_2O and O_2 [18]. It has been observed that peroxisome proliferator-activated receptor delta (PPARδ) upregulates peroxisome stabilization through CAT and inhibits ferroptosis caused by xCT deficiency [19]. Consequently, targeting the β-oxidation of FA in both the mitochondrial and peroxisomal pathways may have implications for the regulation of ferroptosis.

FA ARE CONVERTED TO TRIGLYCERIDES AND STORED IN LIPID DROPLETS

Lipoyl CoA facilitates the reaction between FA and 3-phosphoglycerol, resulting in the esterification of hydroxyl groups at positions 1 and 2, hydrolysis of the phosphate at position 3, and subsequent esterification to form triglycerides. These triglycerides are stored in lipid droplets and can be released through lipase-mediated lipolysis or lipophagy (the autophagic degradation of lipid droplets) when the body needs FA [20]. Thus, lipid droplets act as antioxidant organelles that regulate the balance between triglyceride and PUFA/MUFA ratios in PL pool, thereby reducing membrane lipid peroxidation and maintaining homeostasis regulating ferroptosis sensitivity by regulating membrane unsaturation [20]. However, it is worth noting that abnormal increases in lipid droplet catabolism can also lead to the release of PUFA, induce lipid peroxidation, and the promotion of ferroptosis induced by RLS3 [21]. Therefore, it is essential to properly regulate lipid

droplet synthesis and catabolism, as well as FA cycling, to explore potential strategies for mitigating ferroptosis.

FA INSERTED INTO PL

Incorporation of PUFA into PLs requires activation and acylation processes. Among the ACSL family, ACSL4 plays a pivotal role in the initial step of FA oxidation, a process that involves the activation of PUFA and their conversion into long-chain acyl CoA, lysophosphatidylcholine acyltransferase 3, which then integrates long-chain acyl CoA into the plasma membrane's PLs [22]. ACSL4 was found to be affected by a variety of regulatory mechanisms, and PKCβII (a specific isoform of protein kinase C [PKC]) was identified as a key mediator of lipid peroxidation sensing. Specifically, PKCβII was observed to directly phosphorylate the ACSL4Thr328 site, thereby facilitating lipid peroxidation and triggering ferroptosis [23]. The adhesion protein E-cadherin, involved in cell-cell interactions, was found to modulate ferroptosis susceptibility by regulating ACSL4 expression through the Merlin-Hippo-YAP signaling pathway [24]. Furthermore, RB1-deficient cancer cells, known for their tumor suppressor deficiency, were found to enhance ferroptosis and impede prostate cancer metastasis by activating E2F, leading to an upregulation of ACSL4 expression [25]. Furthermore, the lipidomic analysis performed in this study has demonstrated that the ACSL4-SOAT1 pathway plays a crucial role in the synthesis of PUFA-CE, a cholesterol ester containing PUFAs. Additionally, silencing of SLC47A1 has been observed to lead to increased susceptibility to cell death induced by iron, which is mediated by ACSL4-SOAT1 [26]. Moreover, other members of the ACSL family, such as ACSL3, have been found to be involved in intracellular lipid metabolism as a protein associated with lipid droplets, contributing to their formation and maturation. ACSL3 also plays a vital role in the activation of MUFA, which can replace PUFA and modify the PL composition of the cell membrane, ultimately reducing the sensitivity of the plasma membrane to lipid peroxidation [27].

Ether phospholipids (ePLs) are composed of SFAs at the sn-1 position connected to the glycerol backbone through ether bonds, constitute approximately 20% of the total PLs. The synthesis of ePLs involves the participation of peroxisomes and the endoplasmic reticulum (ER). In peroxisomes, the enzymes FAR1, GNPAT, and AGPS are responsible for producing the ether lipid precursor 1-o-alkyl-glycero-3-phosphate, which is subsequently transported to the ER. In the ER, AGPAT3 plays a crucial role in the synthesis of PUFA-ePLs [28]. CRISPR-Cas9 screen has successfully identified multiple peroxisomal genes that play a crucial role in the ePL synthesis pathway, potentially triggering ferroptosis. Additionally, it has been observed that elevated levels of polyunsaturated ePLs (acetal PLs) can heighten susceptibility to ferroptosis [29]. Specifically, the FAR1 enzyme facilitates the reduction of C16 or C18 SFAs into fatty alcohols, which are essential for the synthesis of alkyl ether lipids and plasma proteins involved in the regulation of ferroptosis, whereas TMEM189 gene encodes a 1-O-alkyl-PE desaturase that introduces vinyl ether double bonds into alkyl ether lipids, leading to the production of plasma proteins and inhibits FAR1 alkyl ether lipid axis-induced ferroptosis [30].

