Epigenetic regulation of ferroptosis in gastrointestinal cancers (Review)

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Abstract. Ferroptosis is a type of iron-dependent cell death characterized by excessive lipid peroxidation and may serve as a potential therapeutic target in cancer treatment. While the mechanisms governing ferroptosis continue to be explored and elucidated, an increasing body of research highlights the significant impact of epigenetic modifications on the sensitivity of cancer cells to ferroptosis. Epigenetic processes, such as DNA methylation, histone modifications and non-coding RNAs, have been identified as key regulators that modulate the expression of ferroptosis-related genes. These alterations can either enhance or inhibit the sensitivity of gastrointestinal cancer (GIC) cells to ferroptosis, thereby affecting the fate of GICs. Drugs that target epigenetic markers for advanced-stage cancer have shown promising results in enhancing ferroptosis and inhibiting tumor growth. This review explores the intricate relationship between epigenetic regulation and ferroptosis in GICs. Additionally, the potential of leveraging epigenetic modifications to trigger ferroptosis in GICs is investigated. This review highlights the importance of further research to elucidate the specific mechanisms underlying epigenetic control of ferroptosis and to advance the development of novel therapeutic approaches.

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Contents

1. Introduction

Gastrointestinal cancers (GICs) account for >25% of all new cancer cases worldwide and contribute to more than one-third of cancer-related deaths (1). These cancers primarily include gastric cancer (GC), colorectal cancer (CRC), esophageal squamous cell carcinoma (ESCC), hepatocellular carcinoma (HCC), cholangiocarcinoma (CCA), gallbladder cancer (GBC) and pancreatic cancer. Traditional treatments for GICs, including surgery intervention, radiation therapy, chemotherapy, targeted therapies and immunotherapies, have long been the primary approaches for management (2,3). However, early diagnosis of GICs is challenging and a proportion of patients are diagnosed in the first instance with advanced-stage cancer. For patients diagnosed with advanced-stage cancer, traditional therapies, although essential, often fall short due to the inherent chemoresistance of GIC cells, frequently leading to tumor recurrence and distant metastasis (4), resulting in poor clinical outcomes for patients with advanced GICs (5).

Ferroptosis, a type of regulated cell death (RCD), characterized by excessive lipid peroxidation and iron accumulation,

has gained significant attention in recent years given its critical role in cancer biology (6,7). Unlike apoptosis or necrosis, ferroptosis occurs due to the buildup of toxic lipid peroxides, resulting from impaired cellular antioxidant systems, particularly disruptions in glutathione (GSH) metabolism (6). Research has increasingly linked impaired ferroptosis with cancer progression, suggesting that triggering ferroptosis could be a potential approach for combating tumors, particularly in overcoming therapeutic resistance (8-16).

Epigenetic processes, including DNA methylation, histone modifications and regulatory non-coding (nc)RNAs, profoundly influence gene expression and can affect cell death pathways, including ferroptosis (17-19). In GICs, these modifications may either promote or inhibit ferroptosis, thereby affecting tumor behavior and treatment responsiveness. For instance, epigenetic modifications can regulate genes associated with iron metabolism, antioxidant systems and lipid peroxidation, thereby affecting the susceptibility of GIC cells to ferroptosis.

Understanding the intricate relationship between epigenetic regulation and ferroptosis in GICs could reveal novel therapeutic strategies and targeting epigenetic modifications to induce ferroptosis may serve as a novel approach to suppress tumor progression and overcome resistance to conventional treatments. The present review explores the current understanding of how epigenetic regulation influences ferroptosis in GICs, highlighting its implications for cancer progression, treatment and potential future therapies.

2. Ferroptosis: Mechanisms and implications

The term ferroptosis was coined in 2012 (6), referring to an iron-dependent form of RCD caused by unrestricted lipid peroxidation and subsequent plasma membrane rupture (20). Iron overload and lipid peroxidation serve as critical triggers for oxidative membrane damage in ferroptosis (6). The fundamental process of ferroptosis revolves around maintaining the equilibrium between oxidative stress and cellular antioxidant systems (21). This section delves into the core mechanisms underlying ferroptosis, focusing on three essential aspects: Iron metabolism, lipid metabolism and antioxidant defense (Fig. 1).

Iron metabolism regulates ferroptosis. Iron is an essential nutrient that facilitates cell proliferation and growth (22). Cancer cells often have defects in cell death executioner mechanisms. To enable growth, cancer cells exhibit an increased iron demand compared with normal, non-cancer cells (23). Being a redox-active metal, iron contributes to lipid peroxidation through two primary pathways: Facilitating reactive oxygen species (ROS) generation via the iron-driven Fenton reaction and activating iron-dependent enzymes such as lipoxygenases (20,23,24). Therefore, the regulation of iron influx, efflux, sequestration and metabolism plays a crucial role in determining cellular vulnerability to ferroptosis. Heme oxygenase 1 facilitates the liberation of Fe^{2+} from heme, a key source of intracellular iron, essential for maintaining iron homeostasis (25). Transferrin (TF) transports ferric iron (Fe^{3+}) through the bloodstream and enables its cellular uptake by binding to TF receptors (TFR) on the cell membrane (Fig. 1). It has been demonstrated that iron uptake mediated by serotransferrin or lactotransferrin promotes ferroptosis (26,27). Ferroportin (FPN), the sole identified iron efflux transporter, facilitates dietary iron absorption by transferring ferrous iron (Fe^{2+}) across the basolateral membrane of intestinal epithelial cells (28-30). When serum iron levels are high, liver-secreted hepcidin (HAMP) reduces dietary iron absorption and decreases circulating iron levels by inducing the ubiquitination, internalization and degradation of FPN (31-34). Growing evidence has shown that ferroptosis can be regulated by targeting FPN in cancer cells (35,36).

Ferritin, a protein complex responsible for storing iron, consists of two components: Ferritin heavy chain 1 (FTH1) and ferritin light chain (FTL). A specialized form of autophagy, known as ferritinophagy, enhances the susceptibility of a cell to ferroptosis by increasing the intracellular bioavailability of Fe^{2+} (37-40). More specifically, ferritin is identified by nuclear receptor coactivator 4 (NCOA4), which directs FTH1 to autophagosomes for lysosomal breakdown, resulting in the liberation of free iron (Fig. 1) (39). Reducing lysosomal activity (41) or downregulating NCOA4 expression has been demonstrated to block ferroptosis effectively (37,38). For instance, a relatively recently discovered ferroptosis inhibitor called Compound 9a can directly bind to recombinant NCOA4 protein. This binding disrupts the NCOA4-FTH1 interaction, reducing the intracellular bioavailability of Fe^{2+} and ultimately blocking ferroptosis (42). As a key regulator of ferroptosis, NCOA4 represents a potential target for therapeutic intervention. Of note, ferritin and FPN can be simultaneously upregulated by ATM, thereby rescuing ferroptosis in multiple cancer cells triggered by cystine deprivation or erastin (43).

Lipid peroxidation. Polyunsaturated fatty acids (PUFAs), such as adrenic acid and arachidonic acid, are highly susceptible to peroxidation. Enzymes like lysophosphatidylcholine acyltransferase 3 and Acyl-CoA synthetase long-chain family member 4 (ACSL4) play essential roles in incorporating these PUFAs into membrane phospholipids, thereby promoting lipid peroxidation and ferroptotic cell death (44-47) (Fig. 1).

Lipid peroxidation can proceed through two pathways: Non-enzymatic, driven by free radicals like ROS, and enzymatic pathways, catalyzed by arachidonate lipoxygenases (ALOXs) and other enzymes (48-51).

Non-enzymatic lipid peroxidation is a process driven by free radicals, where ROS initiate the oxidation of PUFAs (23). The most potent ROS is the hydroxyl radical. This radical is primarily formed through Fenton or Fenton-like reactions, which result from the interaction of hydrogen peroxide (H_2O_2) with free Fe^{2+} (52,53).

ALOXs hold a crucial role in catalyzing enzymatic lipid peroxidation. This family of iron-containing enzymes encompasses six distinct isoforms (ALOXE3, ALOX5, ALOX12, ALOX12B, ALOX15 and ALOX15B), which facilitate the dioxygenation of PUFAs and PUFA-containing lipids within biological membranes to produce a variety of lipid hydroperoxides in a highly specific manner (54). This suggests the potential involvement of ALOXs in initiating ferroptosis. Previous studies have indicated that certain pharmacological ALOX inhibitors can effectively hinder ferroptosis (55,56). However, it is noteworthy that the deletion of ALOX15 did

