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REVIEW

Mechanism and role of ferroptosis in the development of gastric cancer

Fang Wei[1] · Yu Meng[1] · Dan-Xia Zhu[1] · Jun Wu[1]

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Abstract

Gastric cancer (GC) represents a prevalent form of malignant neoplasm characterized by elevated incidence and fatality rates, limited early detection capabilities, and unfavorable clinical outcomes. Its occurrence and development involve complex biological processes. As a recently identified form of cellular demise, ferroptosis has been observed across multiple cancer types, garnering significant research interest in contemporary studies. Nevertheless, the precise regulatory networks governing ferroptosis in gastric cancer, along with its functional implications in the initiation and advancement of this malignancy, remain unclear. This study seeks to elucidate the functional significance of ferroptosis in the pathogenesis of GC, systematically review the dysregulated metabolic pathways associated with this cell death process, and elucidate the intricate interactions among ferroptosis-related signaling cascades. These investigations are expected to establish a novel conceptual framework for understanding the molecular pathogenesis of gastric cancer and identifying potential therapeutic interventions. A comprehensive literature search was conducted using PubMed to identify relevant original research articles and review papers examining the molecular mechanisms underlying ferroptosis in gastric carcinoma. The search strategy incorporated the following key terms: "Ferroptosis," "Ferroptosis and gastric cancer," "Ferroptosis and GSH," "Ferroptosis and GPX4," "Ferroptosis and system Xc-," "Iron metabolism," "lipid peroxidation," "FSP1-CoQ10," "DHODH-CoQH2," "GCH1-BH4," "ferroptosis inducer," etc. Emerging evidence from contemporary research indicates that targeted ferroptosis represents a novel and potentially efficacious treatment modality for patients with gastric cancer. Along with the identification of precise molecular targets for therapeutic intervention, the metabolic regulatory networks associated with ferroptosis remains an essential area for future research endeavors.

Keywords Ferroptosis · Gastric cancer · Iron · ROS · Metabolism

Introduction

Globally, GC ranks as the fifth most frequently diagnosed malignancy and represents the third primary contributor to cancer-associated mortality [1]. The insidious nature of gastric cancer, characterized by its asymptomatic presentation in the majority of cases, frequently results in delayed clinical detection and intervention. This diagnostic challenge, compounded by the limited availability of efficacious therapeutic modalities, often leads to forfeiture of optimal treatment windows during the disease's initial stages. At the moment, those suffering from advanced gastric cancer have an unfavorable prognosis and a short lifespan. For patients with advanced gastric cancer, in addition to surgical treatment, the commonly used therapeutic methods also include chemotherapy, immunotherapy, radiotherapy, etc. These traditional therapies are much less effective due to tumor

Fang Wei and Yu Meng have contributed equally to this work.

✉ Jun Wu
wujun68@sina.com

Fang Wei
m15830810796@163.com

Yu Meng
19856263346@163.com

Dan-Xia Zhu
zhudanxia66@163.com

[1] Department of Oncology, The Third Affiliated Hospital of Soochow University, Changzhou, China

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recurrence and resistance to multiple drugs [2]. Ferroptosis constitutes a distinct form of regulated cellular demise, characterized by three hallmark features: excessive iron deposition within cells, elevated lipid peroxidation levels, and pathological accumulation of reactive oxygen species (ROS). This unique cell death modality differs fundamentally from other programmed cell death mechanisms through its intricate regulation by three interconnected metabolic networks—amino acid homeostasis, lipid biosynthesis, and iron regulation—which collectively drive iron-catalyzed peroxidation of membrane lipids, ultimately leading to cellular destruction [3]. Emerging research demonstrates that ferroptosis is orchestrated by diverse organelle-derived signals, particularly those emanating from lysosomes, mitochondria, and the endoplasmic reticulum [4]. The morphological features of ferroptosis include preserved nuclear structure, mitochondrial shrinkage, ridge depletion, and heightened mitochondrial membrane density [5]. With advancing investigations into ferroptosis mechanisms, researchers have progressively elucidated its regulatory functions across multiple cellular metabolic processes, including amino acid homeostasis, lipid metabolism, and iron regulation. The distinct biological features of ferroptosis-mediated cell death offer promising opportunities for developing novel anticancer strategies. Such approaches could potentially circumvent the limitations of conventional therapies, including multidrug resistance resulting from impaired apoptotic pathways and target specificity challenges in treatment-resistant malignancies. Emerging evidence indicates that ferroptosis plays a critical role in modulating the proliferation of diverse tumor cells, including gastric [6], breast [7], head and neck squamous cell [8], cervical [9], and pancreatic [10]. These findings reveal multiple potential therapeutic targets, highlighting the translational relevance of ferroptosis in gastric cancer treatment. This programmed cell death modality has been shown to significantly impact essential tumorigenic pathways in GC, encompassing tumor proliferation, metastatic progression, chemoresistance development, and tumor microenvironment modulation. Despite being a prevalent malignancy, gastric cancer has limited studies investigating the potential involvement of ferroptosis in its pathogenesis. In light of these findings, the present review offers a comprehensive examination of the molecular mechanisms underlying ferroptosis and their clinical significance in GC pathogenesis, disease progression, treatment resistance, and therapeutic strategies.

The prerequisite for ferroptosis

Ferroptosis is primarily driven by iron-dependent lipid peroxidation of phospholipids containing polyunsaturated fatty acids (PUFAs), leading to iron-mediated cell death caused by the excessive buildup of lipid peroxides on cell membranes that surpasses the cellular antioxidant capacity. The initiation of oxidative membrane damage in this cell death process is characterized by two critical biochemical events: intracellular iron overload and elevated lipid peroxidation levels [11].

