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Targeting ferroptosis in *Helicobacter pylori*-associated gastric cancer development: From molecular mechanisms to application prospects (Review)

CHEN-YI WANG[1*], MENG-HUI WANG[1,2*] and CHUAN XIE[1]

[1]Department of Gastroenterology, The First Affiliated Hospital of Nanchang University, Jiangxi Medical College, Nanchang University, Nanchang, Jiangxi 330006, P.R. China; [2]Department of Gastroenterology, Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200080, P.R. China

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Abstract. Gastric cancer (GC) has a high incidence, resistance to chemotherapeutic drugs and a bleak prognosis. *Helicobacter pylori* (*H. pylori*) can promote GC development through Correa's cascade by impacting various forms of programmed cell death (PCD). As an iron-dependent form of PCD, ferroptosis has emerged as a major focus in biomedical research. Notably, there have been developments in elucidating the mechanisms underlying ferroptosis dysregulation throughout Correa's cascade. On one hand, targeting ferroptosis may provide a promising direction for the development of drugs for chronic atrophic gastritis (CAG) and intestinal metaplasia (IM). On the other hand, targeting ferroptosis in GC may be a potential option to overcome the challenges in conventional therapies such as resistance to chemotherapy. Consequently, the present review aims to deliver a comprehensive understanding of the mechanisms underlying ferroptosis dysregulation in *H. pylori*-associated GC and summarize the latest progress of ferroptosis-related studies in CAG, IM and GC. The present study identifies key regulators of ferroptosis at distinct pathological stages, thereby providing insight of novel strategies for the management of precancerous lesion-related diseases and GC.

Contents

1. Introduction

Programmed cell death (PCD) is defined as an intrinsic component of physiological developmental programs or tissue renewal, occurring independently of exogenous environmental factors (1). Importantly, accumulating evidence indicates that PCD has strong effects on a number of lesions

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Correspondence to: Dr Chuan Xie, Department of Gastroenterology, The First Affiliated Hospital of Nanchang University, Jiangxi Medical College, Nanchang University, 17 Yong Waizheng Street, Donghu, Nanchang, Jiangxi 330006, P.R. China
E-mail: xcsghhz@ncu.edu.cn

[*]Contributed equally

Abbreviations: GC, gastric cancer; PLGC, precancerous lesions of gastric cancer; *H. pylori*, *Helicobacter pylori;* PCD, programmed cell death; IL, interleukin; TNF, tumor necrosis factor; GSH, glutathione; GPX, glutathione peroxidase; PLOOHs, phospholipid hydroperoxides; SLC3A2, solute carrier family 3 member 2; ROS, reactive oxygen species; PUFA, polyunsaturated fatty acid; 4-HNE, 4-hydroxynonenal; LOX, lipoxygenase; FSP1, ferroptosis suppressor protein 1; PI3K, phosphatidylinositol-3-kinase; AKT, protein kinase B; mTOR, mammalian target of rapamycin; mTORC1, mechanistic target of rapamycin complex 1; VacA, vacuolar cell toxin; CagA, cytotoxin-associated gene A; RNS, reactive nitrogen species; Bcl-2, B-cell lymphoma-2; Mtb, Mycobacterium tuberculosis; YWHAE, tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein epsilon; OMVs, outer membrane vesicles; TFRC/TFR1, transferrin receptor/transferrin receptor protein 1; CAG, chronic atrophic gastritis; IM, intestinal metaplasia; STAT3, signal transducer and activator of transcription 3; EMT, epithelial-mesenchymal transition; HIF-1α, hypoxia-inducible factor 1α

Key words: programmed cell death, *Helicobacter pylori*, ferroptosis, Correa's cascade, gastric cancer

including chronic inflammation and cancer (2-4). Ferroptosis, a term introduced by Brent Stockwell in 2012, is a distinct form of iron-dependent PCD characterized by the accumulation of lipid peroxides and subsequent disruption of the cell membrane, ultimately leading to cell death (5). Recent advances in molecular biology have revealed the critical involvement of ferroptosis in the pathophysiology of gastrointestinal diseases, establishing it as a rapidly evolving research frontier in gastroenterology (6).

According to the global cancer statistics in 2022 released by GLOBOCAN, gastric cancer (GC) ranks fifth in both incidence and mortality worldwide, with >950,000 new cases and >650,000 mortalities in the whole year (7). *Helicobacter pylori* (*H. pylori*) infection, the most prevalent chronic bacterial infection worldwide, is a major etiological factor for GC (8). Studies have demonstrated that *H. pylori* mediates chronic inflammation by upregulating proinflammatory cytokines, including interleukin (IL)-8, IL-1β and tumor necrosis factor (TNF) (9-11). *H. pylori*-associated chronic gastritis, also referred to as type B gastritis, can progress to GC through a sequence of histopathological changes, a process first described in 1975 and termed as Correa's cascade (12). Despite significant advancements in the prevention and treatment of GC based on Correa's cascade, several critical challenges persist. In the precancerous lesions of GC (PLGC), traditional therapies such as *H. pylori* eradication and symptomatic treatment often fail to effectively suppress chronic inflammation or halt the progression of Correa's cascade (13,14). Moreover, the early detection of GC is substantially hampered by the absence of specific clinical manifestations in the initial stages, the suboptimal sensitivity of current screening biomarkers, and the low popularity rate of endoscopic screening (15,16). Consequently, a substantial proportion of patients are diagnosed at advanced stages of disease progression. In the management of advanced GC, several therapeutic limitations remain unresolved, including the development of chemoresistance, the paucity of novel molecular targets for targeted therapies, and the low response rate of immunotherapy, all of which represent pressing unmet needs in contemporary oncology practice (17-20). Targeted regulation of ferroptosis-related strategies, characterized by precision targeting, antioxidant properties, anti-inflammatory effects and potential anticancer activity, represents a promising approach to overcoming these limitations.

This comprehensive review systematically investigated the intricate interplay between *H. pylori* infection and ferroptosis, while proposing novel promising strategies for GC prevention and treatment through targeted regulation of ferroptosis-related pathways across several different stages of the Correa's cascade.

2. Regulation of ferroptosis

Oxygen serves as the terminal electron acceptor in the majority of metabolic oxidation-reduction reactions for most organisms, highlighting the necessity of oxidative stress. Oxidative stress induces oxidative modifications of the cell's bilayer membrane, particularly lipid oxidation, which impacts various cellular physiological processes such as developmental regulation, immune response, tumor suppression, metabolic balance and aging. Ferroptosis, a form of PCD, is characterized by extensive lipid peroxidation (21). Since its introduction in 2012, ferroptosis research has centered around several fundamental components: i) The systemic x_c^--glutathione (GSH)-glutathione peroxidase (GPX)4 ferroptosis suppression pathway; ii) phospholipid hydroperoxides (PLOOHs); iii) iron regulation; iv) GPX4-independent regulatory pathways; and v) other important regulators such as tumor suppressor p53 and related signaling pathways.