CHOLESTEROL

Cholesterol is an important lipid constituent of cellular membranes, and plays a vital role in preserving membrane integrity and fluidity. In mammals, cholesterol is mainly obtained through internal synthesis and external absorption, and endogenous cholesterol is synthesized through the mevalonate pathway [31]. Cholesterol is involved in iron-induced cell death manifests in two distinct manners. Firstly, exogenous cholesterol hydroperoxides elicit cell death in a dose-dependent manner [32]. Secondly, cholesterol precursors, specifically 7-dehydrocholesterol (7-DHC), possess the potential to regulate lipid peroxidation and iron-induced cell death. The enzyme 7-dehydrocholesterol reductase (DHCR7) is responsible for the synthesis of cholesterol from 7-DHC. Inhibition of DHCR7 the reactivity of 7-DHC against per oxyradicals [33]. Similarly, another study showed that a reduction in squalene monooxygenase, an enzyme that regulates the rate of cholesterol biosynthesis, leads to the accumulation of squalene and the inhibition of iron-induced cholesterol deficient cell death [34]. These findings suggest that all of the aforementioned mechanisms interfere with cholesterol metabolism intermediates to enhance antioxidant mechanisms and prevent iron-induced cell death. However, in contrast to the above mechanisms, the cholesterol uptake process, particularly low density lipoprotein-mediated cholesterol uptake, has been observed to raise the cholesterol content of the cell membrane, decrease membrane fluidity, promote the formation of lipid rafts, consequently impacting the diffusion of lipid peroxides and diminishing iron-induced cell death [35-37]. Furthermore, cholesterol has the ability to undergo esterification and its products can be oxidized to form PUFA-CE, a less stable compound that is more susceptible to lipid peroxidation. Recently, it has been discovered that the activation of SLC47A1 is facilitated by peroxisome proliferator-activated receptor alpha (PPARα), which promotes the expression of solute carrier family 47 member 1 (SLCA47A1), a gene responsible for encoding the PL transport protein. This activation process inhibits the production of CE esterified with PUFA and plays an important role in the inhibiting iron-induced cell death [35].

LIPID PEROXIDATION

Lipid peroxidation induced destruction of the PL bilayer and subsequent membrane damage are known to contribute to iron-induced cell death. The oxidation of PUFA on cell membrane

lipids by lipoxygenases (LOXs) and ROS, leading to the formation of lipid hydroperoxide (L-OOH), L-OOH turns into toxic lipid radicals (LO-) resulting in the presence of iron, which causes the breakdown of PUFAs in cell membrane lipids and ultimately results in cell death [38].

Lipid peroxidation can be divided into enzymatic and non-enzymatic processes. Non-enzymatic reactions include the Fenton reaction, in which iron and H_2O_2 react to generate an excess of hydroxyl radicals. These free radicals then attack PLs containing PUFA, leading to lipid peroxidation, a process is considered a crucial step in iron-induced cell death [39,40]. However, LOX, intracellular oxidoreductases (cytochrome P450/B5 oxidoreductase, POR, and CYB5R1), which are essential for PL peroxidation, may be involved in enzymatic events that lead to lipid peroxidation. LOX (5/12/15-LOX), a protein with non-heme iron that facilitates PUFA oxygenation to produce conjugated double-bond peroxides involved in ferroptosis [41-43]. A class of heme-containing monooxygenases known as cytochrome P450 and B5 oxidoreductases (POR, CYB5R1) mediates lipid peroxidation in an ALOX-independent manner by transferring electrons from NAD(P)H to oxygen to produce H_2O_2. The H_2O_2 then reacts with iron to produce reactive hydroxyl radicals, which compromises membrane integrity [44,45].

AMINO ACID METABOLISM-CYSTEINE

Cysteine, a sulphur-containing amino acid, that is the rate-limiting substrate for the biosynthesis of reduced glutathione (GSH). The availability of cysteine to cells can be obtained by various means. The primary pathway for accessing extracellular cysteine is the cysteine transporter protein system Xc-. Once inside the cell, cysteine is generated through reduction reactions mediated by GSH or thioredoxin reductase 1 (TXNRD1). Endogenous cysteine is synthesized mainly *de novo* through the sulfur transfer pathway, with glycine N-methyltransferase, S adenosine homocysteine hydrolase, and cystathione beta synthase (CBS) and cystathione gamma lyase (CTH) are the main catalytic enzymes. In addition, cysteine can also be obtained through GSH and proteolytic autophagy [46].

System xc- is a sodium-independent reverse transporter that promotes extracellular cystine uptake and extracellular cystine and the excretion of intracellular glutamate in a 1:1 ratio. The system consists of two subunits, the heavy chain subunit solute carrier family 3 member 2 (SLC3A2; also known as CD98 or 4F2hc) and the light chain subunit solute carrier family 7 member 11 (SLC7A11; also known as xCT), which are connected by disulfide bonds. SLC7A11 is a multichannel transmembrane protein, that mainly promotes the reverse transport of cystine and glutamate in the xc- system. The xCT subunit plays a crucial role in maintaining adequate levels of intracellular cysteine and in the biosynthesis of GSH [47]. Several factors, controlling the expression of SLC7A1146 include ATF4, Nrf2, p53, ATF3, BAP1, mTORC, *etc*. [47]. SLC7A11 has a significant impact on how ferroptosis is suppressed. Numerous tumour suppressors, including P53 and KRAS, can block xCT, lessen cysteine absorption, and encourage ferroptosis [48].