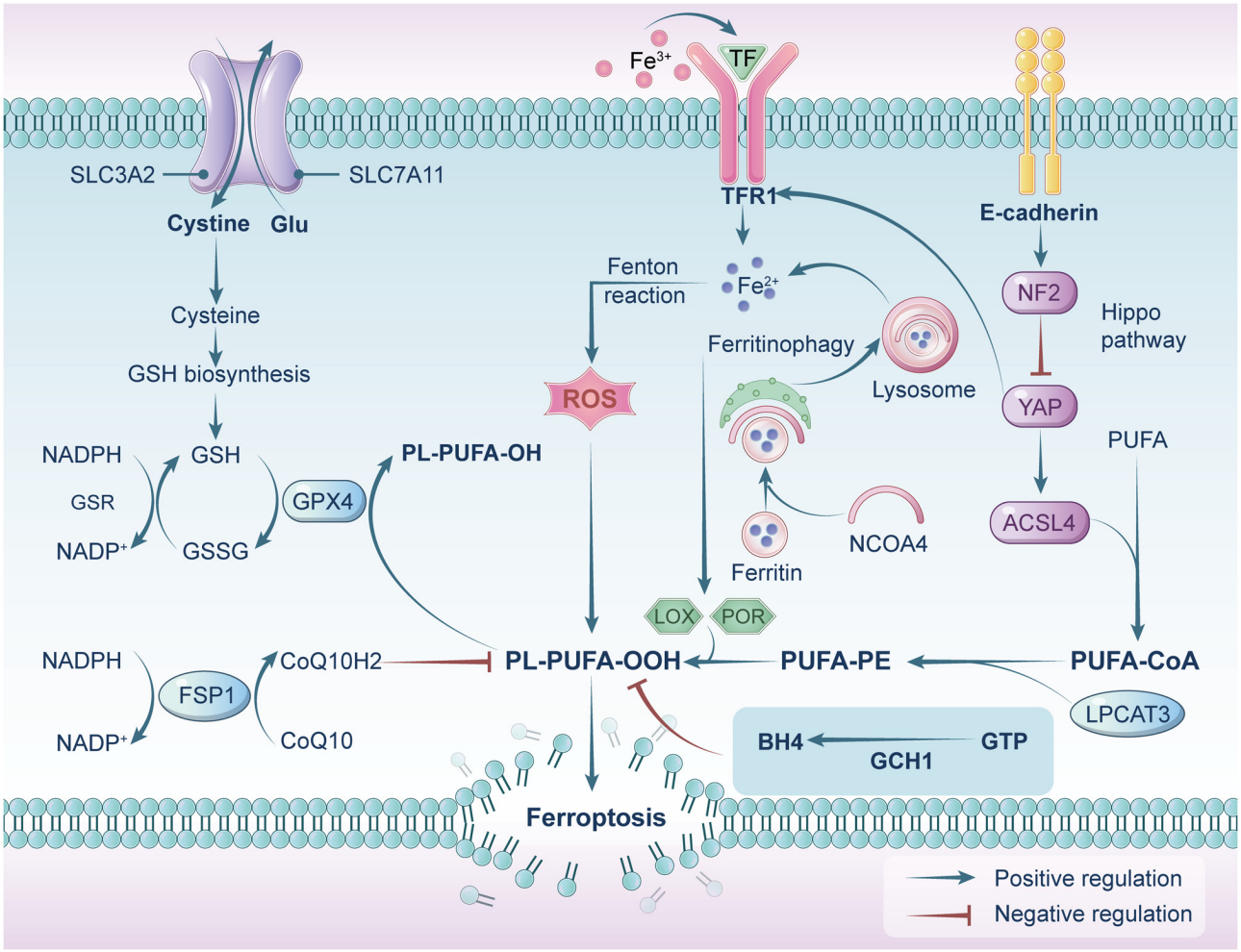

Figure 1. Key mechanisms underlying ferroptosis. Ferroptosis is a regulated form of cell death driven by iron accumulation and excessive lipid peroxidation. Several key molecular pathways orchestrate this process. TF, TFR1 and ferritin are essential for maintaining iron homeostasis within cells. Circulating Fe^{3+} binds to TF, which then interacts with TFR1 on the cell membrane, enabling Fe^{3+} uptake. Once inside the cell, Fe^{3+} is converted to Fe^{2+}, which participates in the Fenton reaction to generate •OH, thereby exacerbating oxidative stress. Fe^{2+} also enhances lipid peroxidation by activating LOX and POR, both of which contribute to the enzymatic oxidation of PUFAs. Ferritin is a key iron-storage protein. Ferritinophagy, a process mediated by NCOA4, involves the selective autophagic degradation of ferritin, leading to the release of Fe^{2+}. This enhances ferroptosis by increasing iron availability, which promotes lipid peroxidation. System Xc^- plays a crucial role in ferroptosis regulation by importing cystine into the cell while exporting glutamate. Once inside, cystine is reduced to cysteine, which is essential for GSH synthesis. GPX4 utilizes GSH to neutralize lipid hydroperoxides, preventing ferroptosis. In addition to the GPX4-GSH system, the FSP1-CoQ10 and GCH1-BH4 pathways also counteract ferroptosis by mitigating lipid peroxidation. ACSL4 catalyzes the conversion of PUFAs into PUFA-CoA, which is then incorporated into phospholipids by LPCAT3, producing PUFA-PE. LOX and POR further oxidize PUFA-PE to generate PL-PUFA-OOH, a critical step in ferroptosis induction. Notably, E-cadherin suppresses ferroptosis by inhibiting TFR1 and ACSL4 expression through the NF2-YAP signaling axis. GSH, glutathione; PUFA, polyunsaturated fatty acid; Fe^{3+}, ferric iron; Fe^{2+}, ferrous iron; ACSL4, acyl-CoA synthetase long-chain family member 4; •OH, hydroxyl radicals; GCH1, guanosine triphosphate cyclohydrolase 1; BH4, tetrahydrobiopterin; CoA, coenzyme A; CoQ10, coenzyme Q10; FSP1, ferroptosis suppressor protein 1; system Xc^-, cystine/glutamate transporter; GPX4, glutathione peroxidase 4; LOX, lipoxygenase; POR, cytochrome P450 oxidoreductase; LPCAT3, lysophosphatidylcholine acyltransferase 3; NF2, neurofibromin 2; PE, phosphatidylethanolamine; PL-PUFA-OOH, oxidized PUFA-containing phospholipids; ROS, reactive oxygen species; TF, transferrin; TFR1, TF receptor 1; NCOA4, nuclear receptor coactivator 4; YAP, yes-associated protein 1.

not successfully rescue ferroptosis triggered by the knockout of glutathione peroxidase 4 (GPX4) (57). These results imply the presence of compensatory mechanisms that could offset the loss of ALOX15 activity (58). Although ALOXs are crucial for enzymatic lipid peroxidation, their contribution to ferroptosis appears context-dependent. ALOX12 is crucial for p53-induced ferroptosis, but it is not involved in ferroptosis triggered by erastin or GPX4 inhibitors (59), suggesting differential regulation of ferroptosis by ALOX isoforms.

Consequently, ALOXs may specifically participate in certain scenarios within the domain of ferroptosis. To gain a more precise understanding, further research is needed to clarify the precise function of ALOXs in ferroptosis. Of note, ALOXs may not be the only factors governing lipid peroxidation during ferroptosis. In fact, it has been indicated that cytochrome P450 oxidoreductase actively contributes to the initiation of lipid peroxidation (60).

Antioxidant defense. Under physiological conditions, the process of iron-driven lipid oxidation is carefully regulated by cellular antioxidant defense systems. A central player in this defense mechanism is GPX4, a pivotal antioxidant enzyme that plays a crucial role in reducing membrane lipid hydroperoxides to non-toxic lipid alcohols (9,61). GPX4

accomplishes this task by relying on reduced GSH as an essential cofactor (62). Thus, the proper functioning of GPX4 is intricately linked to the availability of GSH (9,63). GSH is produced through the combination of three amino acids: Cysteine, glycine and glutamic acid. Notably, the availability of cysteine stands out as the primary limiting factor in this biosynthesis process (64,65). Within mammalian cells, the cystine/glutamate antiporter system x_c^-, composed of solute carrier family 7 member 11 (SLC7A11) and SLC3A2, is responsible for transporting extracellular cystine (the oxidized form of cysteine) into the cell while releasing intracellular glutamate in a 1:1 exchange (66,67). The inhibition of system x_c^- or GPX4, either pharmacologically or genetically, triggers lipid peroxidation and ferroptosis (48,68,69). Furthermore, SLC7A11 expression and function are enhanced by nuclear factor E2-related factor 2 (70) but suppressed by tumor suppressors, including TP53 (71), BRCA1-associated protein 1 (BAP1) (72) and beclin 1 (73). Therefore, SLC7A11 serves as a critical regulatory point in the initiation of ferroptosis, making it an important factor in the control of this cellular process.

Ferroptosis suppressor protein 1 (FSP1) functions as a GSH-independent coenzyme Q (CoQ) oxidoreductase and serves as an essential antioxidant defense system alongside GPX4, making it a key regulator of ferroptosis (50,51,74). FSP1 utilizes NADH/NADPH to convert CoQ10 into its reduced, active form, CoQ10H2. In this reduced form, CoQ10H2 functions as a lipid-soluble antioxidant, neutralizing free radicals and inhibiting lipid peroxidation, thereby protecting cells from ferroptosis (50,75). In addition to GPX4/GSH and FSP1, guanosine triphosphate cyclohydrolase 1 (GCH1) provides an alternative ferroptosis defense by producing tetrahydrobiopterin (BH4), which operates independently of the GPX4 system (76).

3. Epigenetic regulation of ferroptosis in GICs

Epigenetics refers to regulatory mechanisms that modify gene expression through DNA methylation, histone modifications and ncRNAs without changing the underlying DNA sequence (77,78).

DNA methylation and ferroptosis. In eukaryotic cells, DNA methylation predominantly occurs at the 5' position of the cytosine ring within CpG dinucleotides, exerting regulatory control over gene transcription by influencing promoters and enhancers (79). This modification involves the enzymatic actions of DNA methyltransferases (DNMTs) and DNA demethyltransferases (also named TET enzymes) (80-83). CpG dinucleotides are concentrated in specific regions known as CpG islands (CGIs), and 50-60% of gene promoters are situated within these CGIs. In healthy cells, CGIs, particularly those associated with promoters, tend to remain unmethylated. However, disruptions in DNA methylation processes are intricately involved in cancer development (84). Promoter hypermethylation-induced transcriptional silencing of tumor suppressor genes is a common observation in the majority of cancers (85-87).