GSH is a crucial intracellular reductant, and also functions as a cofactor for enzymes such as GPXs and GSH-S-transferases. GSH biosynthesis relies on cysteine, which can be imported from the environment via neutral amino acid transporters, taken up in its oxidized form (cystine) through the x_c^--cystine/glutamate antiporter system [comprising solute carrier family 7 member 11 and solute carrier family 3 member 2 (SLC3A2 subunits)], or synthesized through the trans-sulfuration pathway utilizing methionine and glucose (21-23). The transporter protein in the x_c^- system is a disulfide-linked heterodimer consisting of a light chain (xCT) and a heavy chain (4F2hc) (24). GPX4 plays a pivotal role in the ferroptosis process, serving as the primary enzyme that catalyzes the reduction and detoxification of PLOOHs in mammalian cells (25).

As a type of lipid-derived reactive oxygen species (ROS), PLOOHs mark the beginning of lipid peroxidation. This process begins with the abstraction of a bisallylic hydrogen atom from the polyunsaturated fatty acid (PUFA) acyl chain of phospholipids within the lipid bilayer, generating a carbon-centered phospholipid radical (PL•). This radical subsequently reacts with molecular oxygen to form a phospholipid peroxyl radical (PLOO•) (26), which abstracts hydrogen from another PUFA, resulting in PLOOH formation. In the absence of timely reduction of PLOOHs to their corresponding alcohols (PLOH) by GPX4, the chain reaction products, including lipid peroxide breakdown products [e.g., 4-hydroxynonenal (4-HNE) and malondialdehyde] and oxidized/modified proteins, disrupt membrane integrity and ultimately lead to organelle and/or membrane breakdown (21).

The regulation of ferroptosis has emerged as a critical focus in disease mechanism research. In the context of ferroptosis modulation, two distinct mechanisms have been identified: Erastin exerts its effect through indirect inhibition of GPX4 by targeting system x_c, thereby disrupting cystine uptake, while RSL3 demonstrates direct GPX4 inhibition. These compounds represent two fundamental classes of ferroptosis inducers, as indicated in previous studies (27,28). Furthermore, PUFAs and PUFA-containing lipids within biofilms are susceptible to direct oxidation by certain lipoxygenases (LOXs), suggesting that LOXs may also constitute a target for ferroptosis induction (29). Additionally, iron is also crucial for the regulation of ferroptosis. Inhibition of GPX4 triggers the Fenton reaction, leading to a rapid accumulation of PLOOHs, a characteristic of iron toxicity (26). Moreover, it has been shown that cytochrome P450 oxidoreductase can directly or indirectly trigger lipid peroxidation by removing hydrogen from PUFAs or by reducing ferric iron (Fe^{3+}) to its ferrous form (Fe^{2+}) after its downstream electron acceptor is reduced (30).

Apart from the GSH-GPX4 inhibitory pathway, which is recognized as the predominant ferroptosis regulatory system (31), one such mechanism involves ferroptosis suppressor protein 1 (FSP1, also known as AIFM2), which inhibits lipid peroxidation and ferroptosis by synthesizing panthenol and rejuvenating oxidized α-tocopherol radicals (vitamin E) (32,33). Another mechanism entails guanosine triphosphate cyclohydrolase 1 protecting against ferroptosis through its metabolites tetrahydrobiopterin and dihydrobiopterin (34).

3. Dysregulation of ferroptosis is an important component of the cancer mechanisms

There is compelling evidence linking ferroptosis to a spectrum of pathologies involving tissue damage, encompassing cancer, neurodegeneration, inflammation and infection (35). Targeting ferroptosis mostly may offer a therapeutic avenue for related disorders. However, a number of cancer cells exhibit heightened vulnerability to ferroptosis, suggesting its potential as an anticancer strategy. Ferroptosis has been closely implicated in several cancer-associated signaling pathways. A study on the interplay between energy stress and ferroptosis has revealed that energy stress can inhibit ferroptosis through AMP-activated protein kinase pathway (36). Furthermore, lactate produced by cancer cells under energy stress may inhibit ferroapoptosis of tumor cells and promote their metastatic spread (37). The phosphoinositide 3-kinase (PI3K)-protein kinase B (AKT)-mammalian target of rapamycin (mTOR) signaling axis has also been shown to shield cancer cells from oxidative stress and ferroptosis through sterol regulatory element-binding protein 1/stearoyl-CoA desaturase 1-mediated lipid synthesis (38).

In addition, the regulation of ferroptosis is also related to cell density (39). Specifically, E-cadherin, a key regulator of epithelial cell-cell adhesion, is positively associated with cell density and functions upstream to repress Yes-associated protein activity in the nucleus (40,41). Components of the Hippo pathway, directly involved in this regulatory network, are frequently mutated in cancer. Secondly, a variety of tumor suppressants, including p53, have been shown to increase the sensitivity to ferroptosis. Specifically, p53 has been shown to enhance ferroptosis by inhibiting the transcription of the systemic x_c^--subunit SLC7A11 (42). Conversely, p53 has also been reported to inhibit ferroptosis in cancer cells under cysteine deprivation by regulating the transcriptional target cyclin-dependent kinase inhibitor 1A and limiting erastin-induced ferroptosis by blocking dipeptidyl peptidase-4 activity in a transcription-independent manner (43,44). Therefore, the interaction between these tumor suppressors and ferroptosis appears to be influenced by a multitude of complex factors. Finally, some chemotherapeutic agents and targeted agents, such as cisplatin and sorafenib, have previously been shown to be able to achieve antitumor effects by inducing ferroptosis (45,46).

At present, cancer management research targeting ferroptosis has achieved breakthroughs in a number of aspects (Fig. 1). First, the identification of ferroptosis-related biomarkers is one of the promising strategies in cancer management (47,48). Secondly, in addition to being transformed in chemoradiotherapy and immunotherapy, therapeutic strategies to induce ferroptosis have also been applied in the emerging field of nanotherapy (49). Additionally, some external factors that can lead to the dysregulation of ferroptosis are also worthy of attention. It has been documented that some infectious pathogens such as *H. pylori* can cause dysregulation of ferroptosis (50). Furthermore, N-3 PUFA peroxidation has been shown to selectively induce ferroptosis in cancer cells. Consequently, N-3 long-chain PUFA-rich foods may be a dietary strategy for patients with cancer (51). In general, targeting ferroptosis is a promising strategy for cancer treatment in the future.

4. *H. pylori* can cause dysregulation of PCD including ferroptosis

Autophagy and apoptosis represent the most prominent forms of PCD in GC, with their dysregulation being closely linked to specific virulence factors of *H. pylori* infection (52,53). Vacuolar cell toxin (VacA), a key virulence factor, induces autophagic cell death through endoplasmic reticulum (ER) stress in gastric epithelial cells (54), while simultaneously promoting apoptosis via the p38/MAPK pathway-mediated downregulation of TNF receptor-associated protein 1 (55). Another critical virulence determinant, cytotoxin-associated gene A (CagA), triggers mitochondrial membrane depolarization by elevating hydrogen peroxide (H_2O_2) levels through spermine oxidase activation, subsequently initiating caspase-dependent apoptosis (56). The oxidative stress induced by *H. pylori* infection, characterized by excessive production of ROS and reactive nitrogen species (RNS) from neutrophils, leads to DNA damage (57,58), which may be mitigated through apoptosis induction to prevent oncogenic mutations (59). The mitochondrial apoptotic pathway is further regulated by *H. pylori* through modulation of the B-cell lymphoma-2 (Bcl-2)-associated X/Bcl-2 ratio by outer inflammatory protein A and VacA (60,61).