TRNR, an NADPH-dependent selenase, functions as a component of the thioredoxin (Trx) system alongside Trx and NADPH. Its role not only to reduce cysteine to cysteine after entering the cell, it also serves as a significant antioxidant system in conjunction with the GSH antioxidant system [49]. Inhibition of Trx reductase TXNRD leads to lipid peroxidation and ferroptosis poisoning, implying that TXNRD may play a crucial role in regulating ferroptosis [50]. It has been further suggested that cysteine can affect TXNRD1 activity and that ferroptosis due to cysteine depletion may be the result of both GSH/GPX4 and TXNRD1 antioxidant defence systems being affected [51].

The resynthesis of cysteine *via* the trans sulphur pathway is another mechanism for maintaining a stable intracellular cysteine pool. Sulphur is transferred from methionine (MET) to serine through a series of events in the trans sulfur pathway, where serine supplies the carbon and nitrogen atoms for the newly formed cysteine, and homocysteine is a metabolite in the pathway, with CBS and CTH facilitating the conversion of Hcy to cysteine [52]. When exogenous cystine is exhausted, cells maintain cysteine and redox balance by activating the trans sulfur pathway through positive transcriptional feedback of CBS and CTH [53,54]. Moreover, cystine deficiency enhances the expression of CBS and CTH in tumor cells that are less susceptible to iron-induced cell death, whereas pharmacological inhibiting both enzymes pharmacologically leads to cells that are prone to iron-induced cell death [55,56].

CYSTEINE ROUTING

In addition to being involved in the synthesis of GSH, which plays a crucial role in the inhibition of iron-induced cell death, cysteine is involved in various pathways that contribute to iron-induced cell death. The sulfhydryl group in cysteine is catabolized by two enzymatic processes, CBS and cystathionine γ-lyase, to produce pyruvate, a-ketoglutarate, and H2S. Pyruvate is further metabolized to acetyl CoA, which is involved in the TCA cycle and lipid synthesis. A-ketoglutarate serves as an intermediate in the TCA cycle or for glutamate synthesis, while H2S is implicated in mitochondrial energetics and ATP production. The second enzyme, known as dioxygenase (CDO1), promotes the conversion of cysteine to taurine, thus competing for the synthesis of GSH. Additionally, the mitochondrial enzyme cysteine desulfurase (NSF1) breaks down cysteine and releases sulphide, which is subsequently utilized for the formation of iron-sulphur clusters. These clusters play a crucial role in electron transport and the stability of protein structure [57]. Whether the cysteine metabolite CoA acts synergistically with GSH to regulate iron-

induced cell death in genetically engineered mice, or is further metabolized to coenzyme Q (CoQ) and reduced to panthenol by ferroptosis inhibitory protein 1 (FSP1) to prevent lipid peroxidation and inhibit ferroptosis, or by modulating CDO1 to regulate the ferroptosis process, all suggest that cysteine is involved in the regulation of ferroptosis, either directly or indirectly [58]. Lack of CDO1 prevents ferroptosis and aids in intracellular GSH levels restoration [59]. On the other hand, CDO1 overexpression, results in increased cysteine catabolism, elevated ROS, and decreased cell viability [60]. NSF1 inhibition causes to ferroptosis in cancer cells [61].

GLUTAMINE

Glutamine is the most common amino acid in the human body, providing both carbon for the TCA cycle and nitrogen for the production of amino acids, nucleic acids, and lipids. The glutamine transporter protein SLC1A5 (ASCT2) transports glutamine into the cell through four main metabolic pathways. First, glutaminase GLS catalyses its conversion to glutamate, which, together with cysteine Cys and glycine Gly, synthesize GSH and maintain normal redox homeostasis [62]. Secondly, ammonia produced by catabolism of glutamate is converted to urea by ornithine, which plays a role in the urea cycle. Thirdly, glutamate can be metabolized by either glutamate dehydrogenase or aspartate aminotransferase, resulting in the production of a-ketoglutarate, which actively participates in the TCA cycle. Fourthly, glutamine serves as a crucial substrate for the synthesis of various amino acids, nucleic acids, and lipids [63].