DNA methylation is a key regulatory mechanism that influences ferroptosis by modulating the expression of critical genes associated with this pathway (88). In intestinal GC cells, DNA methylation silences fatty acid desaturase 1 and elongation of very long-chain fatty acid protein 5, reducing PUFA synthesis and inhibiting lipid peroxidation, thus suppressing ferroptosis (89). Similarly, aberrant hypermethylation of the protocadherin gene 14 promoter in HCC leads to its inactivation, but p53 activation can reverse this, promoting ferroptosis by reducing SLC7A11 expression (90). Iron homeostasis is largely controlled by the HAMP-FPN axis, where HAMP plays a crucial role in regulating iron absorption, distribution and overall balance (91). In individuals with HCC, HAMP expression is suppressed, coinciding with hypermethylation of a highly conserved CpG island within its promoter region (92,93). In GBC, DNMT1-mediated methylation downregulates runt-related transcription factor 3 (RUNX3), impairing ferroptosis. However, activating RUNX3 induces ferroptosis by enhancing inhibitor of growth 1 transcription, which in turn downregulates SLC7A11 in a p53-dependent manner (94) (Fig. 2).

Histone modifications and ferroptosis. Histone modifications play a key role in shaping chromatin structure and thus impact gene expression and cancer development (95,96). This discussion will primarily center on how histone acetylation, methylation and ubiquitination contribute to the regulation of ferroptosis.

Histone acetylation modification and ferroptosis. Histone acetylation modification refers to the process of adding acetyl groups to histone proteins, which are crucial for regulating chromatin structure and gene expression. Acetylation of histone is typically associated with open chromatin conformation, allowing for increased accessibility of DNA to transcriptional machinery, and thus, increased gene transcription. This process is facilitated by histone acetyltransferases, which add acetyl groups, while histone deacetylases (HDACs) remove them, leading to chromatin compaction and suppression of gene expression.

Hydroxymethylglutaryl-CoA lyase (HMGCL) catalyzes the conversion of HMG-CoA into β-hydroxy-butyric acid (β-OHB) and acetoacetate. Notably, β-OHB acts as a natural inhibitor of HDAC, promoting elevated histone acetylation levels (97). Recent studies have demonstrated that HMGCL, via β-OHB, enhances H3K9 acetylation, thereby upregulating the expression of dipeptidyl peptidase 4 (DPP4). Of note, DPP4, crucial for intracellular lipid peroxidation, renders HCC cells susceptible to ferroptosis (98). In addition, C-terminal-binding protein 1 binds with HDAC1 and HDAC2, creating a transcriptional complex that downregulates the expression of methionine adenosyltransferase 1A (MAT1A) through histone deacetylation modification. Consequently, decreased MAT1A levels reduce ferroptosis in HCC cells, potentially through direct mechanisms or by impairing CD8+ T-cell and interferon-γ production, thereby facilitating the progression of HCC (99). Furthermore, RB1-inducible coiled-coil 1 facilitates the recruitment of elongator acetyltransferase complex subunit 3 to enhance H4K12Ac at ferroptosis-associated enhancers, promoting the transcription of ferroptosis-associated genes, such as coiled-coil-helix-coiled-coil-helix domain containing 3 (CHCHD3), and sensitizing cancer cells to ferroptosis (100) (Fig. 3).

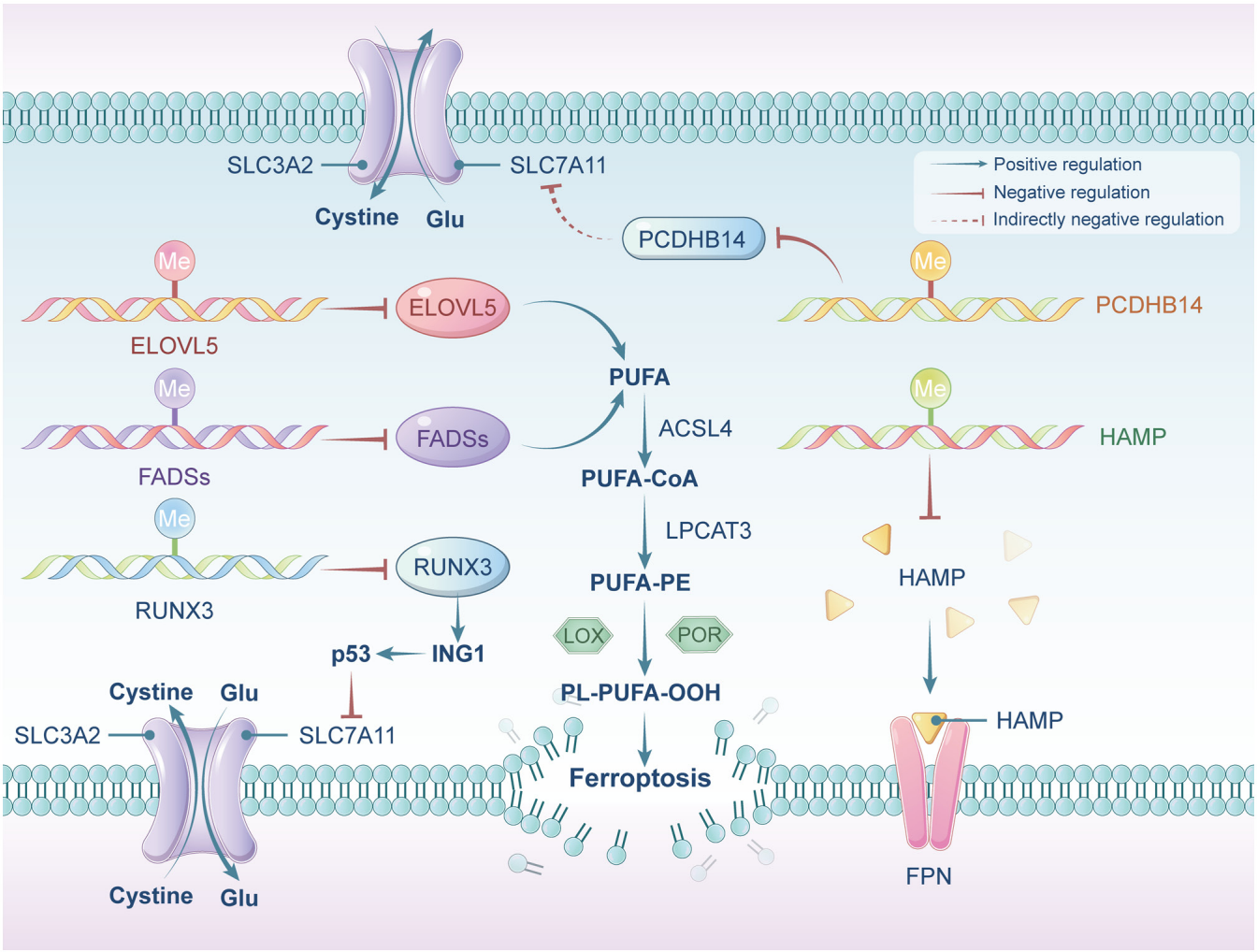

Figure 2. DNA methylation-mediated regulation of ferroptosis in gastrointestinal cancers. PCDHB14 is silenced in HCC due to abnormal promoter methylation. Notably, PCDHB14 contributes to ferroptosis induction in HCC by suppressing SLC7A11 expression. In HCC, hypermethylation of the HAMP promoter leads to its transcriptional repression. As a result, the reduced levels of HAMP fail to bind effectively to FPN, causing a decrease in iron ion concentration within HCC cells. This reduction in iron levels subsequently affects the sensitivity of HCC cells to ferroptosis. In gastric cancer cells, DNA methylation silences the genes ELOVL5 and FADSs, reducing PUFA synthesis, which suppresses ferroptosis. In gallbladder cancer cells, RUNX3 expression is suppressed due to aberrant DNA methylation, but when expressed, it promotes ferroptosis by upregulating ING1 transcription, which represses SLC7A11 in a p53-dependent manner. HCC, hepatocellular carcinoma; PCDHB14, protocadherin gene; HAMP, hepcidin gene; FPN, ferroportin; ELOVL5, elongation of very long-chain fatty acid protein 5; FADS1, fatty acid desaturase 1; ING1, inhibitor of growth 1; RUNX3, runt-related transcription factor 3; SLC7A11, solute carrier family 7 member 11; PUFA, polyunsaturated fatty acid; CoA, coenzyme A; PL-PUFA-OOH, oxidized PUFA-containing phospholipids; PE, phosphatidylethanolamine; LOX, lipoxygenase; POR, cytochrome P450 oxidoreductase; LPCAT3, lysophosphatidylcholine acyltransferase 3; ACSL4, acyl-CoA synthetase long-chain family member 4.

Histone methylation modification and ferroptosis. Histone methylation modification involves the addition of methyl groups to histone proteins, altering their structure and affecting gene expression. This process can take place on various amino acid residues within histone tails, including lysine and arginine. Depending on the specific site and extent of methylation, it can either activate or repress gene transcription.

In the context of ferroptosis, histone methylation modifications regulate the expression of genes involved in this process. For instance, MAT2A promotes S-adenosylmethionine production, leading to elevated H3K4me3 levels at the promoter region of acyl-CoA synthetase long-chain family member 3, thereby conferring resistance against ferroptosis in GC cells (101). Similarly, in ESCC, stanniocalcin 2 induces the activation of protein methyltransferase 5 (PRMT5), which enhances the symmetric dimethylation of histone H4 at arginine 3 (H4R3me2s). This activation, in turn, triggers the PRMT5-ATF4-SLC3A2/SLC7A11 axis, effectively inhibiting ferroptosis in ESCC. Furthermore, this process also induces radioresistance by facilitating DNA damage repair mechanisms (102) (Fig. 3). To date, to the best of our knowledge, there has been no study on the regulation of ferroptosis by H3K9me3 in GICs.