Notably, *H. pylori* exhibits bidirectional regulation of apoptosis, as evidenced by its ability to attenuate caspase-8-dependent apoptosis through the type IV secretion system-mediated formation of pAbl^{T735} (62). Beyond autophagy and apoptosis, emerging evidence implicates other PCD pathways, including pyroptosis, necroptosis and ferroptosis, in *H. pylori*-associated pathogenesis (Fig. 2) (63-65).

Accumulating evidence indicates that bacterial infection can promote ferroptosis following tissue damage. Mycobacterium tuberculosis (Mtb), for instance, secretes protein tyrosine phosphatase A, which inhibits GPX4 expression, thereby inducing ferroptosis and enhancing Mtb pathogenicity and transmission (66). Similarly, *Pseudomonas aeruginosa* utilizes host polyunsaturated phosphatidylethanolamine to induce lipid peroxidation and ferroptosis in bronchial epithelial cells (67). *H. pylori* infection elicits a robust inflammatory response in the gastric mucosa, leading to the generation of ROS and RNS, which in turn facilitates lipid peroxidation (68). In *H. pylori* infection, the release of virulence factors also affects ferroptosis (Fig. 3). Inhibition of GPX4 by RSL3 renders cells unable to eliminate accumulated lipid hydroperoxides, ultimately leading to ferroptosis. A study has corroborated that phosphorylase kinase G2 promotes RSL3-induced ferroptosis in GC cells by enhancing arachidonate 5-lipoxygenase expression in

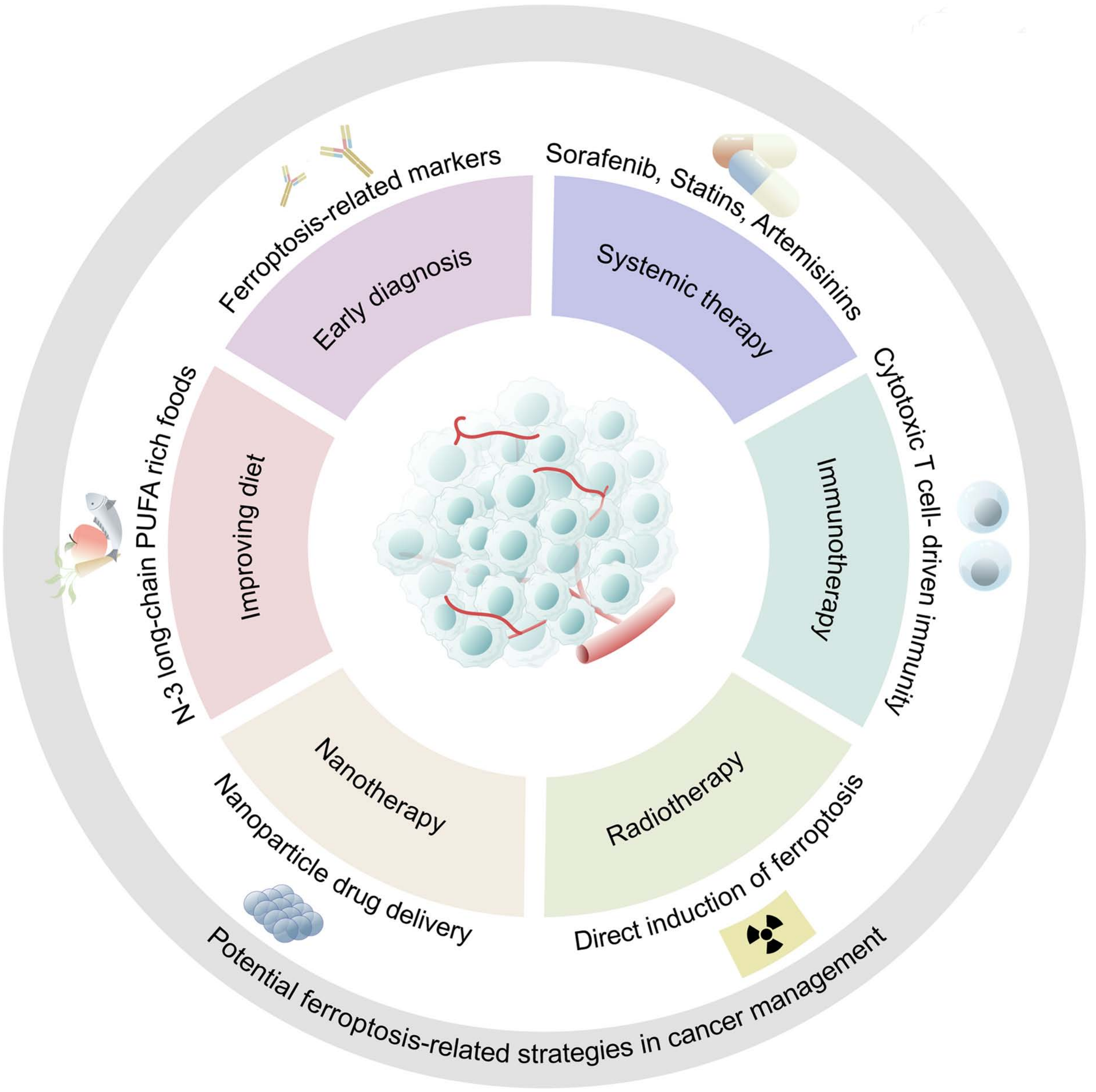

Figure 1. Potential ferroptosis-related strategies in cancer management. PUFA, polyunsaturated fatty acid.

CagA-positive *H. pylori* infections, but the mechanism of action of CagA in this process requires further investigation (50). Another study clarified that CagA could promote the synthesis of polyunsaturated ether phospholipids through the MEK/ERK/serum response factor pathway, leading to the susceptibility to ferroptosis (69). An investigation into the iron toxicity-associated gene tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein epsilon *(YWHAE)* demonstrated significantly elevated YWHAE expression levels in *H. pylori*-induced GC, which was positively correlated with ferroptosis in GC (70).

Beyond CagA and YWHA, *H. pylori* outer membrane vesicles (OMVs) also contribute to aberrant ferroptosis regulation. *H. pylori* and its OMVs modulate ferroptosis through three primary mechanisms: i) Reducing cellular iron uptake and lipid peroxide production by downregulating transferrin receptor/transferrin receptor protein 1 (TFRC/TFR1) and the endosomal metal reductase six-transmembrane epithelial antigen of the prostate 3; ii) upregulating expression of the cystine/glutamate antiporter subunit SLC3A2 and GSH synthesis genes; and iii) inhibiting ferroptosis by decreasing substrate availability for arachidonic acid-associated lipid peroxidation through downregulation of lysophosphatidylcholine acyltransferase 3 (71). Concurrently, *H. pylori* can epigenetically influence cell ferroptosis, such as by triggering demethylation and upregulating glucocerebrosidase, thereby inhibiting ferroptosis in GC cells (72).