Lipid peroxidation

Ferroptosis is distinguished by increased levels of lipid peroxidation, highlighting the essential role of regulating lipid peroxide metabolism. PUFAs, particularly arachidonic acid (AA) and adrenic acid (AdA), contain reactive diallyl hydrogen groups that readily interact with ROS, resulting in membrane destabilization and increased permeability. These molecular events ultimately drive lipid peroxidation and ferroptosis. The enzymatic activation of PUFAs, mediated by Acyl-CoA synthase long-chain family member 4 (ACSL4), facilitates their conjugation with Coenzyme A (CoA), generating acyl-CoA derivatives that serve as substrates for non-enzymatic lipid peroxidation reactions [12]. Through the action of various lysophosphatidylcholine acyltransferases (LPCATs), Acyl-CoA can be reesterified into phospholipids, forming membrane phosphatidylethanolamine (PE), and PE containing AA or AdA is a key phospholipid in inducing ferroptosis [13]. Modulation of ACSL4 and LPCATs activity consequently influences cellular susceptibility to ferroptosis. Within the enzymatic lipid peroxidation pathway, phospholipid hydroperoxides (PLOOH) are generated via catalytic activity of both lipoxygenase (LOX) enzymes and cytochrome P450 oxidoreductase (POR) systems [14]. LOX, a non-heme iron-containing enzyme, has demonstrated significant antioxidant properties by safeguarding cells against lipid peroxidation. This process is facilitated through the enzymatic deoxygenation of both non-esterified and esterified polyunsaturated fatty acids, resulting in the generation of PLOOH.

Stearoyl-CoA desaturase-1 (SCD1) is a lipid-modifying enzyme that facilitates the desaturation of fatty acids (FAs) into monounsaturated fatty acids (MUFAs), which are less prone to oxidation compared to PUFA [15]. Acyl-CoA synthetase long-chain family member 3 (ACSL3) serves as an essential mediator in the metabolic activation of MUFAs. Once activated, MUFAs can alter cell membrane properties by replacing PUFAs and prevent the buildup of lipid ROS in the plasma membrane, thereby inhibiting iron-dependent oxidative cell death [16]. Overexpression of SCD1 has been found to suppress ferroptosis and is identified as a critical target in multiple regulatory pathways.

Iron metabolism

Cellular iron overload is a critical trigger for ferroptosis. In physiological homeostasis, virtually all circulating iron is complexed with transferrin (TF), a serum glycoprotein that exhibits high-affinity, reversible iron-binding capacity. Each TF molecule contains two specific binding sites for ferric iron (Fe^{3+}) [17]. The iron-transferrin complex engages with transferrin receptor 1 (TFRC), triggering receptor-mediated endocytosis through membrane invagination and subsequent generation of specialized endocytic vesicles. Following cellular internalization, the endosomal compartment undergoes acidification, inducing conformational changes in transferrin that promote ferric iron (Fe^{3+}) dissociation. This released Fe^{3+} undergoes enzymatic reduction to its ferrous state (Fe^{2+}) through the catalytic activity of six-transmembrane epithelial antigen of prostate 3 (STEAP3), a membrane-associated metalloreductase. The resultant Fe^{2+} ions are then translocated across the endosomal membrane into the cytosolic labile iron pool (LIP) via divalent metal transporter 1 (DMT1/SLC11A2), a member of the solute carrier protein family [18]. The LIP iron represents a highly dynamic cellular iron reservoir that participates in diverse metabolic processes, including immediate utilization for enzymatic functions, storage within ferritin complexes, or export through ferroportin-mediated transport. Within the cytosolic compartment, the predominant fraction (exceeding 80–90%) of LIP iron exists in its reduced ferrous (Fe^{2+}) state, which is biologically active and readily available for cellular requirements. Concurrently, the iron-depleted transferrin undergoes intracellular recycling, returning to the plasma membrane where it dissociates from TFRC, thus completing the iron uptake cycle and maintaining cellular iron metabolism [19].

Typically, the majority of iron in the LIP resides within the mitochondrial outer membrane, specifically being transported by SLC25A37/mitoferrin-1 (25 member of the solute carrier family 37) and SLC25A28/mitoferrin-2 (25 member of the solute carrier family 28). These transporters facilitate the movement of iron into the mitochondria for the synthesis of heme or Fe-sulfur (Fe-S) clusters. Subsequently, these clusters are exported back to the cytoplasm via specific mitochondrial receptors, namely FLVCR1 (FLVCR heme transporter 1) and ABCB7 (B member of the ATP-binding box subfamily 7), respectively. Conversely, CISD1 (CDGSH iron-sulfur domain 1) is an iron-binding protein located on the outer mitochondrial membrane, which serves to regulate mitochondrial iron uptake and thereby suppress ferroptosis [20]. Furthermore, mitochondrial ferritin (FTMT) is a unique ferritin variant exclusively expressed in mitochondria and high-oxygen-consuming tissues of the central nervous system. It has the ability to sequester excess iron ions, forming ferritin complexes that help maintain iron ion homeostasis by storing or releasing iron as needed. Additionally, FTMT exhibits antioxidant properties, enabling it to scavenge excessive oxygen free radicals within cells and shield them from iron-induced oxidative stress [21].

Lipid peroxidation can also occur through the non-enzymatic Fenton reaction, a catalytic process involving the reaction between Fe2+ and H2O2 to produce Fe3+, hydroxyl radicals (HO−), and hydroxide ions (OH−) [22]. Furthermore, superoxide anions (O_2^-) participate in redox cycling with Fe3+, generating Fe2+ through the iron-catalyzed Haber–Weiss reaction cycle. These iron-mediated redox reactions produce highly reactive free radical species capable of inducing oxidative stress and subsequent damage to critical cellular constituents, including membrane phospholipids, structural and enzymatic proteins, and genetic material (DNA/RNA).