Luo *et al*. [63] found that the inhibition of glutamine transporter SLC1A5, leads to a reduction in glutamine uptake by melanoma cells, subsequently decreasing lipid peroxidation and thus ferroptosis. Recent studies have also indicated a correlation between ubiquitination and degradation of SLC1A5 ubiquitination and degradation and the occurrence of ferroptosis [64]. The use of cystine/cysteine as a substrate for the synthesis of GSH is closely associated with ferroptosis. In conditions under cysteine-rich conditions, the catalytic subunit of glutamate-cysteine ligase (GCLC) plays a role in the initial step of GSH synthesis, thereby facilitating GSH production. Conversely, under cysteine deficiency, GCLC regulates the accumulation of glutamate and promotes the synthesis of r-glutamyl peptides, thereby preventing ferroptosis in a GSH-independent manner [65]. The relationship between glutamine and ferroptosis is supported by the observation that catabolic products induce lipid peroxidation and ferroptosis through the TCA cycle, leading to energy stress. This was further substantiated by the finding that supplementation with a-ketoglutarate promotes lipid peroxidation and ferroptosis [66]. Additionally, arginine succinate synthase (ASS1) is a crucial rate-limiting enzyme in the urea cycle and plays a vital role in converting ammonia and aspartate to urea. It has been found that ASS1 promotes cytoplasmic glutamine catabolism into the urea cycle rather than the TCA cycle, which prevents iron death through transammoniation and reductive carboxylation of the carbon skeleton [67]. Furthermore, the glutamine catabolism-related enzyme GLS2 has also been shown to promote ferroptosis [68]. Therefore, inhibition of glutamine uptake and catabolism through multiple pathways may provide new ideas for ferroptosis. In addition, other amino acids such as branched-chain amino acids and tryptophan also affect ferroptosis to varying degrees [69,70].

IRON METABOLISM

Iron is an important micronutrient and the most abundant trace element found in the human body. Insufficient levels of iron can result in various iron deficiency diseases, while excess free iron can lead to iron toxicity. Typically, extracellular iron ions bound to the cell membrane protein transferrin (TF) in a trivalent form. Subsequently, they bind to the transferrin receptor (TFR) and undergo endocytosis to enter the cell lysosome. Within the cell, the trivalent iron ions are reduced to Fe^{2+} by the metal reductase STEAP3 and are then released from the lysosome into the cytoplasm *via* DMT1 to participate in various subsequent physiological and biochemical processes [71].

There are three pathways for Fe^{2+} entered the cells: bonding with iron proteins, chelation with GSH free sulfhydryl groups, or exported through the iron-transporting protein FPN, while excess Fe^{2+} accumulates within the cell, leading to the formation of unstable iron cistere [72]. In situations where cytoplasmic iron levels decrease, ferritin can release iron through the process of ferritin autophagy, a process facilitated by nuclear receptor coactivator 4 (NCOA4) [73]. Free Fe^{2+} in the unstable iron pool actively participates in the Fenton reaction, resulting in the generation of ROS, specifically hydroxyl radicals, which participate in membrane lipid peroxidation and ferroptosis [71].

Mitochondria are the primary organelle responsible for iron utilization in cells. Iron is transported from the cytoplasm into the mitochondria through the transport protein SLC25A37/SLC25A28 located in the inner membrane of the mitochondria or in the membrane-bound portion. The iron that enters the mitochondria plays a crucial role in the biosynthesis of haemoglobin and iron-sulphur clusters. These iron-sulphur clusters are essential cofactors in various cellular processes, including the TCA cycle, respiratory chain complexes, and cytoplasmic enzymes. Furthermore, mitochondria contain iron storage proteins similar to cytoplasmic ferritin, known as mitochondrial ferritin (FtMt), which interacts with NCOA4 to promote the release of iron from mitochondrial autophagy when iron levels in mitochondria are decreased [74].

IRON METABOLISM REGULATION

In the context of ferroptosis, the maintenance of a balanced free iron level within the unstable iron pool holds considerable importance due to the crucial role of iron metabolism. One of the main mechanisms for regulating the intracellular unstable iron pool involves controlling the import of iron. Iron ions are transported into the cells by the TF/TFR-1 transport system, and overexpression of related proteins or hyperactivation of the TFRC gene encoding TFR-1 can result in an overload of intracellular iron ions, thereby inducing varying degrees of ferroptosis [75]. Heat shock protein beta-1 expression decreases TFR-1 expression levels, reduces iron intake and controls iron pool volume [76]. In cancer cells, interaction with TFR-1 *via* the epidermal growth factor receptor or the stem cell marker CD133 is involved in iron uptake [77].

The binding of free iron from unstable iron reservoirs into diverse iron-containing proteins serves as a significant mechanism for intracellular iron ion utilization. In the cells, free iron ions participate in numerous physiological and biochemical processes, facilitated by iron regulatory proteins (IRP1/2). These processes include the synthesis of various iron-binding proteins, such as ferritin, and the formation of ferritin, which functions as a repository for iron storage [72]. Tristetraprolin, expressed under iron-deficient conditions, was found to reduce the synthesis of various iron-binding proteins, especially iron-sulfur proteins, by degrading mRNA transcripts and maintaining the capacity of the cellular iron pool [78]. Furthermore, inhibition key proteins involved in the synthesis of iron-sulfur clusters, namely FXN and NSF1, can hinder the biosynthesis of said clusters, hasten the accumulation of free iron, and facilitate iron-induced cell death [79]. Upregulation of iron response element binding protein (IREB2) leads to increased synthesis of ferritin heavy and light chains of ferritin, as well as stable state of ferric ions in the steady state of ferritin [80]. Additionally, PCBP1, an iron chaperone protein, directly binds to iron and facilitates its loading onto ferritin. The depletion of PCBP1 has been linked to mitochondrial dysfunction and lipid peroxidation [81].