Histone ubiquitination modification and ferroptosis. Histone ubiquitination modification is a key epigenetic process that modulates gene expression and various cellular functions. It involves attaching ubiquitin molecules to histone proteins, which can alter chromatin structure and affect transcriptional activity. Additionally, aberrant histone ubiquitination has been linked to the development of several types of cancer, including GICs.

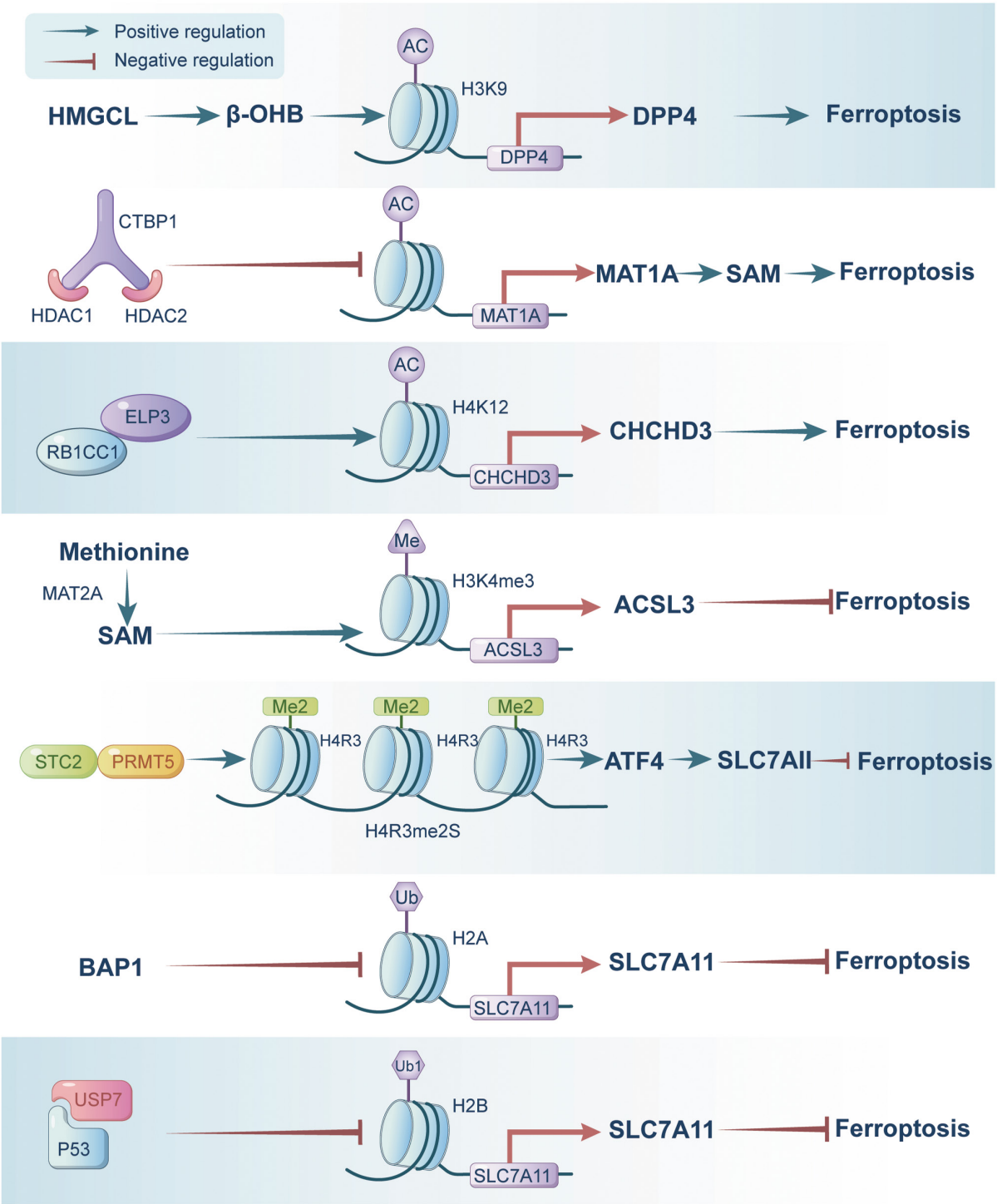

Figure 3. Histone modification-mediated regulation of ferroptosis in gastrointestinal cancers. HMGCL promotes the production of β-OHB, which acts as a natural inhibitor of histone deacetylase, leading to increased H3K9 acetylation of DPP4, making HCC cells more susceptible to ferroptosis. CTBP1 binds with HDAC1 and HDAC2 to establish a transcriptional complex that inhibits MAT1A transcription through histone deacetylation modification. When MAT1A is overexpressed, it increases SAM levels, which in turn promotes ferroptosis in HCC cells. Nuclear RB1CC1 recruits ELP3 to enhance H4K12 acetylation within CHCHD3 enhancers, leading to increased mitochondrial ROS and sensitizing liver cancer cells to ferroptosis. MAT2A promotes the production of SAM, which enhances H3K4me3 at the ACSL3 promoter region, elevating ACSL3 expression and resulting in ferroptosis resistance in GC cells. In ESCC, STC2 induces the activation of PRMT5, which enhances H4R3me2s expression. This activation, in turn, triggers the PRMT5-ATF4-SLC3A2/SLC7A11 axis, effectively inhibiting ferroptosis in ESCC. BAP1, a nuclear deubiquitinating enzyme, modulates the chromatin structure by decreasing H2Aub levels at the SLC7A11 promoter, resulting in reduced SLC7A11 expression and the initiation of ferroptosis. P53 facilitates the nuclear translocation of USP7, which in turn reduces H2Bub1 occupancy at the regulatory region of SLC7A11. This process leads to the suppression of SLC7A11 expression and enhances ferroptosis in human hepatoma cells. SLC7A11, solute carrier family 7 member 11; HMGCL, hydroxymethylglutaryl-CoA lyase; DPP4, dipeptidyl peptidase 4; β-OHB, β-hydroxy-butyric acid; HCC, hepatocellular carcinoma; CTBP1, C-terminal-binding protein 1; MAT1A, methionine adenosyltransferase 1A; HDAC, histone deacetylase; SAM, S-adenosylmethionine; RB1CC1, RB1-inducible coiled-coil 1; FOX, forkhead box; ELP3, elongator acetyltransferase complex subunit 3; CHCHD3, coiled-coil-helix-coiled-coil-helix domain containing 3; SAM, S-adenosylmethionine; H3K4me3, trimethylation of lysine-4 on histone H3; GC, gastric cancer; ESCC, esophageal squamous cell carcinoma; STC2, stanniocalcin 2; PRMT5, protein methyltransferase 5; H4R3me2s, symmetric dimethylation of histone H4 on Arg 3; ATF4, activating transcription factor 4; BAP1, BRCA1-associated protein 1; H2Aub, histone 2A ubiquitination; H2Bub1, monoubiquitination of histone H2B on lysine 120; USP7, a deubiquitinase.

SLC7A11, a pivotal gene involved in ferroptosis, is regulated by histone ubiquitination modification. Tumor suppressors, such as p53 and BAP, impact the expression of histone deubiquitination enzymes, thus modulating the histone ubiquitination modification in the regulatory region of SLC7A11 (Fig. 3). Specifically, BAP1 functions as a nuclear deubiquitinating enzyme that specifically removes ubiquitin from histone H2A at the SLC7A11 promoter, resulting in reduced SLC7A11 transcription. This decrease in SLC7A11 levels leads to increased lipid peroxidation, ultimately triggering ferroptosis in cancerous cells (72). Similarly, p53 facilitates the nuclear import of the deubiquitinase USP7, which in turn reduces H2Bub1 levels at the regulatory region of the SLC7A11 gene, thereby repressing SLC7A11 expression and promoting ferroptosis in human hepatoma cells (103).

ncRNAs and ferroptosis. ncRNAs encompass microRNAs (miRNAs/miRs), long ncRNAs (lncRNAs) and circular RNAs (circRNAs) (104,105). ncRNAs have been widely implicated in the regulation of ferroptosis.

miRNAs and ferroptosis. miRNAs regulate gene expression at the post-transcriptional level by binding to the 3'untranslated regions of mRNA molecules, which either leads to mRNA degradation or blocks its translation into a protein. They directly modulate the expression of genes involved in ferroptosis. Specifically, certain miRNAs may target genes related to lipid metabolism, iron homeostasis or antioxidant defense systems.

miRNAs regulate antioxidant defense systems. SLC7A11, a crucial component of system x_c^-, negatively regulates ferroptosis by enhancing cystine uptake and subsequently GSH synthesis. Numerous studies have revealed that various miRNAs, including miR-375, miR-489-3p, miR-1276, miR-148a-3p and miR-509-5p, target SLC7A11 mRNA. This targeting leads to decreased SLC7A11 expression and consequently increases ferroptosis in both GC and CRC cells (106-110).

GPX4 is essential for cell survival, as it reduces harmful lipid peroxides into their non-toxic alcohol forms, thereby preventing ferroptosis. In CRC and HCC, miR-15a-3p and miR-214-3p directly target GPX4, suppressing its expression and facilitating ferroptosis (111,112). Additionally, miRNAs exert an indirect influence on GPX4. For instance, in CRC, miR-539 activates the stress-activated protein kinase/c-Jun N-terminal kinase pathway by targeting TNF-α-induced protein 8, which leads to reduced GPX4 levels and the induction of ferroptosis (113).