Ferroptosis defense mechanism

Ferroptosis primarily results from the functional impairment or dysregulation of intrinsic cellular antioxidant defense mechanisms. Current studies have found that there are at least four ferroptosis defense systems in cells, namely GPX4/xCT system, FSP1/CoQH system, DHODH/CoQH2 system and GCH1/BH4 system. These pathways can protect cells from ferroptosis by neutralizing lipid peroxides.

GPX4/xCT system

Cysteine (Cys2) metabolism and glutathione (GSH)-lysine antioxidant defense are important components of the mechanism of ferroptosis. Cys2 serves as an essential amino acid crucial for cellular survival, predominantly transported into cells in its oxidized, dimeric configuration (cystine). This vital precursor participates in GSH biosynthesis, a tripeptide synthesized through the conjugation of L-cysteine, L-glutamate, and glycine. As a principal constituent of the intracellular antioxidant defense network, GSH serves as a crucial regulator of cellular redox balance through its capacity to neutralize ROS. Depletion of GSH reserves has been strongly associated with extensive lipid peroxidation cascades, cellular dysfunction, and ultimately, programmed cell death pathways [23].

Glutamate/cystine reverse transporter (System XC-) consists of two structural components: the heavy chain (SLC3A2/CD98hc) and light chain (SLC7A11/xCT) subunits. This membrane transport system primarily facilitates the cellular uptake of extracellular cystine coupled with the efflux of intracellular glutamate, with the transport activity being predominantly regulated by the expression and function of the SLC7A11 subunit. With low expression of SCL7A11, the activity of System XC decreased, resulting in ferroptosis mediated by oxidative stress. In contrast,

elevated expression of SLC7A11 enhances cellular protection against ferroptosis [24]. Under normal circumstances, System Xc- operates through the established concentration gradients of extracellular cystine (Cys2) and intracellular glutamate (Glu), facilitating a stoichiometric 1:1 exchange that results in the efflux of intracellular Glu and concurrent uptake of extracellular Cys2 [25]. Following cellular uptake, cystine undergoes rapid reduction to cysteine through the enzymatic activity of thioredoxin reductase 1 (TrxR1), a critical component of the intracellular antioxidant defense system. Then, under the mediation of glutamate-cysteine ligase (GCL), cysteine and glutamate are linked together to form gamma-glutamylcysteine (GGC), the direct precursor of glutathione. GGC and glycine (Gly) to GSH catalyzed by glutathione synthase (GSS) [26]. The functional significance of GSH in ferroptosis regulation is predominantly mediated through glutathione peroxidase 4 (GPX4), a selenium-dependent antioxidant enzyme that serves as the principal catalyst for PLOOH reduction in mammalian systems. During the GPX4 catalytic cycle, the selenocysteine residue (GPX4-SeH), representing the enzyme's catalytic center, undergoes oxidation by PLOOH to form selenic acid (GPX4-SeOH), concurrently converting toxic lipid hydroperoxides (PLOOH) into their non-toxic alcohol derivatives (PLOH). GSH functions as an essential reducing agent in this process, regenerating the active enzyme by reducing selenic acid while producing oxidized glutathione (GSSG), thereby maintaining GPX4 activity and preventing enzyme inactivation [27]. GSSG is subsequently regenerated into its reduced form (GSH) through the enzymatic activity of glutathione reductase (GR) coupled with NADPH oxidation. Given that cysteine availability represents the rate-limiting factor in GSH synthesis and considering GSH's pivotal role as the major intracellular antioxidant, any disruption in cellular cysteine and GSH homeostasis directly impacts GPX4 enzymatic function. This biochemical cascade demonstrates that GPX4, through its selenocysteine residue (GPX4-SeH), catalyzes the conversion of PLOOH to PLOH, thereby suppressing ferroptotic cell death. Conversely, impaired GPX4 function leads to the abnormal buildup of lipid peroxidation products. Consequently, cellular systems exhibiting reduced GPX4 expression demonstrate enhanced susceptibility to ferroptosis, whereas elevated GPX4 levels confer protection against this form of regulated cell death (Fig. 1).

FSP1/CoQH system

Fsp1-coenzyme Q10(CoQ10)-NAD(P) H-axis and the non-classical redox-reduction cycle of vitamin K that FSP1 participates in are important pathways for FSP1 to regulate ferroptosis. Ferroptosis suppressor protein 1 (FSP1), alternatively designated as apoptosis-inducing factor mitochondria-associated 2 (AIFM2), represents a member of the NAD(P)H/quinone oxidoreductase (NQO) enzyme family. This crucial ferroptosis regulator contains a distinctive myristoylation motif within its N-terminal domain, with structural alterations in this conserved sequence being functionally linked to the promotion of ferroptosis [28]. CoQ10, alternatively referred to as ubiquinone, represents an essential lipophilic component of cellular membranes that plays a crucial role in mitochondrial ATP synthesis.