Notably, ferroptosis interacts with other types of PCD in the process of GC induced by *H. pylori* infection. Ferroptosis-driven lipid peroxidation activates pro-apoptotic signals, while apoptosis-related proteins (e.g., caspases) may conversely enhance ferroptosis by degrading inhibitors such as GPX4 (42,73). Autophagy further promotes ferroptosis sensitivity through ferritin degradation (releasing free iron) or depletion of antioxidants such as GPX4 (74,75). Additionally, ferroptosis-induced oxidative stress in the

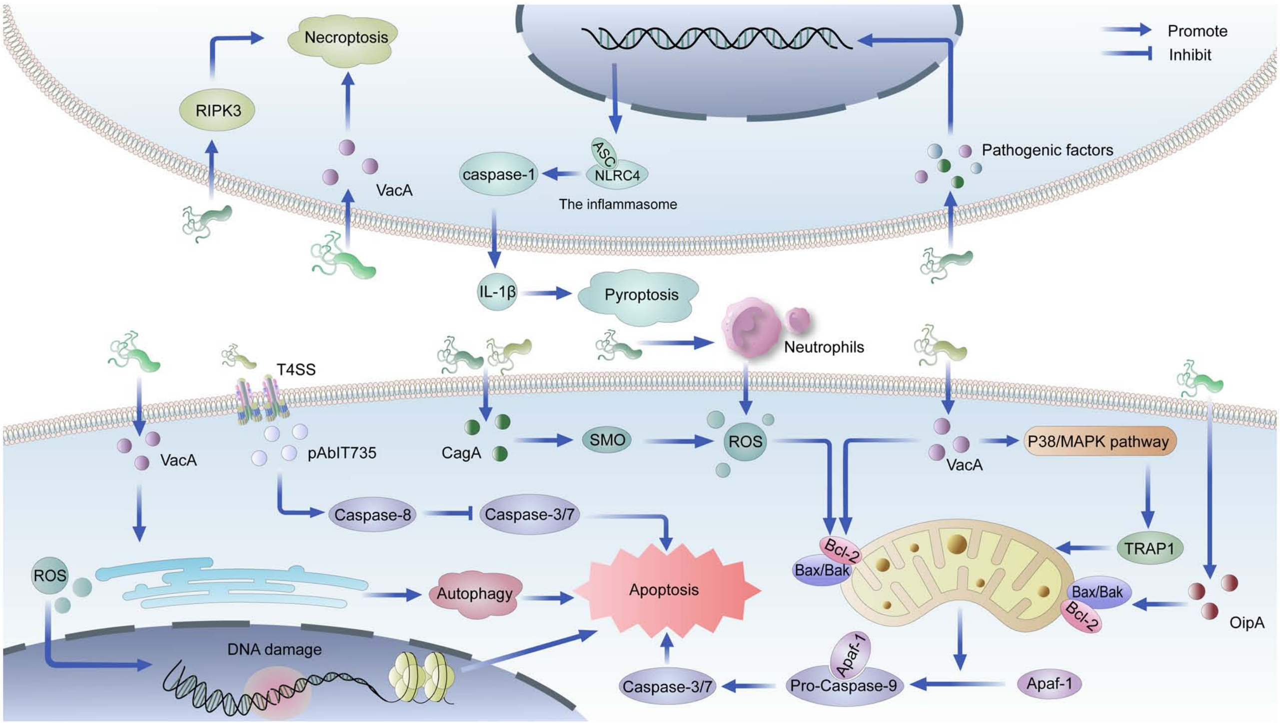

Figure 2. *H. pylori* can cause the dysregulation of apoptosis, autophagy, pyroptosis and necroptosis through various pathogenic virulence factors. VacA, vacuolar cell toxin; CagA, cytotoxin-associated gene A; OipA, outer inflammatory protein A; TRAP1, tumor necrosis factor receptor-associated protein 1; RNS, reactive nitrogen species; Bcl-2, B-cell lymphoma-2; Bax, Bcl-2-associated X; T4SS, type IV secretion system; RIPK3, receptor interacting Serine/Threonine kinase 3; ASC, apoptosis-associated speck-like protein containing a CARD; NLRC4, NLR family CARD domain-containing protein 4; SMO, spermine oxidase; Apaf-1, apoptotic protease activating factor-1.

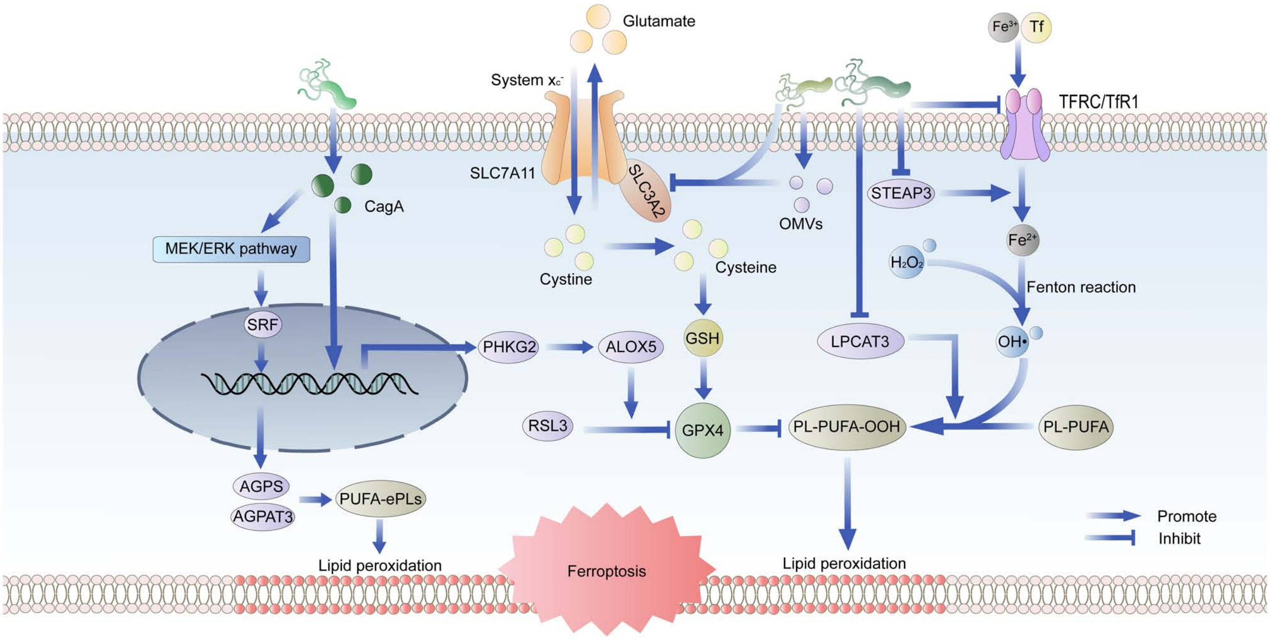

Figure 3. *H. pylori* can bi-directively regulate ferroptosis through the virulence factors CagA and OMVs. PHKG2, phosphorylase kinase G2; ALOX5, arachidonate 5-lipoxygenase; OMVs, outer membrane vesicles; TFRC/TFR1, transferrin receptor/transferrin receptor protein 1; LPCAT3, lysophosphatidylcholine acyltransferase 3; GBA1, glucocerebrosidase; STEAP3, six-transmembrane epithelial antigen of the prostate 3; SRF, serum response factor; AGPS, alkylglycerone phosphate synthase; AGPAT3, 1-acylglycerol-3-phosphate O-acyltransferase 3; PUFA-ePLs, polyunsaturated ether phospholipids.