The release of ferric ions through intracellular ferritin degradation serves as a means to enhance the capacity of the intracellular labile iron pool. NCOA4 protein promotes the release of ferric ions from ferritin through selective autophagy, and in glioblastoma, TRIM7 interacts with and ubiquitinates NCOA4, thereby diminishing NCOA4-mediated ferritin autophagy. Conversely, heme oxygenase 1 (HO-1), under the regulation of the NRF2 gene, catalyzes heme degradation to generate ferrous ions [82,83].

Extracellular translocation of iron from the cell is also a mechanism in maintaining cellular iron homeostasis. Iron transporter (FPN) plays a crucial role in the extracellular export of divalent iron ions, and reduced expression of FPN expression has been shown to facilitate iron-induced cell death [84]. Hepcidin is an iron-regulating hormone, exerts its effects by binding to and deactivating FPN, and the down-regulation of hepcidin expression has been shown to decrease lipid peroxidation and iron-induced cell death [85]. In the context of cancer, hepcidin produced by liver tumors promotes the degradation of FPN, thereby contributing to the dissemination of cancer cells [86]. Additionally, the ferritin transfer protein (Prominin2) promotes the formation of multivesicular structures, including ferritin and exosomes, so that their subsequent released into the extracellular environment [84]. Ectopic expression of ferritin heavy chain resulted in increased efflux of iron ions and a reduction in intracellular iron overload decreased after ferric ammonium citrate treatment [87]. Conversely, decreased expression of ferritin light chain promotes the proliferation of triple-negative breast cancer cells and induces epithelial-mesenchymal transition (EMT) [88]. Moreover, the direct application of iron chelating agents to eliminate iron from unstable state is a commonly employed strategy in iron-induced cell death investigations [89].

FERROPTOSIS DEFENSE SYSTEMS

Glutathione peroxidase 4 (GPX4), a member of the GPX family, utilizes reduced GSH as a cofactor to detoxify lipid peroxides to lipid alcohols and inhibit iron-induced cell death [90,91]. Both GPX4 pharmacological inhibition and genetic inactivation can promotes lipid peroxide accumulation and ferroptosis, while inhibition of GPX4 degradation slows ferroptosis [91-93]. GPX4-GSH systems play a crucial role inthe fight against ferroptosis within cells. FSP1 (also known as AIFM2), located in the cell membrane (and other subcellular compartments), is a NAD(P)H-dependent oxidoreductase that reduces ubiquinone (also known as coenzyme Q or CoQ) to ubiquinol (CoQH2), in addition to its well-known mitochondrial electron transport function, CoQH2 can trap lipid peroxyl radicals, thereby inhibiting lipid peroxidation and ferroptosis [93]. FSP1 is believed to exert its potent anti-ferroptosis activity through the generation of a non-mitochondrial CoQH2 pool, which has the function of free radical trapping antioxidant. Recent studies have demonstrated that targeted inhibition of FSP1 selectively sensitizes cancer cells to ferroptosis [94]. Additionally, dihydroorotic dehydrogenase (DHODH), which is involved in pyrimidine synthesis, plays a role in reducing CoQ in the inner mitochondrial membrane to CoQH2. In the case of significant GPX4 is significantly inactivated, increased DHODH activity leads to enhanced CoQH2 production, which effectively counteracting lipid peroxidation and preventing mitochondrial ferroptosis [95]. Furthermore, the localization of G3P dehydrogenase 2 in the mitochondrial membrane enables the oxidation of glycerol-3-phosphate and the reduction of ubiquinone to panthenol. This process leads to the production of panthenol acid which acts as a free radical trapping antioxidant and plays a crucial role in inhibiting ferroptosis within the mitochondria, the findings from this study suggest that GPD2 is involved in the defense

mechanism of mitochondrial ferroptosis [96]. The ferroptosis defense system can be divided into two main components, GPX4 system and the CoQH2 system, and there are subdivisions in both non-mitochondrial and mitochondrial compartments (cytoplasmic and mitochondrial GPX4 in the GPX4 system, and non-mitochondrial FSP1 and mitochondrial DHODH in the CoQH2 system). Therefore, further studies are needed to confirm the different compartments of the cell in the regulation of ferroptosis.

FERROPTOSIS AND GC

GC is the fourth most common cancer worldwide and the second leading cause of cancer-related death after lung cancer. GC has no specific symptoms in its early stages, and most patients are already at an advanced stage of the disease when it is detected, with its high mortality, poor prognosis and susceptibility to metastasis [97] (Table 1).