Nuclear factor erythroid 2-related factor 2 (NRF2), an essential transcription factor in the antioxidant response, is inhibited by the ubiquitin ligase complex formed by Kelch-like ECH-associated protein 1 (KEAP1) and Cullin 3. NRF2 drives the expression of antioxidant enzymes, including heme oxygenase 1, NAD(P)H:quinone oxidoreductase 1 and superoxide dismutase, which are essential for counteracting ROS, preventing lipid peroxidation and ultimately inhibiting ferroptosis (114). Several miRNAs, including miR-124-3p, miR-507, miR-634, miR-450a, miR-129-5p and miR-142-5p, directly target the 3'-UTR of NRF2 mRNA, leading to decreased NRF2 expression and increased ROS in GC and ESCC (115-117). Furthermore, miRNAs indirectly regulate NRF2 by targeting KEAP1. In ESCC, HCC and GC cells, miR-432-3p, miR-200a, miR-141 and miR-328-3p target KEAP1, resulting in NRF2 upregulation (118-122).

Under conditions of stress, ATF4 expression is upregulated, leading to the induction of SLC7A11 and subsequent inhibition of ferroptosis (123,124). Conversely, in HCC, miR-214-3p directly targets ATF4, thereby promoting ferroptosis (125).

miRNAs regulate lipid metabolism. ACSL4 facilitates the incorporation of PUFAs into phospholipids, thereby increasing the susceptibility of cells to ferroptosis. By modulating ACSL4, miRNAs play a significant role in controlling ferroptosis in GICs. For instance, miR-552-5p and miR-23a-3p specifically target the 3'-UTR of ACSL4 mRNA, leading to the inhibition of ferroptosis in HCC cells and contributing to resistance against sorafenib (126,127). In addition, exosomes derived from cancer-associated fibroblasts (CAFs) transport miR-3173-5p to gemcitabine-treated pancreatic ductal adenocarcinoma (PDAC) cells, where miR-3173-5p targets ACSL4, thereby inhibiting ferroptosis and mediating resistance to gemcitabine (128). Similarly, exosomes released by GC cells deliver miR-214-3p to vascular endothelial cells, where miR-214-3p targets zinc finger protein A20, resulting in the negative regulation of ACSL4 and subsequent inhibition of ferroptosis in these cells (129). Apart from ASCL4, miRNAs have the potential to modulate additional molecules or pathways linked to lipid metabolism, influencing the regulation of ferroptosis. The mevalonate (MVA) pathway, responsible for cholesterol and CoQ10 synthesis, is among the pathways subject to miRNA regulation. Considering the ability of hydroxyacyl-CoA dehydrogenase α subunit (HADHA) to enhance the expression of key MVA pathway enzymes, miR-612 may exert a suppressive effect on this pathway by directly targeting HADHA. This suppression could lead to reduced CoQ10 levels and elevated cellular PUFA levels, which can trigger ferroptosis in HCC cells (130). The family of ALOXs is regarded as the key mediator of lipid peroxidation production, which eventually leads to ferroptosis (56,131). Previous studies have demonstrated that by targeting ALOX15, exosomal miR-522, secreted by CAFs, inhibits ferroptosis in GC cells (132).

miRNAs regulate iron metabolism. miRNAs can regulate ferroptosis in GIC cells by influencing intracellular iron metabolism. Specifically, miR-545 targets TF (133), while several other miRNAs, such as miR-31, miR-141, miR-145, miR-182, miR-194, miR-758, miR-22, miR-200a, miR-320 and miR-152, target TFR in CRC and HCC, thereby reducing TF uptake (134-136). Notably, miR-194 not only inhibits TFR expression but also inhibits FPN expression in CRC (134). FPN serves as the primary means of ferrous iron export (137), and is targeted by miR-150 and miR-485-3p in HCC (138). In CRC, miR-133a targets FTL, one of the components of ferritin responsible for iron storage (134). In addition, miR-19a targets iron-responsive element-binding protein 2, thus suppressing ferroptosis in CRC (139). These intricate regulatory interactions highlight the multifaceted role of miRNAs in modulating ferroptosis through the regulation of intracellular iron dynamics in GICs. Table I gives a comprehensive and detailed overview of how miRNAs regulate ferroptosis in GICs.

lncRNAs and ferroptosis. lncRNAs are long RNA molecules typically >200 nucleotides in length, which have

Table I. miRNA-mediated regulation of ferroptosis in GICs.

miRNA	Role in ferroptosis	Mechanism	(Refs.)
miR-375	Promotes ferroptosis in GC	Targets SLC7A11	(106)
miR-489-3p	Promotes ferroptosis in GC	Targets SLC7A11	(107)
miR-1276	Promotes ferroptosis in GC	Targets SLC7A11	(108)
miR-148a-3p	Promotes ferroptosis in CRC	Targets SLC7A11	(109)
miR-509-5p	Promotes ferroptosis in CRC	Targets SLC7A11	(110)
miR-15a-3p	Promotes ferroptosis in CRC	Targets GPX4	(111)
miR-214-3p	Promotes ferroptosis in liver cancer cells	Targets GPX4	(112)
miR-539	Promotes ferroptosis in CRC	Targets TIPE, triggers the SAPK/JNK signaling pathway, decreasing GPX4	(113)
miR-124-3p	Promotes ferroptosis in GC	Targets NRF2	(115)
miR-507	Promotes ferroptosis in ESCC	Targets NRF2	(116)
miR-634	Promotes ferroptosis in ESCC	Targets NRF2	(116)
miR-450a	Promotes ferroptosis in ESCC	Targets NRF2	(116)
miR-129-5p	Promotes ferroptosis in ESCC	Targets NRF2	(116)
miR-142-5p	Promotes ferroptosis in ESCC	Targets NRF2	(117)
miR-432-3p	Inhibits ferroptosis in ESCC	Targets KEAP1	(118)
miR-200a	Inhibits ferroptosis in ESCC	Targets KEAP1	(119,120)
miR-141	Inhibits ferroptosis in HCC	Targets KEAP1	(121)
miR-328-3p	Inhibits ferroptosis in GC	Targets KEAP1	(122)
miR-214-3p	promotes ferroptosis in HCC	Targets ATF4	(125)
miR-552-5p	Inhibits ferroptosis in HCC	Targets ACSL4	(126)
miR-23a-3p	Inhibits ferroptosis in HCC	Targets ACSL4	(127)
miR-3173-5p	Inhibits ferroptosis in PDAC	Targets ACSL4	(128)
miR-214-3p	Inhibits ferroptosis in vascular endothelial cells	Targets zinc finger protein A20, inhibits ACSL4	(129)
miR-612	Promotes ferroptosis in HCC	Targets HADHA, reduces CoQ10 and elevates PUFA	(130)
miR-522	Inhibits ferroptosis in GC	Targets ALOX15	(132)
miR-545	Inhibits ferroptosis in CRC	Targets TF	(133)
miR-31	Inhibits ferroptosis in CRC	Targets TFR	(134)
miR-141	Inhibits ferroptosis in CRC	Targets TFR	(134)
miR-145	Inhibits ferroptosis in CRC	Targets TFR	(134)
miR-182	Inhibits ferroptosis in CRC	Targets TFR	(134)
miR-194	Inhibits ferroptosis in CRC	Targets TFR and FPN	(134)
miR-758	Inhibits ferroptosis in CRC	Targets TFR	(134)
miR-22	Inhibits ferroptosis in HCC	Targets TFR	(135)
miR-200a	Inhibits ferroptosis in HCC	Targets TFR	(135)
miR-320	Inhibits ferroptosis in HCC	Targets TFR	(135)
miR-152	Inhibits ferroptosis in HCC	Targets TFR	(136)
miR-485-3p	Promotes ferroptosis in HCC	Targets FPN	(138)
miR-133a	Inhibits ferroptosis in CRC	Targets FTL	(134)
miR-19a	Inhibits ferroptosis in CRC	Targets IREB2	(139)

miRNA/miR, microRNA; GC, gastric cancer; CRC, colorectal cancer; TIPE, also named TNFAIP8, tumor necrosis factor-α-induced protein 8; ESCC, esophageal squamous cell carcinoma; NRF2, nuclear factor erythroid 2-related factor 2; HCC, hepatocellular carcinoma; KEAP1, Kelch-like ECH-associated protein 1; ATF4, activating transcription factor 4; PDAC, pancreatic ductal adenocarcinoma; ACSL4, acyl-CoA synthetase long-chain family member 4; HADHA, hydroxyacyl-CoA dehydrogenase alpha subunit; ALOX15, arachidonate lipoxygenases 15; PUFA, polyunsaturated fatty acid; TF, transferrin; TFR, transferrin receptors; FPN, ferroportin; IREB2, iron-responsive element-binding protein 2; FTL, ferritin light chain; GPX4, glutathione peroxidase 4.

been recognized as key regulators of ferroptosis in tumor cells (140). These molecules exhibit a dual capability in modulating ferroptosis in GICs: They can directly target key genes or molecules associated with ferroptosis or indirectly modulate them by acting as miRNA sponges (141). For instance, lncRNAs have been shown to directly or indirectly

modulate the expression of SLC7A11, impacting ferroptosis in HCC and GC (142-145), as well as modulate the expression of GPX4, influencing ferroptosis in ESCC, CCA and liver cancer cells (112,146,147). Additionally, lncRNAs can directly bind to molecules such as FSP1 or Keap1, thereby inhibiting ferroptosis in GICs (148,149).