GC microenvironment activates the nucleotide-binding oligomerization domain-like receptor protein 3 inflammasome, triggering IL-1β release and pyroptosis (76). These findings indicate that *H. pylori* infection induces dysregulation of multiple PCD pathways, which functionally interact during tumorigenesis. Critically, *H. pylori*-driven PCD

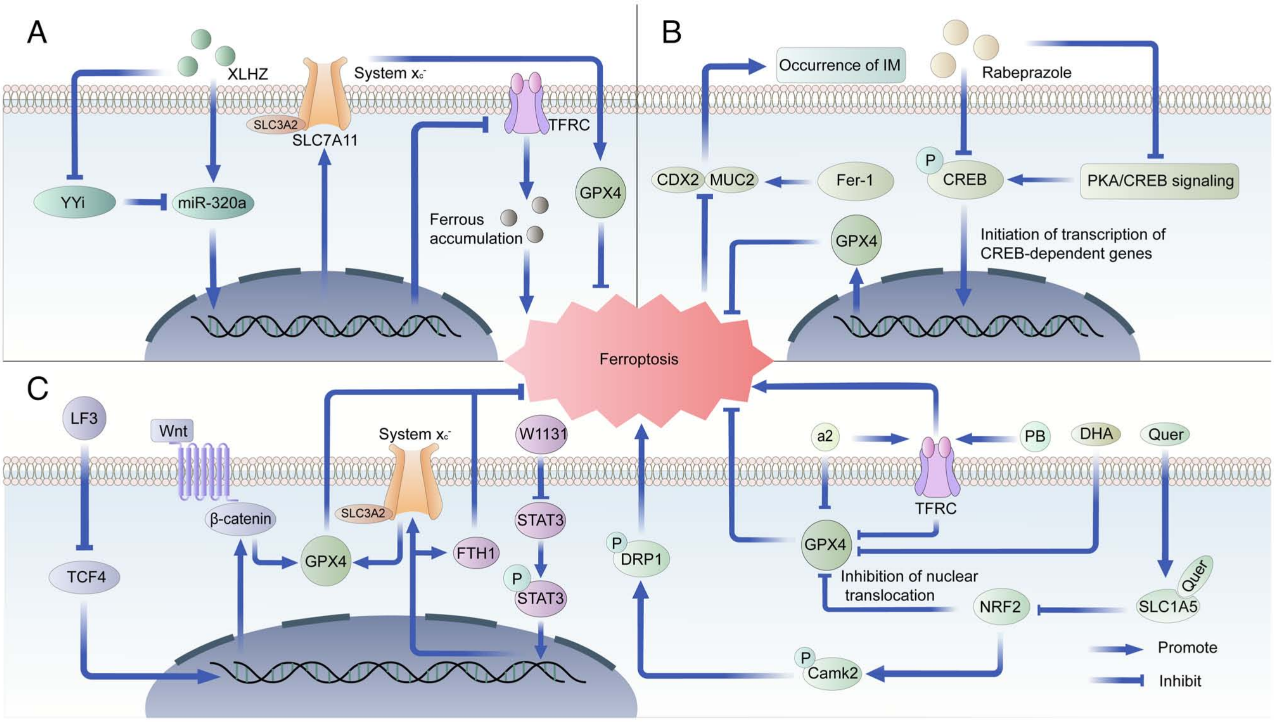

Figure 4. Several compounds have been reported to be able to exert therapeutic effects in the stages of CAG, IM and GC. (A) XLHZ plays a therapeutic role in CAG by inhibiting ferroptosis. (B) Ranolrazole inhibits IM progression by promoting ferroptosis. (C) Compounds a2, PB, Quer and DHA exert antitumor effects by promoting ferroptosis, whereas LF3 and W1131 increase chemotherapy sensitivity by promoting ferroptosis. XLHZ, Xianglianhuazhuo; YY1, Yin Yang 1; PB, polyphyllin B; Quer, quercetin; FTH1, ferritin heavy chain 1; CDX2, caudal type homeobox transcription factor 2; MUC2, mucin 2; Fer-1, ferrostatin-1; CREB, cAMP-response element binding protein; TCF4, transcription factor 4; NRF2, nuclear factor erythroid 2-related factor 2; Camk2, calcium/calmodulin-dependent protein kinase 2; DRP1, dynamin-related protein 1.

dysregulation-including aberrant ferroptosis-significantly accelerates Correa's cascade of GC, underscoring *H. pylori* eradication as a foundational strategy for GC prevention (77). Nevertheless, chronic inflammatory responses and pathological progression frequently persist during intermediate to advanced precancerous stages despite successful *H. pylori* eradication therapy (78,79). This persistent pathological progression highlights the potential therapeutic value of strategies targeting various types of PCD, including ferroptosis, as adjunctive interventions to complement conventional eradication therapy in PLGC.

5. Ferroptosis in PLGC and GC: Corresponding mechanisms and prospects

Studies on the regulation of ferroptosis not only provide a new perspective on the pathogenesis of *H. pylori* but also provide a direction for exploring new therapeutic targets in Correa's cascade. The systematic review of ferroptosis in the three key stages of chronic atrophic gastritis (CAG), intestinal metaplasia (IM) and GC is conducive to bringing new breakthroughs in the prevention and treatment of GC.

6. Targeting ferroptosis in PLGC: A potential strategy to intervene in Correa's cascade

CAG is the initial stage in the 'inflammation-cancer transformation model'. Knowing how to treat CAG timely and accurately, and block or reverse the development of CAG to GC is crucial for the prevention of GC. Conventional therapeutic approaches for CAG primarily encompass *H. pylori* eradication therapy, gastric mucosal protection and gastrointestinal function enhancement. However, clinical evidence indicates that these interventions demonstrate limited efficacy in reversing gastric mucosal damage, particularly in patients presenting with extensive or moderate-to-severe mucosal atrophy (80). Notably, accumulating evidence from multiple studies has demonstrated that pharmacological inhibition of ferroptosis can directly modulate the core pathological processes of CAG through dual mechanisms: Attenuating gastric mucosal injury and suppressing inflammatory responses (81,82).

A number of studies have focused on differentially expressed genes associated with ferroptosis in CAG (83,84). Mechanistically, previous clinical studies have revealed that patients with CAG frequently exhibit abnormal iron metabolism or iron deficiency anemia, which is associated with hepcidin, an antimicrobial polypeptide secreted by gastric parietal cells (Fig. 4) (85,86). Hepcidin inhibits iron efflux by directly binding to ferroportin to cause conformational change and trigger endocytosis and lysosomal degradation, which plays an important role in regulating iron balance (87). Furthermore, CAG has been shown to mediate hepcidin expression via the IL-6/signal transducer and activator of transcription 3 (STAT3) signaling pathway, with increased IL-6 expression being intimately linked to *H. pylori* infection (84,88). Elevated hepcidin levels decrease the expression of divalent metal transporter 1 and ferroportin 1 proteins, inhibiting duodenal iron absorption and leading to disrupted iron metabolism and gastric cell ferroptosis (84).

