

# Regulators of epigenetic change in ferroptosis-associated cancer (Review)

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**Abstract.** The occurrence of tumors is associated with the upregulation or downregulation of certain genes. The identification of novel tumor therapies has revealed that regulation of tumor cell death can either promote or suppress the occurrence and development of tumors. Iron-dependent lipid free oxygen radical accumulation causes tumor cells to die by ferroptosis, a form of regulated cell death. Multiple mechanisms mediate this mode of cell death, including redox homeostasis, iron metabolism, mitochondrial activity, breakdown of amino acids, lipids and sugars and epigenetic regulatory and disease-associated signaling pathways. The present review discussed epigenetic mechanism of ferroptosis with the aim of providing novel insight for optimization of the effects of antitumor therapy.

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## 1. Introduction

Under physiological and pathological conditions, cell life cycle comes to an end with cell death. Necrosis and apoptosis are considered forms of cell death. Studies have reported that certain forms of programmed cell death, such as autophagy and necroptosis, exhibit unique pathophysiological features that are distinct from other forms of programmed cell death, such as necrosis and apoptosis (1,2). In 2012, the concept of ferroptosis was proposed (3). During ferroptosis, lipid reactive oxygen species (ROS) are produced as a result of iron-dependent, non-apoptotic cell death. In ferroptosis, iron reacts with hydrogen peroxide, releasing electrons and generating hydroxyl radicals. These reactions damage intracellular lipids and proteins and cause oxidative damage to DNA, which accelerates death of tumor cells (4). Ferroptosis is morphologically and functionally distinct from necrosis, autophagy and apoptosis; it does not show typical characteristics of necrosis or apoptosis, including cytoplasmic swelling, cell shrinkage and rupture, presence of apoptotic bodies or cytoskeletal disintegration. Additionally, unlike autophagy, it does not involve formation of closed lipid membrane bilayers, but a specific structure known as the autophagic vacuole (5). In terms of morphology, ferroptosis is marked by mitochondrial shrinkage and increased membrane density (6). Ferroptosis is associated with a range of diseases (eg:gastric cancer) (7). Ferroptosis is regulated by epigenetic mechanisms (8). Epigenetic modifications are alterations in gene expression or cell phenotype caused by heritable changes that affect DNA methylation, histone modifications and non-coding RNA (ncRNA) regulation. Epigenetic mechanisms also control gene transcription, cell proliferation, developmental processes and immune function (9). Furthermore, epigenetic regulation is implicated in ferroptosis and tumorigenesis via modulation of metabolic genes and intermediates, thereby regulating and altering lipid peroxidation (10). The epigenetic control of ferroptosis also provides novel directions for development of therapeutic interventions, which may overcome

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the current barriers in antitumor therapy (11). The present review aimed to discuss how epigenetic regulators regulate ferroptosis and how ferroptosis contributes to tumor biology.