GPX4, a central regulator of ferroptosis and is expressed at different levels in all cell lines of GC. Overexpression of GPX4 is associated with poor prognosis in GC. Silencing and inhibiting the GPX4 gene significantly reduced cancer cell proliferation and increased ROS levels [98]. Moreover, the new GPX4 inhibitor polyphyllin B down-regulates the expression of GPX4 in GC cells to induces ferroptosis and inhibit the proliferation, invasion and migration of GC cells [99]. c-Myb is a proto-oncogenic transcription factor, represses CDO1 expression through transcriptional regulation to upregulate GPX4 [59]. BCL6 is a transcriptional suppressor that promotes lipid peroxidation and ferroptosis in GC cells *via* the FZD7/β-catenin/TP63/GPX4 pathway [100]. Dysregulation of the Wnt/β-catenin catenin signaling pathway is closely associated with the development of GC and chemotherapy resistance. The β-catenin/TCF4 transcriptional complex directly binds to the promoter region of GPX4 to induce GPX4 expression and inhibit ferroptosis, and TCF4 deficiency promotes cisplatin-induced ferroptosis and increases chemotherapy sensitivity [101]. This suggests that the of GC therapy may be achieved by directly or indirectly regulating GPX4 expression.

Activating transcription factors belong to a family of transcription factors that regulate transcriptional processes and gene expression. Activation of transcription factor 2 (ATF2) knockdown promotes sorafenib-induced ferroptosis by decreasing the stability of SLC7A11 by reducing interaction of HSPH1 with SLC7A11 [102]. Activated transcription factor 3 (ATF3) promotes ferroptosis and inhibits GC cell proliferation by down-regulating GPX4 and HRD1 transcription [103]. Moreover, ATF3 blocks the Nrf2/Keap1/xCT signaling pathway, promoting the sensitivity of GC cells to the chemotherapeutic drug cisplatin [104]. Twist1 is an inhibitor that activates transcription factor 4 (ATF4) and overexpression of the post-transcriptional regulator cytoplasmic polyadenylation element binding protein 1 (CPEB1) reduces twist1 expression, thereby activating CHAC1-induced GSH degradation and promotes erastin-induced ferroptosis [105].

Telomeric repeat binding factor 2 (TRF2) is an important telomere protective protein and its expression level is increased in GC. Knockdown of TRF2 led to decreased expression of SLC7A11 and GPX4, resulting in ferroptosis in GC cells. In addition, TRF2 deletion also inhibited GC cell growth and proliferation by inducing autophagy and apoptosis in tumor cells together [106]. MET metabolism plays an important role in the regulation of ferroptosis. S-adenosylmethionine (SAM) synthase MAT2A catalyzes the synthesis of SAM from ATP and MET, and SAM increases the trimethylation of lysine-4 on histone H3 (H3K4me3) in the promoter region, thereby upregulating ACSL3 and resisting ferroptosis [107]. STAT3 can be combined with SLC7A11, GPX4 and FTH1 to engage in ferroptosis and restore chemosensitivity to 5-FU in GC [108].

EMT promotes metastasis and invasion of cancer cells, loss of the cell adhesion protein E-cadherin and upregulation of hypoxia-inducible factor 1α. E-cadherin inhibits ferroptosis by activating the Hippo pathway, while E-cadherin deficiency promotes ferroptosis in diffuse-type gastric cancer (DGC) cells, promoting ferroptosis in DGC cells [109]. HIF-1α upregulates PMAN, promotes distribution of ELAVL1 in the cytoplasmic, improves SLC7A11 mRNA stability, increases GSH levels and inhibits ROS and ferroptosis in GC cells [110]. Cysteine protease inhibitor SN (Cystatin SN, CST1) interacts with GPX4, a key protein in the regulation of ferroptosis, to improve GPX4 protein stability and reduce intracellular ROS, thereby inhibiting ferroptosis of GC and promoting metastasis [111]. Therefore, increasing ferroptosis sensitivity by targeting the expression of these proteins can inhibit EMT and thus GC metastasis. Ferritin autophagy and activation of the Keap1/Nrf2/HO-1 pathway both promote ferroptosis to inhibit EMT [112]. In contrast, the BDNF-AS/WDR5/FBXW7 axis regulates ferroptosis and transfer in GC by affecting VDAC3 ubiquitination [113].

Immunotherapy and ferroptosis work in tandem to help con-

Table 1. Important molecules and metabolic processes in the relationship of ferroptosis with gastric and colorectal cancers

Type of cancer	Molecular protein/metabolic process
Gastric cancer	Glutathione peroxidase 4 Activating transcription factors Telomeric repeat binding factor 2 E-cadherin Interleukin-1β Epithelial-mesenchymal transition Inflammation Gastric cancer stem cell activation
Colorectal cancer	P53 Lipocalin 2 Prospero-related homeobox 1 Colorectal cancer stem cell activation Reactive oxygen species

trol cancer progression. Interleukin-1β (IL-1β) is a key protein of inflammation that contributes to tumor progression. In response to IL-1β stimulation, nicotinamide nucleotide transhydrogenase (NNT) acetylation in cancer cells promotes NADPH production, maintains iron-sulfur cluster biosynthesis, prevents ferroptosis in tumor cells and promotes tumor immune escape. Inhibiting NNT acetylation to promote ferroptosis disrupts IL-1β synergistic immunotherapy providing a new idea for GC treatment. In addition, natural killer (NK) cells were reduced in the tumor microenvironment of GC. l-KYN induced NK cell ferroptosis in an ahr-independent manner *via* indoleamine 2,3-dioxygenase production in GC cells, reducing NK cell viability. Overexpression of GPX4 on NK cells can restores the viability and promotes their immunotherapeutic potential against GC [114].