The current clinical drug mechanisms for the treatment of CAG mainly include regulation of gastric acid secretion, eradication of *H. pylori*, protection of gastric mucosa and inhibition of inflammatory factors (89). However, due to the limitations and adverse effects associated with the long-term use of conventional medications, recent studies have explored the therapeutic efficacy and underlying mechanisms of traditional Chinese medicine (TCM) drugs and natural molecular compounds in CAG, particularly focusing on their modulation of inflammation and ferroptosis (81,82). One notable study demonstrated that Xianglianhuazhuo can regulate the Yin Yang 1/miR-320a/TFRC axis, effectively inhibiting gastric epithelial cell proliferation, promoting apoptosis, suppressing ferroptosis, ameliorating gastric mucosa pathology and alleviating CAG symptoms (81). These beneficial effects are postulated to be related to the anti-inflammatory, anticancer and antioxidant properties of components like berberine (Fig. 4) (81). Similar studies have also reported the potential value of Galangin targeting ferroptosis in the treatment of CAG (82). Therefore, the therapeutic strategy of inhibiting ferroptosis in CAG through low-toxicity TCM and natural molecular compounds has potential.

The most controversial issue regarding the stage of IM is whether its progression can be reversed by therapeutic strategies such as eradication of *H. pylori* (90,91). A previous study has revealed an important role of apoptosis in the transformation of IM to GC (92). However, to the best of our knowledge, there are relatively few studies related to other types of PCD in IM. Notably, several studies have identified ferroptosis-related genes in IM as potential biomarkers for IM diagnosis and novel therapeutic targets such as GOT1, ACSF2, SESN2, HMOX1 and FTL (93-95). Furthermore, a recent study reported that ranolrazole could attenuate IM by inhibiting GPX4 expression to enhance ferroptosis (Fig. 4) (96). However, in general, the regulatory mechanism of ferroptosis in IM remains to be elucidated.

Although progress has been made in exploring ferroptosis as a therapeutic target for PLGC, significant limitations remain. First, systematic studies are lacking to definitively establish whether dysregulated ferroptosis constitutes a key mechanism driving lesion progression or regression. Due to the well-documented relationship between ferroptosis and chronic inflammation, research focusing on the inflammation-cancer transformation axis may offer an insight in addressing this fundamental question (97,98). Secondly, suitable experimental models are still deficient for elucidating the temporal dynamics and spatial heterogeneity of ferroptosis regulation within PLGC, particularly in IM. Emerging technologies such as single-cell sequencing and spatial transcriptomics, alongside models such as spasmolytic polypeptide expressing metaplasia, hold promise for providing novel insights and guiding future experimental designs (99,100). Finally, the related research on targeting ferroptosis in PLGC is still at the basic theoretical stage and lacks evidence to achieve clinical translation. The establishment of gastric organoids derived from CAG/IM patient tissues may be a key model to highly mimic the *in vivo* environment in the future (101).

7. Targeting ferroptosis in GC: A promising strategy to overcome challenges

At present, there are notable issues in the first-line conventional treatment regimens and experimental novel treatment regimens for GC. Current therapeutic strategies for GC face significant challenges in both conventional first-line treatments and emerging experimental regimens. Persistent issues including acquired drug resistance, restricted patient eligibility for targeted therapies and dose-limiting toxicities associated with combination therapies necessitate urgent optimization (102,103). Furthermore, the clinical application of innovative approaches such as CAR-T cell therapy is constrained by suboptimal efficacy and the absence of well-defined molecular targets, which substantially impedes the advancement of novel treatment paradigms (104,105).

Emerging evidence has demonstrated that oxidative stress plays a pivotal role in the initial phases of inflammation-associated carcinogenesis. Mechanistic studies have revealed that reduced iron uptake and diminished intracellular iron reserves may significantly contribute to GC pathogenesis. These findings provide a compelling rationale for developing targeted therapeutic strategies against GC through selective induction of ferroptosis in malignant cells (Table I) (106-108). The systemic x_c^--GSH-GPX4 pathway plays a pivotal role in ferroptosis inhibition, thereby promoting the development of GC. Specifically, the transcription factor megakaryocytic leukemia factor 1 binds to CArG box sites in the promoters of SLC3A2 and SLC7A11, enhancing their transcription and subsequently increasing GSH levels, which inhibits ferroptosis in GC cells (109). Glutamate-cysteine ligase, the rate-limiting enzyme for GSH synthesis, is crucial for this process (110). Furthermore, Aldo-keto reductase 1 member B1 participates in lipid metabolism regulation by removing the aldehyde group from GSH. It specifically modulates GPX4 by decreasing ROS accumulation and lipid peroxidation, lowering intracellular ferrous ion and malondialdehyde levels, and increasing GSH expression, thereby inhibiting RSL3-induced ferroptosis in GC.

Previous evidence has increasingly highlighted the pivotal role of ferroptosis in the metastasis and invasion of GC. Epithelial-mesenchymal transition (EMT) is well recognized as a critical mechanism driving tumor metastasis. Specifically, 2,2'-dipyridinone hydrazide dithiocarbamate butyrate demonstrates anticancer efficacy in gastric and esophageal cancer cells. It inhibits transforming growth factor-β1 in GC cells by inducing ferritinophagy and activating the p53 and prolyl hydroxylase domain protein 2/hypoxia-inducible factor 1α (HIF-1α) pathways, ultimately suppressing EMT (111,112). Additionally, its homolog, 2,2'-dipyridyl ketone hydrazine-thiocarbamate, also exhibits inhibitory effects on EMT in GC cells through the induction of ferritinophagy and activation of the p53/AKT/mTOR pathway (113). Furthermore, ferroptosis triggered by ferritin autophagy, coupled with the generation of excessive ROS, further mediates the suppression of EMT (112). Moreover, A previous study revealed that the cystatin inhibitor, cystatin SN, regulates GPX4 protein stability by recruiting OTU domain-containing ubiquitin aldehyde-binding protein 1 to inhibit ferroptosis, thereby promoting GC metastasis (114). Collectively, these findings suggest that targets associated with

Table I. Promising strategies for gastric cancer through induction of ferroptosis and relevant mechanisms.