Furthermore, specific lncRNAs, such as URB1-antisense RNA 1 (AS1), have been implicated in driving ferritin phase separation, which helps lower cellular free iron levels and suppressed sorafenib-induced ferroptosis in HCC (150). Additionally, lncRNA NEAT1 promotes the expression of Myo-inositol oxygenase, leading to increased ROS production and a reduction in intracellular NADPH and GSH levels, thereby intensifying ferroptosis in HCC (151,152). Another crucial enzyme involved is Stearoyl-CoA desaturase 1 (SCD1), which converts saturated fatty acids into monounsaturated fatty acids (MUFAs), affecting cellular membrane composition and susceptibility to lipid peroxidation-induced ferroptosis (153-156). In colon cancer, lncRNA LINC01606 has been reported to enhance SCD1 expression by competing for miR-423-5p, thereby protecting cancer cells from ferroptosis (157).

Furthermore, in hypoxic tumor microenvironments (TMEs), lncRNAs are crucial regulators of ferroptosis. For instance, hypoxia-inducible factor 1α (HIF-1α) activation leads to the transcriptional upregulation of lncRNA PMAN, which enhances the output of ELAV-like RNA binding protein 1 (ELAVL1) in the cytoplasm. ELAVL1 then stabilizes SLC7A11 mRNA, increasing its expression and preventing ferroptosis in GC peritoneal metastasis (145). Similarly, HIF-1α induces lncRNA-CBSLR, which eventually protects GC cells from ferroptosis and confers chemoresistance to GC cells under hypoxic conditions by modulating the stability of cystathionine β-synthase (CBS) mRNA and ACSL4 protein (158).

Furthermore, lncRNAs can utilize exosomes as carriers to regulate ferroptosis in target cells. Exosomes secreted by CAFs carry lncRNA DACT3-AS1 into GC cells, where it targets the miR-181a-5p/sirtuin 1 (SIRT1) axis, inducing ferroptosis and sensitizing GC cells to oxaliplatin (159). These examples illustrate the diverse mechanisms through which lncRNAs modulate ferroptosis in GICs. Table II provides a more comprehensive overview.

circRNAs and ferroptosis. circRNAs, which are single-stranded, covalently closed ncRNA molecules, exhibit distinct characteristics from other ncRNAs (160).

In GICs, numerous circRNAs have been identified as crucial regulators of ferroptosis. circRNAs typically function as miRNA sponges, indirectly influencing the expression of their target mRNAs (161-164), including ferroptosis-associated genes like GPX4 (165) and SLC7A11. These genes are well-established critical regulators of ferroptosis and studies have shown that several circRNAs modulate their expression by sequestering miRNAs, thereby playing a significant role in controlling ferroptosis in GICs (108,166-171). Notably, circRHOT1 facilitates the recruitment of KAT5 (acetyltransferase Tip60), increasing H3K27-mediated acetylation of the GPX4 gene, which promotes its transcription and inhibits ferroptosis in GC (172).

In addition to acting as miRNA sponges, circRNAs can directly bind to RNA-binding proteins involved in ferroptosis signaling pathways, thereby modulating ferroptosis in GICs. For instance, ELAVL1, an RNA-binding protein, enhances the translation efficiency of target mRNAs by interacting with AU-rich elements in their 3'UTRs (173). circRHBDD1 upregulates SCD expression by promoting ELAVL1 binding to SCD mRNA, leading to the suppression of ferroptosis in CRC (174).

A recent study also elucidated the mechanism by which circRNA may contribute to the regulation of ferroptosis. circPDE3B was shown to function as both an miR-516b-5p sponge, resulting in increased CBS expression, and as a direct binder with RNA-binding protein heterogeneous nuclear ribonucleoprotein K, resulting in the stabilization of SLC7A11. Consequently, this dual action of circPDE3B ultimately resulted in the suppression of ferroptosis in ESCC (175). A comprehensive and detailed overview of how circRNAs regulate ferroptosis in GICs is provided in Table III.

Interplay between epigenetic modifications cooperatively regulates ferroptosis in GICs. It is worth noting that certain key genes or molecules related to ferroptosis are not only regulated by a single epigenetic modification but may be influenced by multiple epigenetic modifications simultaneously. For instance, in cancer cells, the upstream region of the GPX4 gene exhibits low DNA methylation, high levels of H3K4 trimethylation and H3K27 acetylation (176), indicating that GPX4 is regulated not only by DNA methylation but also by histone modifications. These modifications work together to create a more complex regulatory framework for ferroptosis.

Aurora kinase A (AURKA), a serine/threonine kinase responsible for regulating mitotic spindle function (177,178), is another key player. miR-4715-3p can directly target the 3'-UTR of AURKA, suppressing its expression, which in turn inhibits GPX4 and promotes ferroptosis (179). However, in upper gastrointestinal cancers, miR-4715-3p itself is downregulated due to hypermethylation of its gene promoter (179). This epigenetic interplay further complicates the regulation of ferroptosis in these types of cancer.

ROS influences epigenetics. ROS are critical in driving ferroptosis and have been implicated in regulating epigenetic processes, including DNA methylation and histone acetylation (180,181). In cancer cells, elevated ROS levels enhance DNA hypermethylation, resulting in the repression of tumor suppressor and antioxidant genes, which promotes cancer cell proliferation under oxidative stress (180,181). A notable example is the epigenetic silencing of RUNX3, a well-established tumor suppressor, which is frequently downregulated in cancer cells due to ROS-induced DNA hypermethylation of its promoter. This methylation process is mediated by DNMT1 and HDAC1, whose expression and activity are upregulated in response to ROS. DNMT1 and HDAC1 bind to the RUNX3 promoter, driving its hypermethylation and silencing (182). Importantly, treatment with the ROS scavenger N-acetylcysteine or the DNMT1 inhibitor 5-aza-2-deoxycytidine has been shown to reverse this epigenetic modification, highlighting the potential for therapeutic intervention. Similarly, ROS-induced promoter hypermethylation has been observed in other tumor suppressor genes. In CRC, ROS enhances the methylation of the caudal type homeobox-1 (CDX1) promoter, leading to its suppression and facilitating cancer progression (183). In

Table II. How lncRNAs regulate ferroptosis in gastrointestinal cancers.

First author, year	lncRNA	Role in ferroptosis	Mechanism	(Refs.)
Shi *et al*, 2023	lncRNA DUXAP8	Inhibits ferroptosis in HCC	Upregulates SLC7A11	(142)
Zhang *et al*, 2022	lncRNA HEPFAL	Promotes ferroptosis in HCC	Downregulates SLC7A11	(143)
Wang *et al*, 2024	lncRNA-CASC2	Promotes ferroptosis in GC	Upregulates SOCS2 by targeting FMR1, downregulates SLC7A11	(144)
Lin *et al*, 2022	lncRNA PMAN	Inhibits ferroptosis in peritoneal metastasis of GC	Upregulates ELAVL1 and SLC7A11	(145)
Yang *et al*, 2023	lncRNA TMEM44-AS1	Inhibits ferroptosis in ESCC	Upregulates GPX4	(146)
Lei *et al*, 2022	linc00976	Inhibits ferroptosis in CCA	Target miR-3202/GPX4	(147)
He *et al*, 2021	lncRNA PVT1	Inhibits ferroptosis in live cancer cells	Target miR-214-3p/GPX4	(112)
Yuan *et al*, 2022	lncFAL	Inhibits ferroptosis in HCC	Upregulates FSP1	(148)
Gao *et al*, 2023	lncRNA URB1-AS1	Inhibits ferroptosis in HCC	Drives ferritin phase separation	(150)
Zhang *et al*, 2022	lncRNA NEAT1	Promotes ferroptosis in HCC	Targets miR-362-3p/MIOX	(151)
Guan *et al*, 2022	lncRNA HULC	Inhibits ferroptosis in HCC	Targets miR-3200-5p/ATF4	(152)
Han *et al*, 2022	LINC00239	Inhibits ferroptosis in CRC	Targets Keap1	(149)
Luo *et al*, 2022	LINC01606	Inhibits ferroptosis in colon cancer cells	Activates SCD1-Wnt/β-catenin-TFE3 feedback loop signaling	(157)
Yang *et al*, 2022	lncRNA-CBSLR	Inhibits ferroptosis in GC	Downregulates CBS and ACSL4	(158)
Qu *et al*, 2023	lncRNA DACT3-AS1	Promotes ferroptosis in GC	Targets miR-181a-5p/SIRT1	(159)
Wu *et al*, 2023	lncRNA ZEB1-AS1	Inhibits ferroptosis in GC	Targets miR-429/BGN	(141)

lncRNA, long noncoding RNA; miR, microRNA; GC, gastric cancer; HCC, hepatocellular carcinoma; ELAVL1, ELAV-like RNA binding protein 1; CCA, cholangiocarcinoma; ESCC, esophageal squamous cell carcinoma; FSP1, ferroptosis suppressor protein 1; SLC7A11, solute carrier family 7 member 11; MIOX, Myo-inositol oxygenase; CRC, colorectal cancer; ATF4, activating transcription factor 4; KEAP1, Kelch-like ECH-associated protein 1; SCD1, stearoyl-CoA desaturase 1; CBS, cystathionine β-synthase; SIRT1, sirtuin 1; BGN, biglycan; TFE3, transcription factor binding to IGHM enhancer 3; ACSL4, acyl-CoA synthetase long-chain family member 4; FMR1, fragile X messenger ribonucleoprotein 1; GPX4, glutathione peroxidase 4.