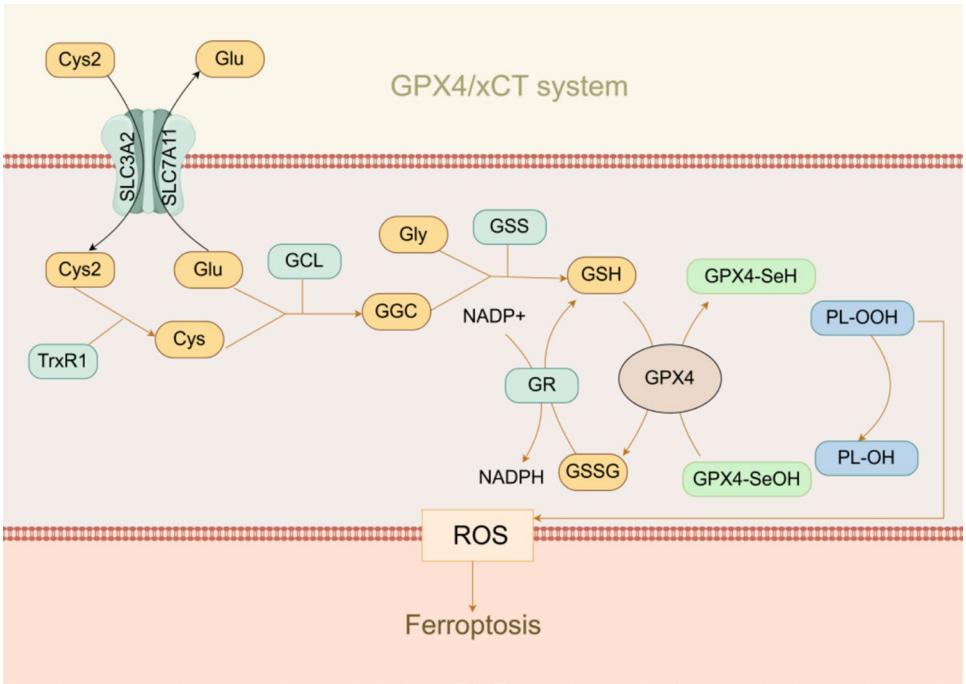

Fig. 1 Mechanism of GPX4/xCT system

FSP1 demonstrates distinct redox functionalities in ferroptosis regulation, encompassing both NAD(P)H-dependent coenzyme Q10 (CoQ10) redox cycling and vitamin K reductase activity. At the molecular level, FSP1 mediates its ferroptosis-suppressive activity via the NAD(P)H-dependent pathway, facilitating the enzymatic conversion of ubiquinone (oxidized CoQ10) to its reduced form, a lipophilic antioxidant predominantly localized in mitochondrial membranes. Ubiquinol (CoQ10H2) functions as a potent lipophilic radical scavenger, effectively neutralizing reactive species and inhibiting lipid peroxidation cascades. Furthermore, this reduced form of CoQ10 participates in the regeneration of α-tocopherol (alpha-To), thereby amplifying the cellular antioxidant defense network and providing additional protection against ferroptosis [29]. Alternatively, the FSP1-mediated non-classical vitamin K cycle contributes to cellular protection against oxidative damage by mitigating lipid peroxidation and preventing ferroptosis. Functioning as a vitamin K reductase (VKR), FSP1 employs NAD(P)H as its electron donor substrate to facilitate the enzymatic reduction of vitamin K, generating its biologically active hydroquinone derivative (VKH2). This reduced vitamin K derivative serves as a potent antioxidant, capable of scavenging reactive free radicals while simultaneously functioning as a robust inhibitor of lipid peroxidation cascades [30] (Fig. 2).

DHODH/CoQH2 system

The DHODH-CoQH2 axis constitutes a mitochondrial-specific defense mechanism against ferroptosis. Dihydroorotate dehydrogenase (DHODH), an enzyme localized at the outer surface of the inner mitochondrial membrane (IMM), facilitates the oxidation of dihydroorotate (DHO) to orotate (OA) through ubiquinone-mediated electron transfer. During this catalytic process, the electron acceptor ubiquinone (CoQ) is concomitantly reduced to its antioxidant form, dihydroubiquinone (CoQH2), within the mitochondrial membrane system. CoQH2 can act as a free radical trapping antioxidant to prevent lipid peroxidation, thereby inhibiting ferroptosis [31]. Notably, the researchers further investigated and found that the system compensates for the loss of GPX4, and when GPX4 is acutely inactivated, DHODH-mediated CoQH2 production is significantly enhanced, thereby neutralizing lipid peroxidation and preventing ferroptosis in the mitochondria [32]. A series of experiments suggest that DHODH and GPX4 work together to inhibit lipid peroxidation and ferroptosis in mitochondria, which constitute the main ferroptosis defense system in mitochondria (Fig. 3).

GCH1/BH4 system

The GTP cyclohydrolase 1 (GCH1)-tetrahydrobiopterin (BH4) axis represents a crucial GPX4-independent regulatory pathway in ferroptosis suppression. BH4, a vital constituent of cellular antioxidant defenses, participates in multiple metabolic processes including nitric oxide biosynthesis, neurotransmitter regulation, and aromatic amino acid metabolism. BH4 biosynthesis occurs through a sequential enzymatic cascade involving GCH1, 6-pyruvoyltetrahydropterin synthase (PTS), and sepiapterin reductase (SPR), with GCH1 serving as the rate-determining enzyme in this metabolic pathway [33]. BH4 readily