## 2. Epigenetics, iron homeostasis and ROS

Iron is a key trace element in the human body. It participates in heme synthesis and serves an important role in various physiological metabolic processes as a co-factor of certain key enzymes (12). The human body maintains iron homeostasis by regulating intestinal circulation and absorption of iron in the reticuloendothelial system via coordination of iron absorption, utilization, storage and circulation (13). There are numerous genes involved in maintaining iron homeostasis. Cellular iron homeostasis is primarily controlled by iron regulatory protein (IRP)-iron response element (14). IRP is involved in regulation of iron absorption, transport and storage, alongside transferrin receptor 1 (TFR1), divalent metal ion transporter (DMT1) and ferritin (15). Iron metabolism in the human body is primarily regulated by hepcidin-ferroportin (HAMP-FPN), in which HAMP regulates iron uptake and release in tissue, as well as iron homeostasis in the body (16). Under iron overload, HAMP binds to FPN on target cell membranes and internalizes and degrades FPN in lysosomes, thereby inhibiting iron absorption by enterocytes and releasing iron from macrophages or hepatocytes into the serum, thus regulating iron absorption and distribution (17). At the molecular level, HAMP is regulated by the bone morphogenetic protein (BMP)/hemojuvelin (HJV)/SMAD signaling pathway (18). HJV is a co-receptor of BMP (19). By enhancing BMP expression, the SMAD signaling pathway is stimulated and HAMP expression is promoted (20). BMP stimulates HAMP expression; this process is also regulated by HFE protein (21). In a high-iron environment, transferrin competes to capture HFE-bound TFR1, resulting in HFE dissociating from TFR1 and binding to TFR2, thereby activating the SMAD signaling pathway and inducing HAMP expression. Membrane-type serine protease 2 inhibits HAMP expression by shear HJV negative feedback. Any gene abnormalities in the signal transduction pathway regulated by HAMP affect the expression of HAMP and cause disorders associated with iron metabolism (22). Recent studies (23-25) on iron metabolism have revealed that epigenetic inheritance serves an important role in iron homeostasis metabolism. DNA methylation generally occurs in cytosine-guanine dinucleotide CpG-rich DNA regions, called CpG islands (CGIs), which are the most widely studied epigenetic modifications and serve an important role in the regulation of gene expression. Vertebrates have a higher methylation rate of CpG dinucleotides than mammals, with ~80% containing 5-methylcytosine (5mC), a gene silencing marker. There are certain exceptions to this hypermethylated state, namely CGIs, which are typically hypomethylated in comparison with the rest of the genome (26). CGIs in promoter regions overlap in the earliest vertebrates and humans, suggesting a coevolutionary CGI-compatible system. DNA sequence features are characteristic of CGI, including hypomethylation of DNA, high CpG and GC content and transcription factor binding (27). Transcription factors and chromatin-modifying enzymes are recruited along with transcriptional activators by these

sequence features. CGIs represent a ubiquitous class of DNA sequences commonly associated with promoters of vertebrate genes whose sequence features make them transcriptionally active (28). DNA sequence and chromatin determinants allow identification of CGIs, including decreased DNA methylation (5mC), increased CpG and GC content and histone H3 trimethylation (H3K4me3) and transcription factor binding sites (29). Increased DNA methylation leads to gene silencing, while decreased DNA methylation activates gene expression. Iron metabolism is associated with DNA methylation and iron level and Oxidation state affect DNA methylation (30). Increased free iron content in the brain due to oxidative stress leads to excessive S-adenosine homocysteine in HFE mutant mice by inhibition of the activity of DNA methyltransferase (31). Treatment with the iron chelator deferoxamine improves activity of DNA methyltransferase and certain breast cancer cells are induced by methylation (32). 3-Hydroxybutyrate dehydrogenase 2 is a rate-limiting enzyme in mammalian ferritin synthesis. Inhibition of its expression causes iron overload in cells and mitochondria (33). In tumor cell proliferation, iron demand is increased and the expression of genes associated with iron metabolism is affected. Previous studies (34,35) have found that low expression of FPN in patients with breast cancer indicates poor survival. *In vitro* studies (36,37) also found that inhibition of FPN expression promotes tumor growth, while overexpression of FPN hinders tumor growth. Low expression of FPN in breast cancer is regulated by nuclear factor erythroid 2-related factor 2 (NRF2) and is inhibited by hypermethylation of CGIs in the FPN promoter region, indicating that breast cancer can be inhibited by targeting FPN or upstream regulatory factors (38). HAMP expression is inhibited in patients with hepatocellular carcinoma (HCC), which is accompanied by hypermethylation of the highly conserved CGI site in its promoter region (38). Demethylating drug treatment removes hypermethylation of the HAMP promoter and upregulates expression of HAMP in HCC cells (39). TFR2 in HCC cells is also regulated by hepcidin in hepatocellular carcinoma. Therefore, regulation of HAMP by hypermethylation is a recently (40) identified form of epigenetic regulation of iron metabolism, which provides a novel area of research on tumors and iron. Since iron can easily change its valence state and switch between  $\text{Fe}^{2+}$  and  $\text{Fe}^{3+}$ , iron is a key catalyst to produce active free radicals within aerobic organisms. Rigid binding between iron and transferrin occurs *in vivo*. The activity of  $\text{O}^{2-}$  and  $\text{H}_2\text{O}_2$  is not sufficient for oxidation of certain macromolecules, such as nucleic acids and proteins. Iron overload is not always toxic and the excess iron can initially be chelated in ferritin or lysosomes in a safe manner. However, once the quantity of accumulated iron exceeds storage capacity, Iron not chelated with ferritin emerges, promoting oxidative stress responses (41). The reaction between  $\text{Fe}^{2+}$  and  $\text{H}_2\text{O}_2$  produces hydroxyl radical ( $\text{HO}\cdot$ ), which is known as the Fenton reaction (42). Iron not chelated with ferritin is more conducive to Fenton reaction than iron chelated with ferritin and unstable iron present in the body passes through  $\text{HO}\cdot$  with  $\text{RO}\cdot$  generation, which enhances the effect of  $\text{H}_2\text{O}_2$  and other organic peroxides in cells (43). The majority of  $\text{O}_2$  consumed by aerobic organisms is safely reduced to  $\text{H}_2\text{O}$  in a four-electron transfer reaction catalyzed by the cytochrome oxidase complex IV of the mitochondrial