HCC, ROS elevates Snail expression, which promotes hypermethylation of the E-cadherin promoter, thereby contributing to tumor growth (184). Overall, ROS-induced epigenetic modifications play a significant role in cancer progression. Targeting ROS represents a promising therapeutic strategy-not only to reverse these epigenetic changes but also to enhance ferroptosis sensitivity in GICs. Future research should further explore the mechanisms of ROS-mediated epigenetic silencing and develop ROS-modulating therapies to improve treatment outcomes in these malignancies.

Role of TME components in ferroptosis regulation. The TME is a complex ecosystem consisting of immune cells, stromal cells, tumor cells and various other elements. Among immune cells, CD8+ T-cells play a crucial role by releasing interferon-γ, which suppresses SLC7A11 expression while enhancing ACSL4 levels, thereby facilitating ferroptosis in cancer cells (185,186).

CAFs, another critical component of the TME, significantly influence both innate and adaptive immunity (187). CAFs suppress ferroptosis in GC cells by secreting miR-522 (132). In GICs, anoctamin 1 inhibits ferroptosis by activating the PI3K-Akt signaling pathway, promoting tumor progression and facilitating CAF recruitment via TGF-β release (188). This disrupts CD8+ T cell-driven anti-tumor responses, contributing to immunotherapy resistance (188). These findings highlight the intricate interactions between cancer cells, immune cells and CAFs in regulating ferroptosis.

One unique feature of the TME is its metabolic profile, marked by high lactate accumulation and restricted glucose supply (189,190). Cancer cells exploit lactate to counteract ferroptosis by either increasing MUFA-phospholipid synthesis or enhancing the acidity of the TME (191,192).

4. Clinical applications

The reversible nature of epigenetic modifications in cancer makes them a valuable target for therapeutic strategies (193). Since ferroptosis plays a key role in limiting cancer progression, leveraging epigenetic mechanisms to regulate ferroptosis has gained interest as a potential treatment strategy, particularly for GICs. Epigenetic drugs have shown promising therapeutic potential in targeting ferroptosis-related cancers, including GICs. A series of preclinical and clinical studies have explored the efficacy of various epigenetic modulators, such as HDAC inhibitors (HDACi), enhancer of zeste homolog 2 (EZH2) inhibitors and IDH inhibitors, in regulating ferroptosis and improving cancer therapy outcomes (Table IV).

Table III. How circRNAs modulate ferroptosis in gastrointestinal cancers.

First author, year	circRNAs	Role in ferroptosis	Mechanism of action	(Refs.)
Xu *et al*, 2020	circIL4R	Inhibits ferroptosis in HCC	Sponges miR-541-3p, upregulates GPX4	(166)
Liu *et al*, 2024	circ_0016142	Suppresses ferroptosis in HCC	Acts as a miR-188-3p sponge, enhancing GPX4	(167)
Tan *et al*, 2024	circ0060467	Suppresses ferroptosis in HCC	Sequesters miR-6085, increasing AIFM2 and GPX4	(168)
Zhai *et al*, 2023	circIDE	Promotes ferroptosis in HCC	Sponges miR-19b-3p, increases RBMS1 expression, downregulates GPX4 expression	(165)
Wang *et al*, 2023	circRHOT1	Inhibits ferroptosis in GC	Recruits KAT5 to promote H3K27Ac of GPX4	(172)
Lyu *et al*, 2021	circ0097009	Inhibits ferroptosis in HCC	Functions as a miR-1261 sponge, increasing SLC7A11 expression	(169)
Li *et al*, 2023	circSTIL	Suppresses ferroptosis in CRC	Sequesters miR-431, leading to SLC7A11 upregulation	(170)
Liu *et al*, 2023	circRPPH1	Suppresses ferroptosis in GC	Functions as a miR-375 sponge, enhancing SLC7A11 expression	(171)
Dong *et al*, 2024	circTMEM87A	Suppresses ferroptosis in GC	Binds miR-1276, leading to SLC7A11 upregulation	(108)
Wang *et al*, 2021	circ_0007142	Suppresses ferroptosis in CRC	Acts as a miR-874-3p sponge, promoting GDPD5 expression	(162)
Long *et al*, 2024	circRHBDD1	Suppresses ferroptosis in CRC cells	Promotes the interaction between the SCD mRNA and ELAVL1, upregulates SCD	(174)
Gao *et al*, 2023	circ0008035	Suppresses ferroptosis in GC	Sequesters miR-302a, resulting in E2F7 upregulation	(163)
Yao *et al*, 2021	circPVT1	Suppresses ferroptosis in ESCC	Functions as a miR-30a-5p sponge, increasing FZD3 levels	(164)
Zhou *et al*, 2024	circPDE3B	Suppresses ferroptosis in ESCC	Recruits HNRNPK/SLC7A11 and miR-516b-5p/CBS axes	(175)

circRNA, circular RNA; miR, microRNA; GICs, gastrointestinal cancers; HCC, hepatocellular carcinoma; AIFM2, apoptosis-inducing factor mitochondria-associated 2; RBMS1, RNA binding motif single stranded interacting protein 1; GC, gastric cancer; KAT5, acetyltransferase Tip60; CRC, colorectal cancer; GDPD5, glycerophosphodiester phosphodiesterase domain containing 5; SCD, stearoyl-CoA desaturase; ELAVL1, ELAV like RNA binding protein 1; ESCC, esophageal squamous cell carcinoma; FZD3, Frizzled 3; HNRNPK, heterogeneous nuclear ribonucleoprotein K; CBS, cystathionine β-synthase; GPX4, glutathione peroxidase 4; SLC7A11, solute carrier family 7 member 11.

HDACis. Preclinical research has demonstrated that the HDACi BEBT-908 can induce ferroptosis in colon adenocarcinoma by hyperacetylating p53, a critical tumor suppressor protein involved in ferroptosis regulation (194). CRC is notoriously resistant to ferroptosis, but preclinical studies have shown that vorinostat, an HDACi, significantly sensitizes CRC cells to ferroptosis. When combined with ferroptosis inducers, vorinostat synergistically suppresses CRC growth (195). Additionally, entinostat, another HDACi, has been shown to promote ferroptosis in GC cells (196). These studies suggest that HDACis may increase ferroptosis susceptibility in GICs, representing a potential strategy for overcoming resistance to therapy.

The enhanced effectiveness of HDACis when combined with other anticancer treatments has led to the development of combination therapies in clinical trials. A phase I/II clinical trial (NCT00943449) assessed the efficacy of combining the HDACi resminostat with sorafenib in patients with HCC who exhibited radiologically confirmed progression after first-line sorafenib therapy. The combination treatment achieved a 62.5% progression-free survival rate following six cycles of treatment (12 weeks), whereas resminostat monotherapy resulted in a 12.5% progression-free survival rate (197). Additionally, a notable phase II clinical trial (NCT03250273) demonstrated that entinostat combined with nivolumab (a programmed cell death-1 inhibitor) yielded sustained responses in a limited group of patients with PDAC (198). Furthermore, the combination of entinostat with immunotherapeutic agents is being tested in ongoing clinical trials for melanoma, non-small cell lung cancer and CRC (ENCORE-601; NCT02437136). These studies highlight the growing clinical interest in HDACis as key modulators of ferroptosis and immune response, highlighting their potential to enhance treatment efficacy across multiple cancer types.

Currently, most approved HDACis are pan-HDACis, which can lead to significant side effects such as hematologic toxicity (199), gastrointestinal toxicity, cardiovascular toxicity (200), metabolic disturbances (201), fatigue and weakness (202), and immune-related side effects (203). Therefore, there has been a growing focus on developing selective HDACis to reduce the toxic side effects of pan-HDACis. Another innovative strategy involves proteolysis-targeting

Table IV. Clinical applications of epigenetic compounds or drugs targeting ferroptosis regulation in gastrointestinal cancers.

First author, year	Treatment	Class of drug	Outcome	Disease/cell line	Research type	(Refs.)
Fan *et al*, 2021	BEBT-908	HDACi	Promotes ferroptosis	Colon adenocarcinoma	Preclinical study	(194)
Yang *et al*, 2025	Vorinostat	HDACi	Promotes ferroptosis	CRC cells	Preclinical study	(195)
Jenke *et al*, 2024	Entinostat	HDACi	Promotes ferroptosis	GC cells	Preclinical study	(196)
Bitzer *et al*, 2016	Resminostat with sorafenib	HDACi and ferroptosis inducer	62.5% PFS rate in the resminostat with sorafenib group compared to 12.5% with resminostat monotherapy	Patients with HCC	Phase I/II clinical trial (NCT00943 449)	(197)
Baretti *et al*, 2024	Entinostat with nivolumab	HDACi and PD-1 inhibitor	ORR=11% (95% CI, 2.4-29.2%) with a median response duration of 10.2 months. PFS=1.89 (95% CI, 1.381-2.301) months; OS=2.729 (95%CI, 1.841-5.622) months.	Patients with PDAC	Phase II clinical trial (NCT03250273)	(198)
Lai *et al*, 2024	Tazemetostat	EZH2 inhibitor	Promotes ferroptosis	Sorafenib-resistant HCC	Preclinical study	(206)
Zarei *et al*, 2024	Ivosidenib	IDH inhibitor	Promotes ferroptosis	PDAC cells	Preclinical study	(214)
Zhu *et al*, 2021	Ivosidenib	IDH inhibitor	OS=10.3 months (95% CI, 7.8-12.4) in ivosidenib group; OS=7.5 months (95% CI, 4.8-11.1) vs. placebo group	Patients with CCA	Phase III randomized clinical trial (ClarIDHy; NCT02989857)	(215)
Chen *et al*, 2022	Anisomycin	Histone H3 phosphorylation at serine 10	Promotes ferroptosis	HCC cells	Preclinical study	(216)

HDACi, histone deacetylase inhibitor; HCC, hepatocellular carcinoma; GC, gastric cancer; CRC, colorectal cancer; EZH2, enhancer of zeste homolog 2; PDAC, pancreatic ductal adenocarcinoma; IDH, isocitrate dehydrogenase; CCA, cholangiocarcinoma; PFS, progression-free survival; OS, overall survival; ORR, overall response rate.

chimeras (PROTACs), small molecules that promote the selective degradation of target proteins within cells (204). HDAC-targeting PROTACs are an emerging therapeutic strategy, offering several advantages over traditional HDACi, including improved safety and the potential to overcome drug resistance (205). Furthermore, it is noteworthy that an increasing body of research demonstrates the effcacy of combining low doses of HDACi with other medications to address the issue of adverse effects.