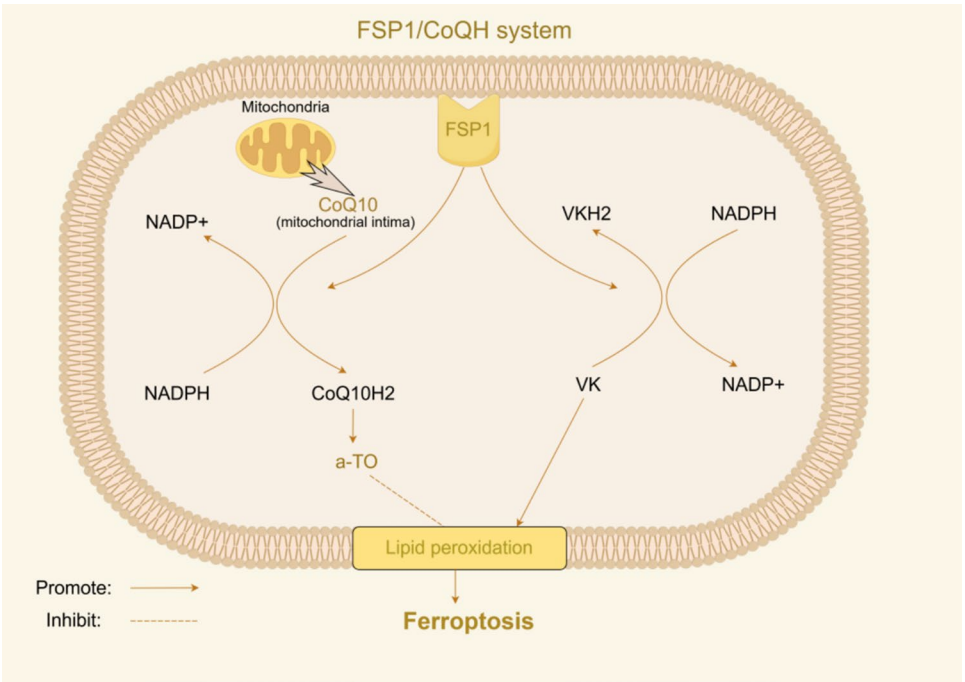

Fig. 2 Mechanism of FSP1/CoQH system

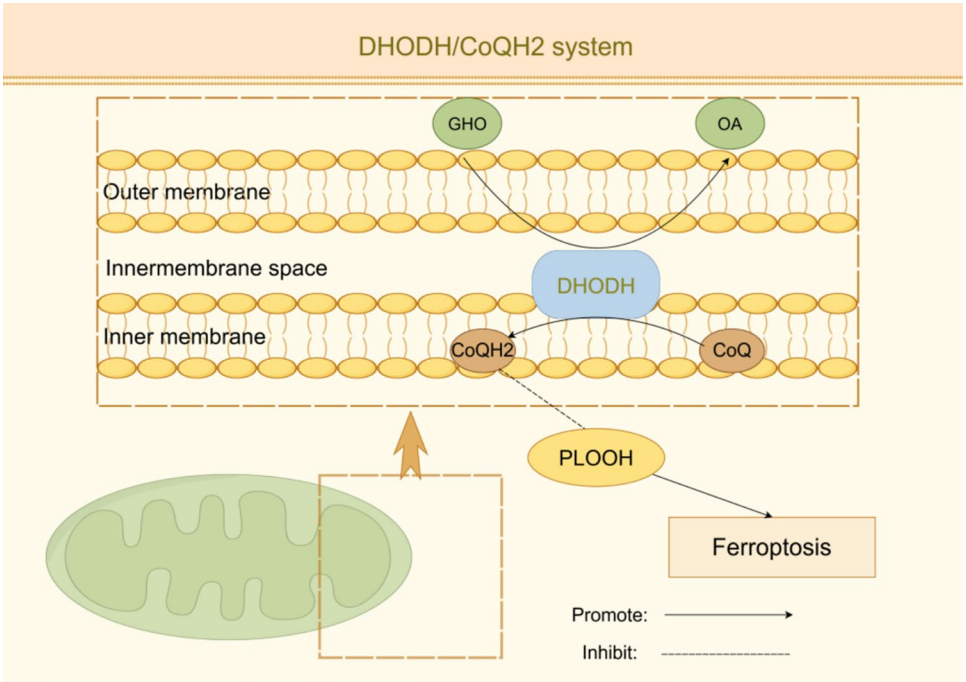

Fig. 3 Mechanism of DHODH/CoQH2 system

oxidizes to dihydrobiopterin (BH2), forming a REDOX cycle to reduce endogenous oxidizing free radicals and protect lipid membranes, thereby inhibiting ferroptosis [34]. BH4 acts as a potent endogenous radical trapping antioxidant that regulates sensitivity to GPX4 inhibitor-induced ferroptosis, protecting cells from lipid peroxidation, and is also used in de novo synthesis of CoQ10, which also protects cells from ferroptosis. Consequently, cellular susceptibility to ferroptosis is predominantly governed by GCH1 expression levels, with inhibition of GCH1 resulting in BH4 depletion that subsequently promotes lipid peroxide accumulation and ferroptosis. In contrast, genetic amplification of GCH1 expression selectively upregulates BH4 production while concomitantly attenuating ROS generation (Fig. 4).

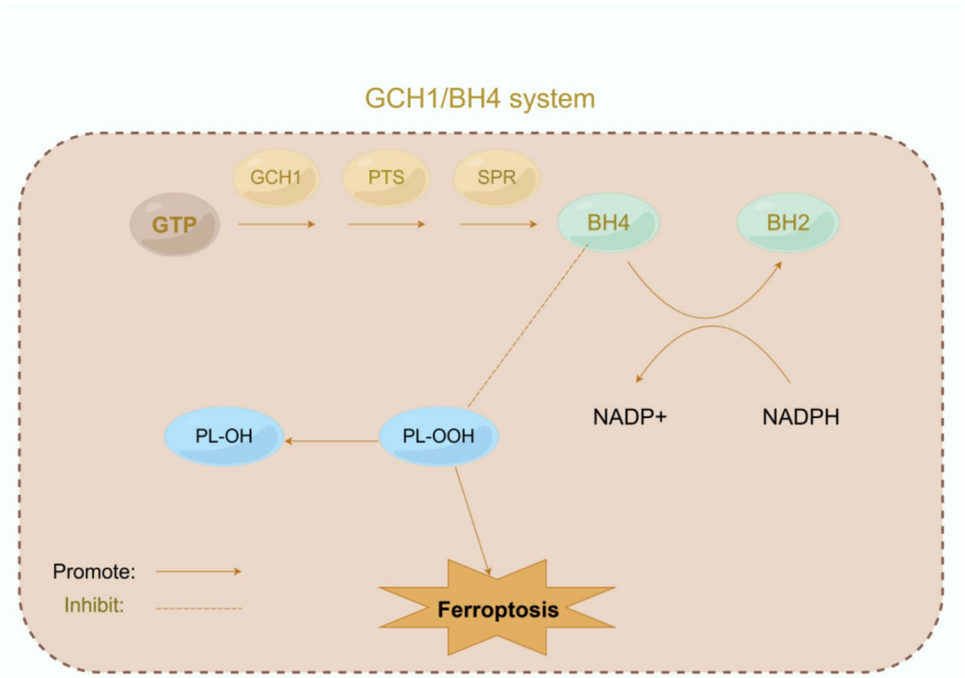

Fig. 4 Mechanism of GCH1/BH4 system

The role of ferroptosis in gastric cancer

As with other cancer types, GC develops from precancerous lesions that may develop into tumors when cells proliferate faster than they die [35]. As a tumor suppressor process, ferroptosis represents not merely an innovative cell death modality, but also exerts significant influence on various oncological characteristics, encompassing epithelial-mesenchymal transition (EMT), immunological responses, genomic instability, tumor progression, and therapeutic resistance mechanisms [4].