Exosomes and non-coding RNAs play an important role in ferroptosis. Gastric cancer stem cells (GCSCs) are an important cause of metastasis and drug resistance in GC, and the role of ferroptosis in tumor stem cells is of wide interest to promote SCD1 expression, which leads to dysregulation of PUFA levels in GCSCs and inhibition of ferroptosis to control GCSC tumorigenicity. Targeting the exo-lncFERO/hnRNPA1/SCD1 axis in combination with chemotherapy may be beneficial for GC therapy of GCSC. MiR-375 can trigger ferroptosis in GCSCs by targeting SLC7A11 to promote GC treatment [115].

FERROPTOSIS AND CRC

CRC is the third most common disease in the world and the second leading cause of cancer death. Current treatment options for CRC include surgery, radiotherapy, chemotherapy, immunotherapy and biologically targeted therapy. Despite the efficacy of these treatments, many cancer cells try to evade apoptosis to enhance drug resistance. Ferroptosis, a form of programmed cell death (PCD) independent of apoptosis, may provide a promising therapeutic strategy for cancer treatment [5,116] (Table 1).

P53, a powerful tumor suppressor, plays an important role in ferroptosis. TIGAR expression is higher in CRC tissues than in adjacent normal tissues. P53 enhances TIGAR expression through transcriptional activation to regulate energy metabolism. TIGAR downregulation leads to AMPK phosphorylation, which inhibits SCD1 (a key enzyme for MUFA synthesis) expression and promotes lipid peroxidation [117,118]. P53 also blocks DPP4 activity and negatively regulates ferroptosis in CRC cells. P53 deficiency promotes the interaction of DPP4 with NOX1 to form the NOX1-DPP4 complex that mediates plasma membrane lipid peroxidation and ferroptosis [119]. Cytochalasin (CYGB) regulates iron prolapse *via* the p53-YAP1 axis with novel tumor suppressive effects and offers a potential therapeutic approach for CRC [120]. In addition, the E3 ligases CUL9 and MDM2 can regulate ferroptosis and overcome CRC resistance by targeting P53 degradation and inhibition [121].

The expression levels of certain genes and proteins in CRC also control ferroptosis to varying degrees, and by regulating their expression can improve the sensitivity of CRC to ferroptosis. Lipocalin 2 (LCN2), a secreted glycoprotein that maintains the integrity of the gastrointestinal mucosa, is expressed in CRC and is an indicator of progression from adenoma to carcinoma in CRC. LCN2 binds iron, inhibits the conversion of iron to ferrous, and promotes the output of iron. LCN2 also stimulates the expression of xCT and GPX4, resulting in increased intracellular GSH levels and increased lipid peroxide clearance. Inhibition of LCN2 expression promotes ferroptosis, and targeting LCN2 offers a new idea for CRC treatment [122]. Nodal overexpression induces MUFA synthesis and reduces ferroptosis susceptibility, while inhibition of SCD1 partially eliminates resistance to ferroptosis. Therefore, a gene based therapeutic strategy targeting Nodal is expected to improve CRC [123]. OTUD1 is a deubiquitinating enzyme of IREB2 that is selectively reduced in CRC. OTUD1 promotes transferrin receptor protein 1 (TFRC)-mediated iron transport through deubiquitination and stabilization of IREB2, leading to increased ROS production and ferroptosis. The OTUD1-ireb2-tfrc signaling axis plays an important role in host anti-tumor immunity [124].

PROX1 is an evolutionarily conserved transcription factor that controls the differentiation of different cell types and a novel target gene. PROX1 can activate CRC cells from ferroptosis by activating SCD1 expression through binding to its promoter. Therefore, the combination of SCD1 inhibitors and ferroptosis inducers may be a promising therapeutic strategy for CRC patients with high PROX1 expression [125]. KLF2 belongs to the zinc finger family and low expression in CRC patient tissues and cell lines is associated with poor prognosis in CRC. Overexpression of KLF2 reduces GSH peroxidase 4 expression to induce ferroptosis and inhibits PI3K/AKT signaling pathway to suppress CRC cell invasion, migration and EMT [126]. Cytochrome P450 1B1 (CYP1B1), a heme sulfate monooxygenase, that is highly expressed in CRC tumor tissue. CYP1B1 metabolizes AA to 20-hydro xyeicosattraenoic acid (20- HETE), which activates the PKC signaling pathway, promoting FBXO10 expression, increasing polyubiquitination of ACSL4 and leading to ACSL4 degradation, CYP1B1 may be a new target for ferroptosis in CRC patients and may help improve the efficacy of anti-immune checkpoint therapy in CRC [127].