Clinical dilemma	Potential strategies	Cores of strategies	Mechanisms involved	Clinical trial phase	(Refs.)
Intolerance to conventional treatment regimens	Novel ferroptosis-inducing compounds can be used in combination to reduce the dependence on highly toxic drugs	A novel compound: a2	Compound a2 reduced GPX4 expression and caused divalent iron accumulation through the autophagy pathway, eventually inducing ferroptosis.	Pre-clinical trials	(117)
		A novel GPX4 inhibitor: PB	PB can induce ferroptosis and inhibit tumor growth by regulating the expression of GPX4, TFR1, NOCA4 and FTH1 *in vivo*.	Pre-clinical trials	(118)
		Quer	Quer can induce lipid peroxidation and ferroptosis in GC cells by targeting SLC1A5 and regulating the p-CAMK2/p-DRP1 and NRF2/GPX4 signaling pathways.	Pre-clinical trials	(119)
		DHA	The combined treatment of DHA and cisplatin induced GC cell death by inhibiting GPX4.	Pre-clinical trials	(120)
Resistance to chemotherapy drugs	Enhancing chemosensitivity by induction of ferroptosis.	Sorafenib	Sorafenib is an important inducer of ferroptosis	Capecitabine plus cisplatin combined with sorafenib has entered phase II clinical trials.	(131,132)
		Sulfasalazine	Sulfasalazine was able to induce ferroptosis by inhibiting x_c^-system.	Sulfasalazine combined with cisplatin has entered phase I clinical trials.	(133,134)
		A 4-thioureido-benzenesulfonamide derivative: LF3	LF3 can affect the interaction between β-catenin and TCF4 and promotes tumor cell ferroptosis.	Pre-clinical trials	(135)
		NPR1	NPR1 can reduce ubiquitin-mediated PARL degradation and ultimately inhibit mitogen-dependent ferroptosis.	Pre-clinical trials	(136)
		ATF3	ATF3 may induce ferroptosis in GC cells by blocking NRF2/Keap1/xCT signal transduction.	Pre-clinical trials	(137)
		BAP31	BAP31 gene knockdown can increase the level of membrane lipid peroxidation and promoted cell ferroptosis.	Pre-clinical trials	(138)

Table I. Continued.

Clinical dilemma	Potential strategies	Cores of strategies	Mechanisms involved	Clinical trial phase	(Refs.)
		MKL-1	MKL-1 can reduce the synthesis of GSH, thereby reducing the level of intracellular lipid peroxidation and ultimately inhibiting the occurrence of ferroptosis.	Pre-clinical trials	(109)
		A selective STAT3 inhibitor: W1131	Gene inhibition of STAT3 activity can lead to lipid peroxidation and Fe^{2+} accumulation in GC cells, and eventually trigger ferroptosis.	Pre-clinical trials	(121)
		A novel lncRNA DACT3-AS1	DACT3-AS1 promotes ferroptosis by targeting miR-181a-5p/SIRT1 axis, and ultimately inhibits tumor cell proliferation, migration and invasion.	Pre-clinical trials	(139)
Resistance to targeted drugs	Enhancing the efficacy of targeted drugs targeting ferroptosis	HSPH1 and ATF2	Knockdown of HSPH1 partially reversed the effect of ATF2 overexpression on sorafenib-induced ferroptosis in GC.	Pre-clinical trials	(132)
Immune escape of GC cells limits efficacy	Targeting ferroptosis combined with immunotherapy	CAR T-cell therapy and ferroptosis-resensitizing treatments	The antitumor effect of cytotoxic T cells is dysregulated by inhibiting the x_c^--system due to the enhanced ferroptosis defense of tumor cells.	Pre-clinical trials	(126)
		FSTL1 and NK cells	FSTL1 secreted by CAFs up-regulates the expression of NCOA4 in NK cells through the DIP2A-P38 pathway, and finally mediates ferroptosis of NK cells.	Pre-clinical trials	(140)
Lack of innovative solutions for precise treatment	Targeting induction of ferroptosis to treat GC by some new materials.	Atranorin complexes comprising SPION	The constructed Atranorin@SPION can induce oxidative stress damage and ferroptosis by inhibiting the expression of key molecules in x_c^-/GPX4 pathway.	Pre-clinical trials	(122)

PB, polyphyllin B; Quer, quercetin; DHA, dihydroartemisinin; NOCA4, nuclear receptor coactivator 4; TCF4, transcription factor 4; NPR1, natriuretic peptide receptor A; ATF2, activation transcription factor 2; ATF3, activation transcription factor 3; BAP31, B-cell receptor-associated protein 31; MKL-1, megakaryocytic leukemia factor 1; DACT3-AS1, disheveled binding antagonist of beta catenin 3 antisense 1; SIRT1, sirtuin 1; HSPH1, heat shock protein family H (Hsp110) member 1; FSTL1, follistatin-like protein 1; SPION, superparamagnetic iron oxide nanoparticles; CAMK2, calcium/calmodulin-dependent protein kinase 2; DRP1, dynamin-related protein 1; p-, phosphorylated; NRF2, nuclear factor erythroid 2-related factor 2; GPX4, glutathione peroxidase 4; TFR1, transferrin receptor protein 1; FTH1, ferritin heavy chain 1; GC, gastric cancer; SLC1A5, solute carrier family 1 member 5; x_c^-, system x_c^-; PARL, presenilin-associated rhomboid-like; Keap1, Kelch-like ECH-associated protein 1; xCT, light chain; GSH, glutathione; STAT3, signal transducer and activator of transcription 3; miR, microRNA; CAF, cancer-associated fibroblast; NK, natural killer cells; DIP2A, disco-interacting protein 2 homolog A; Atranorin@SPION, Atranorin complexes comprising superparamagnetic iron oxide nanoparticles.

Table II. Several ferroptosis-related prognostic markers in GC.

Name of markers	Corresponding prognosis	Relevant mechanisms	(Refs.)
GPX4	High GPX4 expression is associated with poor prognosis	Overexpression of GPX4 promoted GC cell proliferation, migration, invasion and EMT.	(127,141)
SLC2A3	High SLC2A3 expression is associated with poor prognosis.	The functions of SLC2A3 related to ferroptosis and transmembrane glucose transport are affected by the regulation of miRNAs.	(128,142)
ATF2, ATF3	High expression of ATF2 and low expression of ATF3 are associated with poor prognosis.	Silencing ATF2 expression can inhibit the malignant phenotype of GC cells and promote sorafenib-induced ferroptosis. ATF3 alleviates cisplatin resistance in GC by inducing ferroptosis.	(132,137)
MGST1	High MGST1 expression is associated with poor prognosis.	MGST1 inhibits ferroptosis by enhancing Wnt/β-Catenin pathway through AKT regulation in GC.	(143)
SCD1	High SCD1 expression is associated with poor prognosis.	SCD1 can accelerate the migration and growth of GC cells.	(144)
PLIN2	High PLIN2 expression is associated with poor prognosis.	PLIN2 inhibits ferroptosis by regulating ferroptosis related genes, thereby affecting the proliferation and apoptosis of GC cells.	(145)
FSP1, CISD1	High expression of FSP1 and CISD1 is associated with poor prognosis.	FSP1 and CISD1 may have a specific part in the immune infiltration of GC.	(127,146)
AKR1B1	High AKR1B1 expression is associated with poor prognosis.	AKR1B1 can promote the proliferation and invasion of GC cells.	(147)
HTR2B	High HTR2B expression is associated with poor prognosis.	HTR2B activity stimulates GC cell survival by regulating the PI3K/Akt/mTOR signaling pathway.	(148)
BAP31	High BAP31 expression is associated with poor prognosis.	BAP31 upregulation facilitates GC cell growth and promotes G^1/S transition. It also regulates cell proliferation and ferroptosis by directly binding to VDAC1.	(138)
CTH, MAP1LC3B	Low expression of CTH and high expression of MAP1LC3B are associated with poor prognosis.	CTH, MAP1LC3B and monocyte-macrophage dynamics are critical determinants of the poor prognosis associated with GC.	(149)
CDH19	High CDH19 expression is associated with poor prognosis.	CDH19 promoted the migration and proliferation of GC cells.	(150)
NFS1	High NFS1 expression is associated with poor prognosis.	NFS1 expression is highly associated with tumor invasion depth, lymph node metastasis and tumor stage.	(151,152)
AKR1C2	High AKR1C2 expression is associated with a good prognosis.	AKR1C2 expression was significantly associated with the immune response in GC.	(153)