Non-coding RNA associated with ferroptosis and gastric cancer

Emerging evidence has increasingly demonstrated that dysregulation of ferroptosis-associated non-coding RNAs, including microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs), plays a pivotal role in gastric carcinogenesis and progression. Specifically, miR-103a-3p functions as an oncogenic miRNA that is significantly upregulated in gastric cancer, with its elevated expression correlating with unfavorable clinical outcomes in advanced-stage patients. Mechanistic studies reveal that physcion 8-O-β-glucopyranoside (PG) induces ferroptosis through miR-103a-3p-mediated upregulation of glutaminase 2 (GLS2), a p53-regulated metabolic enzyme that catalyzes the conversion of glutamine to glutamate, thereby facilitating glutathione biosynthesis [36]. Therefore, miR-103a-3p regulates GC by altering cellular GSH levels. As a member of the LOX enzyme family, arachidonic lipoxygenase 15 (ALOX15) plays an important role in lipid peroxidation in GC cells, and miR-522 is a potential inhibitor of ALOX15. Zhang et al. revealed that cancer-associated fibroblast (CAF)-derived exosomal miR-522 suppresses ferroptosis and facilitates GC cell proliferation through ALOX15 inhibition, thereby attenuating lipid peroxidation [37]. Wang et al. confirmed through experiments that lncLASTR was involved in regulating the proliferation and migration of gastric adenocarcinoma cells through ferroptosis [38]. Li et al. found that the upregulation of circ_0008035 impeded apoptosis and ferroptosis in GC by regulating the miR-599/EIF4A1 axis [39]. Circ0000190 has been identified as significantly upregulated in GC cells, where it suppresses tumor cell proliferation and migration through ferroptosis induction [40].

Ferroptosis and helicobacter pylori infection

Helicobacter pylori infection is known to be one of the main risk factors for gastric adenocarcinoma [41], the mechanism that causes gastric cancer involves a variety of complex biological processes, including bacteria-induced inflammatory response, toxins and proteins produced by bacteria, and damage and repair of host cells. Among the several Helicobacter pylori virulence factors that have been discovered so far, CagA (cytotoxin-related gene A) plays a central role in the development of gastric cancer [42]. Mechanistically, CagA can activate the MEK/ERK/SRF pathway to up-regulate the expression of polyunsaturated ether phospholipids (PUFA-ePLs) biosynthase, alkyl glycerol phosphate synthase (AGPS) and 1-acylglycerol-3-phosphate O-acyltransferase 3 (AGPAT3), and induce the sensitive state of ferroptosis in GC cells. Serum response factor (SRF), a crucial transcriptional regulator, enhances AGPS gene expression through direct binding to its promoter region [43]. Consequently, GC cases exhibiting CagA positivity demonstrate enhanced susceptibility to ferroptosis-inducing therapeutic interventions. Previous studies have shown that miR-375 suppresses Helicobacter pylori-mediated gastric carcinogenesis through inhibition of the JAK2-STAT3 signaling pathway [44], and miR-375 can trigger ferroptosis by targeting SLC7A11 [45]. Despite the well-established correlation among Helicobacter pylori infection, gastric carcinogenesis, and ferroptosis regulation, comprehensive investigations remain necessary to elucidate the underlying molecular mechanisms and pathophysiological processes.

The regulation of ferroptosis function protein mediates gastric carcinogenesis and tumor progression

Emerging research has demonstrated that multiple regulatory proteins implicated in ferroptosis modulation are critically involved in gastric cancer pathogenesis. Hao et al. found that cysteine dioxygenase 1 (CDO1), a non-heme iron-containing metalloenzyme that regulates cysteine homeostasis through its catalytic conversion to cysteine sulfinate, as a key mediator of Erastin-induced ferroptosis in GC cells. Therefore, inhibiting CDO1 expression can inhibit ferroptosis in GC by upregulating GPX4 expression and preventing ROS production [29]. Activating transcription factor 3 (ATF3) and activating transcription factor 4 (ATF4) are common members of the ATF/cAMP response element binding (CREB) protein family. Dazhi Fu et al. showed that the decreased expression of ATF3 in GC cells and tissues was positively correlated with the overall survival of GC patients, and it was also found that the increase in ATF3 induced iron death by inhibiting Nrf2/Keap1/xCT signaling, which could make cisplatin resistant GC cells sensitive to cisplatin [30]; therefore, ATF3 may be a promising treatment for gastric cancer. Cytoplasmic polyadenylate binding protein (CPEB) is a key factor regulating mRNA translation, with its diminished expression being correlated with metastatic progression in gastric cancer. Decreased CPEB1 increased the expression of

ATF4 inhibitor Twist1, thereby weakening the ATF4/ GSH-specific γ-glutamyl cyclotransferase 1(CHAC1) pathway to inhibit GSH degradation and further protect gastric cancer cells from ferroptosis [46]. Perilipin2 (PLIN2) is a key gene and protein in preventing ferroptosis in gastric cancer caused by abnormal fat metabolism. By regulating related genes involved in the ferroptosis pathway acyl-Coenzyme-Coenzyme synthetase long-chain family member 3 (ACSL3), arachidonic acid 15-lipoxygenase (ALOX15), microtubule-associated protein 1 light chain 3α (LC3A), pr/set domain 11 (PRDM11), and importin 7 (IPO7) affect the proliferation and apoptosis of gastric cancer cells [32].