inner membrane respiratory chain (44). However, a fraction of unused  $O_2$  is involved in other physiological reactions, such as phagocytosis and immune activation. The toxic intermediates that form are called ROS. Under normal conditions, specific enzymes rapidly metabolize ROS, such as glutathione peroxidase (GPX) (45). There are a variety of biochemical and physiological oxidative processes in the body that produce ROS; these processes are also linked to numerous physiological and pathological processes, eg: heart disease (46). By regulating intracellular signal transduction and homeostasis, ROS exert beneficial effects at low concentrations. At high concentrations, however, ROS primarily cause protein, lipid and DNA damage. Endogenous ROS are primarily derived from byproducts of subcellular organelles such as mitochondria. A normal cell can become malignant if it contains high levels of ROS. It has been shown that ROS influence epigenetic inheritance, including DNA methylation (47). In cancer cells, ROS enhance DNA methylation, leading to silencing of tumor suppressor and antioxidant genes, and cancer cell proliferation under oxidative stress. In colorectal cancer cells, ROS increase expression of caudal type homeobox 1 (CDX1) (48). Treatment with  $H_2O_2$  increases expression and activity of CDX1, DNA methyltransferase 1 (DNMT1) and histone deacetylase (HDAC1) in cancer cells, which promotes cancer progression (49). In Parkinson's disease, peroxisome proliferators-activated receptors coactivator 1 $\alpha$  (PGC-1 $\alpha$ ) downregulation is associated with mitochondrial dysfunction, oxidative stress and inflammation. PGC-1 $\alpha$  is required by nerve cells to induce proteins that detoxify ROS, such as GPX (50). In PGC-1 $\alpha$  knockout mice, glial cells are more susceptible compared with normal mice to neuroinflammation induced by Toll-like receptor 4 agonists. PGC-1 $\alpha$  downregulation leads to increased ROS and neurological damage (51,52). Previous studies (53,54) have shown that proinflammatory fatty acid palmitate leads to atypical cytosine methylation in the PGC-1 $\alpha$  gene promoter and decreases gene expression and mitochondrial content. Thus, PGC-1 $\alpha$  promoter methylation is associated with dysfunctional inflammatory signaling (55). Cells in the body continuously produce and remove ROS in a dynamic equilibrium under physiological conditions. Once redox imbalance occurs in cells, redox signals are generated, which lead to adaptive changes in gene expression. Iron and iron derivatives bind to ROS-producing enzymes, such as the NADPH and cytochrome P450 enzyme systems. Lysosomes also contain redox-active iron pools from extracellular sources that catalyze the generation of damaging free radicals via the Fenton reaction (56).