MGST1, microsomal glutathione transferase 1; PLIN2, perilipin 2; CISD1, iron sulfur domain 1; HTR2B, 5-hydroxytryptamine receptor 2B; CTH, cystathionine gamma-lyase; MAP1LC3B, microtubule associated protein 1 light chain 3 beta; CDH19, cadherin 19; NFS1, cysteine desulfurase; AKR1C2, aldo-keto reductases family 1 member C2; GPX4, glutathione peroxidase 4; GC, gastric cancer; EMT, epithelial-mesenchymal transition; miRNA, microRNA; SLC2A3, solute carrier family 2 member 3; ATF, activation transcription factor; SCD1, stearoyl-CoA desaturase 1; FSP1, ferroptosis suppressor protein 1; AKR1B1, aldo-keto reductase 1 member B1; BAP31, B-cell receptor-associated protein 31; VDAC1, voltage dependent anion channel 1.

ferroptosis may offer promising avenues for inhibiting tumor metastasis and progression.

Epigenetic modulation of ferroptosis also constitutes a pivotal mechanism in the development and progression of GC. A recent study has demonstrated that mesenchymal GC cells exhibit upregulated expression of very long chain fatty acid elongation protein 5 and fatty acid desaturase 1, sensitizing them to ferroptosis. Conversely, intestinal-type GC cells display resistance to ferroptosis due to the silencing of these enzymes via DNA methylation (115). Additionally, non-coding RNAs are linked to ferroptosis regulation. Furthermore, research on long non-coding RNA (lncRNA) PMAN has revealed that HIF-1α inhibits ferroptosis in peritoneal metastasis of GC by upregulating lncRNA-PMAN, which is highly expressed in peritoneal metastases and is associated with poor prognosis (116).

The induction of ferroptosis as a novel strategy for the treatment of GC has made some achievements in recent years. On the one hand, emerging studies indicate that novel molecular compounds exert antitumor effects in GC through ferroptosis induction, offering a promising therapeutic alternative for patients with compromised tolerance to conventional chemoradiotherapy-associated systemic toxicity (Fig. 4) (117-120). On the other hand, inducing ferroptosis to improve the chemoresistance of GC has been shown to be an indirect way to inhibit the development of GC. Related studies have further explored and developed substances that can regulate ferroptosis-related genes (121,122) (Fig. 4). Ferroptosis negative regulation-related genes (GPX4, SLC7A11 and ferritin heavy chain 1) and STAT3 have been reported to be upregulated in 5-FU-resistant cells and xenografts (121). W1131 can alleviate chemoresistance in GC by inducing ferroptosis as a novel STAT3 inhibitor, which makes it combine with chemotherapeutic drugs for the treatment of chemotherapy-resistant GC (121). In addition to the aforementioned strategies, there are some innovative studies that provide novel perspectives for the treatment of GC. One study has proposed that atanorin driven by nanomaterials superparamagnetic iron oxide nanoparticles can be used to induce ferroptosis of GC stem cells (122).

In summary, ferroptosis-targeting strategies hold significant therapeutic promise for GC. However, several key challenges require further elucidation. The current mechanistic understanding remains insufficient. Critical unresolved questions include the differential regulation of ferroptosis across molecular GC subtypes and the influence of the tumor microenvironment on ferroptosis sensitivity (123,124). Future investigations should prioritize applying single-cell multi-omics analyses and GC organoid/immune cell co-culture models to address these gaps (124). In addition, the clinical translation of ferroptosis induction faces substantial limitations. Specifically, existing ferroptosis inducers lack tumor-specific targeting, and the synergistic potential of ferroptosis induction combined with immunotherapy or targeted therapy lacks robust theoretical and experimental validation. Consequently, future research efforts should focus on integrating advanced drug delivery technologies (e.g., responsive nanocarriers) and rigorously exploring novel combination therapeutic strategies (125,126).

8. Ferroptosis-related biomarkers: Emerging strategies in the management of GC

The high diagnosis rate of advanced GC indicates that the prevention and treatment of GC remain to be improved. The prognostic markers related to ferroptosis screened by relevant studies have important clinical significance in guiding the treatment of GC (Table II). A study from Japan investigated the relationship between GPX4, FSP1 and 4-HNE in tissues of patients with GC and their prognosis (127). In this study, by combining 163 pT3 or pT4 GC tissue samples and OS analysis, it was found that patients with high GPX4 expression and low 4-HNE accumulation had a poor prognosis ($P=0.023$), while patients with low FSP1 expression and high 4-HNE accumulation had an improved prognosis ($P=0.033$) (127). The results also suggest that GPX4 and FSP1 may be potential therapeutic targets for patients with GC with poor prognosis. SLC2A3 is another ferroptosis marker. Univariate and multivariate Cox regression analysis revealed that high expression of SLC2A3 was associated with poor prognosis of patients with GC. Functional enrichment analysis showed that SLC2A3 was related to cytokine-cytokine receptor interaction, epithelial-mesenchymal transition, T cell receptor signaling pathway, B cell receptor signaling pathway, immune checkpoints and tumor microenvironment regulation. SLC2A3 and related miRNAs are potential prognostic biomarkers and therapeutics (128).

In addition, lncRNAs can regulate ferroptosis on the epigenetic mechanism of GC, and the use of a variety of lncRNAs to construct GC risk models has shown great advantages. A relative study developed a novel ferroptosis-related prognostic model incorporating 2 mRNAs and 15 lncRNAs to predict outcomes in patients with GC. The model combined clinical features and key factors, showed good predictive ability, and performed well in external patient data validation, which is expected to improve the clinical treatment effect of patients with GC (129). Another study identified 26 ferroptosis-related lncRNAs with independent prognostic value and constructed a risk score model based on four high-risk lncRNAs associated with poor prognosis of gastric adenocarcinoma (130).

9. Conclusion

Ferroptosis, a newly identified form of regulated cell death, plays a key role in numerous physiological and pathological processes. While significant progress has been made in elucidating the molecular mechanisms of ferroptosis through basic research, its precise role in diseases-particularly *H. pylori*-associated GC-remains incompletely understood. In the context of limited effective treatments for GC, systematic investigations into ferroptosis dysregulation during *H. pylori* pathogenesis and the identification of ferroptosis-related therapeutic targets within Correa's cascade are critical for developing novel and effective strategies. By integrating multidisciplinary approaches, including systems biology, nanotechnology and computational drug design, innovative drug platforms can be developed to precisely modulate ferroptosis pathways. These advancements could pave the way for novel strategies to halt or even reverse the progression of Correa's cascade. In conclusion, targeting ferroptosis represents a promising strategy with significant potential for the timely intervention of PLGC, as well as the early diagnosis and precision treatment of GC.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

CW wrote the manuscript. MW and CX revised the manuscript. CY and MW contributed to the manuscript equally. All authors have read and approved the final read manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

These authors declare that they have no competing interests.

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