Ferroptosis is involved in the tumor microenvironment in gastric cancer

Tumor microenvironment (TME) is a complex biological environment composed of numerous cells and factors, including infiltrating inflammatory cells, bone marrow-derived hematopoietic and endothelial progenitor cells, tumor-associated fibroblasts, extracellular matrix and secretory factors, such as cytokines, lipid mediators and growth factors. Tumor cells in TME actively contribute to the progression of gastric cancer. It has been shown that tumor cells and their surrounding microenvironment can undergo phenotypic remodeling through modulation of ferroptosis activation states [47].

Iron serves as an indispensable element for cellular proliferation and fundamental metabolic functions, and from this perspective, cancer cells often exhibit a high proliferation rate and high metabolic turnover rate, so neoplastic populations are believed to exhibit significantly greater iron requirements compared to their non-transformed counterparts. Iron influences tumor cell proliferation through multiple mechanisms: (1) catalyzing non-enzymatic reactive oxygen species (ROS) generation, (2) serving as an essential cofactor for cell cycle-regulating enzymes including ribonucleotide reductase, (3) modulating cell cycle regulatory proteins, (4) participating in both oncogenic and tumor-suppressive signaling pathways, (5) functioning as a crucial element in hypoxia response and metabolic regulation, and (6) mediating epigenetic modifications through 2-oxoglutarate-dependent dioxygenase activity [48]. Beyond their well-established role in phagocytic clearance of foreign antigens, tumor-associated macrophages (TAMs) perform crucial physiological functions in maintaining tissue iron homeostasis. This functionality positions macrophages as pivotal regulators in GC pathogenesis and progression. According to the traditional M1/M2 classification, M1-like macrophages with high (ferritin) FT and low iron-pumping protein (FPN1) are easy to extract, restrict, and store iron, whereas M2-like macrophages with low FT and high FPN1 promote iron export and redistribution to the extracellular space [49]. In most types of malignancies, TAMs are typically M2-like cells, and a meta-analysis suggests that the number of infiltrated M2 macrophages and total Tams may be poor prognostic factors in GC patients, while M1 macrophage infiltration may be associated with good survival [50]. Targeted elimination of TAMs or phenotypic reprogramming of M2-polarized TAMs to their M1 state has emerged as a novel therapeutic approach in GC management. Damage-related molecular models in various cell death processes (DAMPs), such as the release of high mobility group box 1 (HMGB1), can mediate the polarization of macrophages into M2 phenotypes and promote the inflammatory response during ferroptosis [51].

In addition, interferon-γ (IFN-γ) released by CD8 + T cells down-regulated the expression of SLC3A2 and SLC7A11, two subunits of the glutamine-cystine antitransporter system XC-, inhibiting Gys uptake by tumor cells, thereby promoting lipid peroxidation and ferroptosis in tumor cells [52]. Pathologically activated neutrophils (PMN), known as myeloid suppressor cells (PMN-MDSC), are major negative regulators of anti-tumor immunity, and tumor-associated PMN-MDSC have been shown to be prone to ferroptosis [53].

Treatment of gastric cancer targeting ferroptosis

A fundamental challenge in oncology research lies in developing therapeutic strategies that selectively eliminate malignant cells while preserving normal cellular integrity. Recent advancements have increasingly demonstrated the critical involvement of ferroptosis in GC pathophysiology, offering novel insights for targeted therapeutic interventions in GC management.

Pharmacological agents targeting system Xc- or GPX4 including sorafenib, sulfasalazine (SAS), and artesunate (ART), have demonstrated potent ferroptosis-inducing capabilities, significantly suppressing gastric cancer cell proliferation and tumor growth [54]. Erastin, a potent small-molecule inhibitor of system Xc-, disrupts cellular cysteine uptake and compromises GSH homeostasis, ultimately inducing GSH depletion and triggering ferroptosis. In addition, mitochondrial voltage-dependent anion channels (VDAC) are also one of Erastin's direct molecular targets. Ferroptosis of gastric cancer cells can be selectively induced by RAS-RAF-MEK signaling pathway [5]. Previous studies of GC cells showed Erastin-induced ferroptosis in GC cells, while CDO1 silencing inhibited Erastin-induced ferroptosis in GC cells [55]. Analogous to Erastin's mechanism, pharmacological agents including SAS, glutamate, and sorafenib exert their anticancer effects through system Xc- inhibition across various malignant cell types,

thereby inducing ferroptosis. Ferroptosis represents a crucial mechanism in enhancing the chemosensitivity of gastric carcinoma cells, potentially overcoming therapeutic resistance to conventional anticancer agents. Studies have shown that cisplatin resistant cells induced by repeated cisplatin treatment show high SLC7A11 (xCT) expression. Clinical studies have demonstrated a significant association between increased xCT expression and poor clinical outcomes in GC patients receiving adjuvant chemotherapeutic treatment. Therapeutic interventions targeting xCT, including pharmacological inhibitors (SAS or Erastin), xCT-specific siRNA, or glutathione synthesis inhibitors (buthionine sulfoximine, BSO), have demonstrated efficacy in restoring cisplatin sensitivity in previously resistant tumor cells [56]. RAS selective lethal compound 3 (RSL3) functions as a direct GPX4 inhibitor that forms covalent bonds with GPX4, resulting in enzyme inactivation. This molecular interaction triggers lipid peroxidation cascades and subsequent reactive oxygen species (ROS) generation, ultimately inducing ferroptosis and suppressing tumor cell proliferation [57]. Artesunate, a semisynthetic artemisinin derivative, elevates intracellular iron levels through enhanced ferritin degradation and subsequently induces ferroptosis via iron-dependent mechanisms [58], in the treatment of hepatocellular carcinoma, artesunate acts synergistically with sorafenib in inducing ferroptosis in hepatocellular carcinoma [59]. Statins, a class of pharmacological agents that induce ferroptosis through inhibition of selenoprotein biosynthesis pathways (including GPX4 and coenzyme Q10 production), represent a promising therapeutic approach for oncological management [4]. However, the precise molecular mechanisms underlying drug-induced ferroptosis in GC require comprehensive clinical validation through further investigation.