Colorectal cancer stem cells (CSCs) have long been thought to be the source of CRC progression compared to CRC cells. Due to their low levels of ROS and high levels of cysteine, GSH and SLC7A11, CSCs can resist antioxidant damage and defend against ferroptosis. The study found that knocking down or reducing SLC7A11 expression increased ROS levels and decreased the viability of CSCs. Targeting SLC7A11 may selectively kill CSCs and attenuate CRC chemoresistance and progression [128,129].

ANTICANCER DRUGS AND ANTICANCER THERAPY RELATED TO FERROPTOSIS IN GC

A large number of previous studies have shown that ferroptosis plays an important role in the treatment of GC. For example, in GC responses to anticancer drugs, ferroptosis scores were highly negatively correlated with drugs targeting MAPK signaling and PI3K/mTOR signaling, and positively correlated with drugs targeting cell cycle, mitosis, and metabolism [130]. Ye *et al*.'s study [131] showed that 3,3'-diindolyl methane can induce ferroptosis in BCC-823 GC cells and can induce ferroptosis through BAP1-IP3R axis to play an anticancer role, suggesting its effective therapeutic potential in GC. In addition, some studies have found that inducing ferroptosis is the main mechanism of the antitumor activity of a2, and a2 is expected to be a promising compound for the treatment of GC [132]. Yang *et al*. [133] demonstrated a new mechanism by which HIF1α/CBSLR regulates GC iron apoptosis/chemotherapy resistance. And, many anti-cancer drugs in GC have also been confirmed to be related to ferroptosis. For example, polyphyllin B may be a promising new drug for the treatment of GC, showing good anti-tumor efficacy by inducing iron sag in GC cells and mouse models [134]. Tanshinone IIA may inhibit the proliferation of GC by inducing p53 up-regulation mediated ferroptosis [135]. Polyphyllin VII is a potential drug to treat GC by targeting TOPK to activate autophagy mediated iron apoptosis [136]. Polytheophylline I inhibits GC growth by promoting ferroptosis of cancer cells [99].

ANTICANCER DRUGS AND ANTICANCER THERAPY RELATED TO FERROPTOSIS IN COLON CANCER

In addition, we also understand that ferroptosis plays a crucial role in the treatment of CRC. Previous studies have shown that the effect of Wei-Tong-Xin on CRC cells is mainly mediated by the PI3K/AKT signaling pathway, which regulates endogenous apoptosis [99]. The PI3K/AKT signaling pathway is associated with ferroptosis and the expression of apoptotic mRNA [137]. The dual PI3K/HDAC inhibitor BEBT-908 can induce effective anti-tumor responses, effectively induce immunogenic iron ptosis in CRC tumor cells, and enhance cancer immunotherapy [138]. Zhang *et al*.'s [139] research indicates the therapeutic potential of resveratrol (RSV) as an anticancer drug that induces iron apoptosis, and it may pave the way for the application of RSV loaded nano systems in the treatment of CRC. Other studies have shown that Pt3R5G mainly inhibits colon cancer cell proliferation by downregulating SLC7A11 and inhibiting iron ptosis, it can serve as a potential anti colon cancer drug [140]. In addition, many anticancer drugs in CRC have also been proven to be associated with ferroptosis. For example, IL-15 is a potential molecular biomarker that can be used to predict prognosis, immune response, and iron/copper ptosis in patients with pan cancer [141]. Palmitic acid is involved in anticancer properties by activating ER stress/ER calcium release/tf dependent iron ptosis. It may act as a compound to activate iron ptosis in colon cancer cells with high CD36 expression [142]. HNK, as a potential therapeutic drug, can induce iron ptosis in colon cancer cells by reducing the activity of GPX4 [143]. Camellia nitidisima Chi regulates the progression of colon cancer through the iron ptosis pathway, which may be an attractive treatment method for colon cancer [144]. B. etnensis Raf. extract promotes oxidative cell microenvironment, leading to iron ptosis mediated by high expression of HO-1 and leading to colon cancer cell death [145].

CONCLUSIONS

Research on the mechanisms and applications of ferroptosis, a recently identified form of cell death, is undergoing rapid development. The main mechanism of ferroptosis is lipid peroxide production involving Fe^{2+}. The induction of ferroptosis exhibits the potential to eliminate numerous cancer cells, including those found in GC and CRC, thereby presenting diverse targets for cancer treatment. However, many questions remain to be addressed regarding the process of ferroptosis, such as alternative pathways for intracellular lipid peroxide production, and more powerful antioxidant mechanisms other than the GPX4-GSH antioxidant system to remove lipid peroxides. Furthermore, the relationship between ferroptosis and progression of gastric and colorectal carcinogenesis is still poorly understood. In this review, we detail what is known about the relationship between intracellular lipid, amino acid and iron metabolism and ferroptosis, as well as the potential role of ferroptosis in the treatment of GC and CRC, providing a theoretical basis for the study of ferroptosis mechanisms and their role in GC and CRC.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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