EZH2 inhibitors. EZH2 is a histone methyltransferase that represses gene expression through H3K27 trimethylation (H3K27me3). Preclinical studies suggested that EZH2 contributes to the inhibition of ferroptosis in HCC by downregulating TFR2 expression via H3K27me3 modifications. Of note, combining tazemetostat, an EZH2 inhibitor, with sorafenib in sorafenib-resistant HCC cells promotes ferroptosis and significantly enhances the therapeutic effects of sorafenib (206). This combination therapy approach demonstrates the potential of EZH2 inhibition in overcoming resistance to standard treatments and improving ferroptosis induction in GICs.

IDH inhibitors. Alterations in IDH, particularly IDH1 and IDH2, are common in several types of cancer, including CCA (207-209). These mutations result in the accumulation of 2-hydroxyglutarate (210), a byproduct that suppresses α-ketoglutarate-dependent dioxygenases, such as histone and DNA demethylases (211-213). This disrupts cellular differentiation and contributes to cancer development. Preclinical studies suggest that mutant IDH1 can promote cancer cell survival by supporting mitochondrial function and antioxidant defenses, thus reducing the sensitivity to ferroptosis. Pharmacologic inhibition of mutant IDH1 with ivosidenib has been shown to synergize with conventional chemotherapeutics, enhancing ferroptosis sensitivity in PDAC cells (214).

A phase III randomized clinical trial (NCT02989857) demonstrated that Ivosidenib has significant overall survival benefits in patients with advanced CCA harboring IDH1 mutations (215). A current clinical trial (NCT05209074) is testing the combination of ivosidenib with chemotherapy in PDAC, demonstrating the promising potential of IDH inhibitors in improving ferroptosis sensitivity and cancer treatment outcomes.

In addition to the use of specific inhibitors, epigenetic modifications such as histone modifications have been identified as crucial regulators of ferroptosis in GICs. For instance, anisomycin, an activator of the p38-MAPK pathway, enhances histone H3 phosphorylation at serine 10 on the NCOA4 promoter. NCOA4 is crucial for ferroptosis as it facilitates ferritinophagy, a mechanism that liberates iron from ferritin, triggering lipid peroxidation. In HCC cells, anisomycin-induced NCOA4 expression sensitizes the cells to ferroptosis, suggesting that targeting epigenetic modifications like histone phosphorylation could serve as a potential approach to overcoming ferroptosis resistance in certain cancer types (216).

ncRNAs encapsulated in exosomes or vesicles. ncRNAs, particularly those contained in exosomes, are essential regulators of ferroptosis and significantly impact the survival and progression of GIC cells. These exosomal ncRNAs can deliver miRNAs, lncRNAs and circRNAs directly to cancer cells, offering significant therapeutic potential for GIC. Preclinical studies have shown that exosomal lncRNAs, such as DACT3-AS1 derived from CAFs, can be transferred to GC cells. There, DACT3-AS1 induces ferroptosis through its regulation of the miR-181a-5p/SIRT1 pathway (159). Additionally, heat shock protein family B (small) member 1 (HSPB1) inhibits ferroptosis by reducing iron uptake through TFRC (217). An interesting study utilized small extracellular vesicles (sEV) to deliver miR-654-5p, resulting in engineered vesicles (m654-sEV). The findings revealed that m654-sEV efficiently transfers miR-654-5p to HCC cells, targeting HSPB1 and amplifying sorafenib-induced ferroptosis (218). This combined approach using m654-sEV and sorafenib holds the potential for overcoming sorafenib resistance in HCC, thereby improving therapeutic efficacy. These findings suggest that ncRNAs, which promote ferroptosis in GICs, could be packaged into exosomes or sEVs to target and treat GICs more effectively. Investigating the role of ncRNAs in modulating ferroptosis in GICs may offer valuable therapeutic insights and contribute to the development of more effective clinical strategies for treating these cancers.

Epigenetic drug combination with ferroptosis inducers for the treatment of GICs: Preliminary exploration of resistance mechanisms. Numerous preclinical investigations and clinical trials have explored the possibility of combining epigenetic drugs with ferroptosis inducers in GICs. Sorafenib, a multi-target kinase inhibitor that acts on Raf kinases, has been approved by the US Food and Drug Administration as a first-line therapy for advanced HCC (219). Research has shown that sorafenib can induce ferroptosis in HCC cells by suppressing the activity of system Xc^-; therefore, sorafenib acts as a ferroptosis inducer like erastin (220). However, the clinical effectiveness of sorafenib in HCC is often compromised by both primary and acquired resistance. A phase I/II clinical trial involving patients with HCC who had experienced disease progression with first-line sorafenib treatment investigated the combination of sorafenib with the HDACi resminostat. The study reported a 62.5% progression-free survival rate after six treatment cycles (12 weeks, primary endpoint) with the combination therapy, whereas resminostat alone resulted in a 12.5% progression-free survival rate (197). These results indicate that epigenetic drugs combined with sorafenib can overcome the resistance of HCC cells to sorafenib. Preclinical studies have shown that lncRNAs play a crucial role in sorafenib resistance in HCC, and lncRNA metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) is dysregulated in sorafenib-resistant HCC cells. MALAT1 contributes to sorafenib resistance in HCC cells by stabilizing SLC7A11 mRNA through direct interaction with ELAVL1, promoting its translocation to the cytoplasm and subsequently inhibiting sorafenib-induced ferroptosis (221). The combination of a MALAT1 inhibitor with sorafenib markedly improved the therapeutic effectiveness of sorafenib in both *in vitro* and *in vivo* models of HCC (221).

5. Conclusions and future perspectives

Ferroptosis has emerged as a critical mechanism in the progression and treatment of GICs. The epigenetic regulation

of ferroptosis, involving DNA methylation, histone modifications and ncRNAs, represents a complex but promising avenue for therapeutic intervention. These modifications collectively influence key genes involved in ferroptosis, including GPX4 and AURKA, which underscores the potential of targeting epigenetic regulators to modulate ferroptosis in GIC therapy. Current findings underscore the importance of epigenetic drugs in modulating ferroptosis and their potential to enhance therapeutic efficacy in GICs. However, there remain significant challenges in translating these insights into widely effective clinical therapies.

There is a need for more extensive research to map the full range of epigenetic regulators involved in ferroptosis across different types of GICs. Advanced technologies such as single-cell RNA sequencing (seq) and multi-omics approaches, including single-cell assay for transposase-accessible chromatin seq (222) and chromatin immunoprecipitation-seq (223), may provide a high-resolution view of the epigenetic landscape governing ferroptosis. These techniques can help elucidate context-specific regulatory mechanisms and identify novel therapeutic targets.

As the knowledge of the epigenetic mechanisms governing ferroptosis expands, there is potential for the development of more selective and effective epigenetic modulators. The application of CRISPR/Cas9-based epigenome editing could enable precise modifications of ferroptosis-related genes, allowing researchers to dissect their functional roles and develop targeted epigenetic therapies (224). Furthermore, artificial intelligence (AI)-driven drug discovery and high-throughput screening platforms could accelerate the identification of small-molecule inhibitors or activators that modulate ferroptosis through epigenetic mechanisms (225).

Identifying epigenetic markers that predict a tumor's sensitivity to ferroptosis-inducing therapies could be crucial for personalizing treatment. Techniques such as DNA methylation arrays and bisulfite sequencing may be employed to assess the methylation status of ferroptosis-related genes (226,227). In addition, liquid biopsy approaches using circulating tumor DNA and epigenetic profiling of cell-free DNA may provide minimally invasive strategies for monitoring ferroptosis sensitivity and treatment response in real-time (228).

Resistance to ferroptosis-based therapies remains a significant barrier. Investigating how epigenetic alterations contribute to ferroptosis resistance could reveal new targets for overcoming this challenge, particularly in refractory GICs. The integration of CRISPR screens and epigenetic drug libraries could help identify key regulatory elements driving resistance (229). Furthermore, single-cell transcriptomics and spatial transcriptomics could provide insights into intra-tumoral heterogeneity and epigenetic adaptations that enable cancer cells to evade ferroptosis (230).

In conclusion, epigenetic regulation plays a crucial role in modulating ferroptosis sensitivity in GICs, offering a promising avenue for therapy. While epigenetic drugs enhance ferroptosis and inhibit tumor growth, challenges remain in clinical translation. Advancing technologies like single-cell sequencing, CRISPR/Cas9 and AI-driven drug discovery may help overcome resistance and enable personalized ferroptosis-targeted therapies.

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Availability of data and materials

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Authors' contributions

LG, LW, SL, HY and PJ conceived the study. LG and LW interpreted the relevant literature and wrote the original manuscript. SZ, SX and XC prepared figures and tables. YZ and FL revised the manuscript. SL, HY and PJ reviewed and edited the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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