Emerging research has identified nanocarrier-based delivery systems as a promising strategy for targeted induction of ferroptosis in malignant cells. Specifically, iron oxide nanoparticles have demonstrated potent anticancer effects through mechanisms containing elevating intracellular iron concentrations and amplifying ROS generation. Following cellular internalization and subsequent degradation within the acidic tumor microenvironment, these nanoparticles release bioavailable iron ions, thereby potentiating Fenton chemistry and augmenting ROS-mediated cytotoxicity [60] (Table 1).

Discussion

Recent scientific investigations have progressively highlighted the crucial involvement of ferroptosis in gastric carcinogenesis, tumor progression, and therapeutic interventions. This regulated cell death process significantly

Table 1 Key ferroptosis regulatory factors in GC

Category	Name	Mechanism
Genes	SLC7A11	Cystine/glutamate transporter, maintains GSH synthesis
	GPX4	Glutathiones peroxidase, scavenges lipid ROS
	ACSL4	Catalyzes esterification of polyunsaturated fatty acids (PUFAs), promotes lipid peroxidation
	TFR1	Mediates iron uptake, increases intracellular free iron
	SCD1	Promotes the generation of MUFAs, scavenges lipid ROS
	CISD1	Limits the uptake of iron by mitochondria
	FSP1	Protects cells from harmful lipid peroxidation and ferroptosis
	DHODH	Inhibits lipid peroxidation and ferroptosis in mitochondria in a synergistic manner with GPX4
	BH4	Effective endogenous free radical scavenging antioxidants, regulates the sensitivity to GPX4 inhibition-induced ferroptosis, protects cells from lipid peroxidation
	GCH1	Selectively enhances the biosynthesis of BH4, reduces the production of ROS
	CDO1	Up-regulates the expression of GPX4, prevents the generation of ROS
Non-coding RNA	miR-103a-3p	Alters the GSH level of cells
	miR-522	ALOX15 inhibitor
	circ_0008035	Regulates the miR-599/EIF4A1 axis
	miR-375	Blocks JAK2-STAT3 signal transduction to inhibit Helicobacter pylori, targets SLC7A11
Drugs	Sorafenib	Inhibits System Xc^-, reduces GSH synthesis
	Sulfasalazine	System Xc^- inhibitor, blocks cystine uptake
	Erastin	Inhibits System Xc^-, increases ROS
	RSL3	Directly inhibits GPX4 activity
	ART	Increases ferritin hydrolysis
	Statins	Inhibits the biosynthesis of selenoproteins

contributes to gastric cancer pathogenesis and can be modulated through targeted regulation of iron homeostasis, lipid peroxidation pathways, and cellular antioxidant defense mechanisms. This article provides an in-depth analysis of the molecular pathways involved in ferroptosis and its potential implications in gastric cancer pathogenesis, while evaluating the therapeutic prospects of ferroptosis modulation in gastric carcinoma management. Nevertheless, contemporary knowledge regarding ferroptosis involvement in GC development and therapeutic strategies likely represents merely the surface of a complex biological phenomenon, leaving numerous mechanistic questions to be addressed through future investigations. For now, extensive research efforts are required to elucidate strategies for selective induction of ferroptosis in gastric cancer cells while identifying patient subgroups most likely to benefit from such therapeutic approaches, alongside rigorous validation of treatment safety and efficacy profiles. Current investigations into ferroptosis in gastric cancer are transitioning from fundamental mechanistic studies toward clinical applications. Nevertheless, dedicated clinical trials exploring ferroptosis-targeted interventions remain limited. The majority of existing research concentrates on either repurposing known ferroptosis inducers (e.g., sorafenib, sulfasalazine) or developing combinatorial approaches with conventional therapies, including chemotherapy and immunotherapy. Utilizing ferroptosis-linked lncRNA profiling, twelve candidate drugs demonstrating anti-gastric adenocarcinoma activity were identified, including: (1) apoptosis modulators (ABT-263), (2) kinase inhibitors (AMG-706, AP-24534, imatinib, nilotinib), (3) epigenetic regulators (CCT007093, DMOG), and (4) targeted agents (JNJ-26854165, JNK inhibitor VIII, KIN001-135, lenalidomide, AKT inhibitor VIII) [61]. All of the above drugs have varying degrees of anti-tumor effects and significant clinical significance. Preclinical studies indicate that PD-1/PD-L1 inhibition may sensitize cancer cells to ferroptosis. This synergistic effect is now being clinically explored in a phase II trial (NCT04170535) assessing a novel therapeutic triad: sorafenib, camrelizumab (anti-PD-1), and XELOX chemotherapy for advanced GC [62]. Such combination strategies represent a promising convergence of targeted ferroptosis induction and immunotherapy paradigms. Additionally, the phase I/II clinical trial (NCT05063019) is currently investigating the safety profile and therapeutic efficacy of sulfasalazine in combination with FOLFOX chemotherapy (oxaliplatin plus 5-fluorouracil) for GC treatment [63]. This study represents another important clinical exploration of ferroptosis modulation in gastrointestinal malignancies. At present, clinical research on ferroptosis in gastric cancer is still in its early stage. In the future, more biomarker-driven clinical trials and the development of novel ferroptosis inducers are needed to promote the progress in this field. Ongoing research exploring the molecular pathways regulating ferroptosis and its interconnected signaling cascades will enable the creation of innovative, precision-based treatment approaches for GC therapy.

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Data availability No datasets were generated or analyzed during the current study.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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