### 3. Mechanisms of ferroptosis in cancer

Cell death mediated by ferroptosis occurs in numerous types of disease, including cancer. Unlike autophagy and apoptosis, ferroptosis is characterized by dependence on intracellular free iron ions and ROS (57). Activated circulating iron ( $Fe^{3+}$ ) enters cells and is reduced to  $Fe^{2+}$  by ferrooxidoreductase six transmembrane epithelial antigen 3 (58). Once endosomes release  $Fe^{2+}$  via DMT1, it is transported to the cytoplasm, where it couples with ROS, leading to lipid peroxidation and ferroptosis (59). ROS are molecules containing reduced oxygen, which include superoxide ( $O_2^-$ ) and peroxides ( $H_2O_2$

and ROOH), as well as free radicals (HO and RO). In cells, increased ROS production induces ferroptosis (60). In cases of lipid peroxidation and oxidative stress, the permeability of the cell membrane directly leads to reduction or disappearance of intracellular mitochondria and the rupture or aggregation of mitochondrial membranes (61). In the case of malignant tumors, ferroptosis serves a crucial role in eradicating tumor cells as an adaptive process (62). Tumor cells are highly sensitive to ferroptosis, which controls the abundance of iron by activating expression of transferrin receptor and ferritin, thus activating the RAS/MEK signaling pathway. When the RAS/MEK signaling pathway is activated, tumor cells are prevented from absorbing cystine and ROS are released through mitochondrial voltage-dependent anion channels (63). For example, activated RAS/MEK signaling induces expression of SOSC1, which controls expression of P53, decreases expression of cystine transporter and sensitizes cells to ferroptosis (64). In addition, various components (Beclin1) promote ferroptosis and indirectly decrease activity of system Xc (65). Low member 11 of the solute carrier family 7 (SLC7A11) expression prevents Cys2 transport and activation of the glutathione (GSH)-independent thioredoxin (TXN) system, leading to dysfunction of the GSH/GPX4 lipid peroxidation pathway (66). Mechanistically, this may be due to the inability to transfer a sufficient quantity of reducing equivalents from Cys2 to TXN (via TXN reductase) to maintain the endogenous antioxidant lipid  $\alpha$ -tocopherol in a reduced state, thereby promoting ROS accumulation and ferroptosis (67). In cancer, the mechanism of ferroptosis primarily involves three major systems (Fig. 1).

**Xc-/GSH/GPX4 system.** The antioxidant system Xc- consists of transporters located on cell membranes. The primary system maintains homeostasis of glutamate and cystine on cell membranes, where it pumps out glutamate molecules and pumps in cystine molecules (68). The functional subunits of the system Xc- are SLC7A11 and SLC3A2 (68). GSH is synthesized by reduction of cystine to cysteine by system Xc-. Glutamyl-L-cysteine-L-glycine (GSH) is an endogenous antioxidant consisting of glutamic acid, cysteine and glycine that scavenges free radicals. Its production is dependent on activity of glutamate-cysteine ligase and inhibition of system Xc- attenuates its activity, resulting in GSH depletion and leading to ferroptosis (69). Trans-sulfuration is another mechanism by which methionine synthesizes cysteine. Cysteine is still synthesized when intracellular system Xc- is inhibited (70). Thus, ferroptotic inducers that negatively regulate system Xc- cannot effectively kill cells. The trans-sulfuration pathway is activated by interfering with RNA dynamics to decrease expression of cysteine transfer RNA synthetase. As a result, cells become less sensitive to ferroptosis-inducing agents (71). Cells that contain GPX4 decrease lipid peroxidation, which promotes their survival. Aberrant expression of GPX4 is linked to a range of diseases (breast cancer) in humans and depletion of GPX4 increases  $H_2O_2$ -containing phospholipids (72), promotes lipoxygenase-mediated lipid peroxidation and induces ferroptosis (73). GPX4 is highly expressed in tumor tissue, while histone H3 is trimethylated at lysine 4 (H3K4me3) and

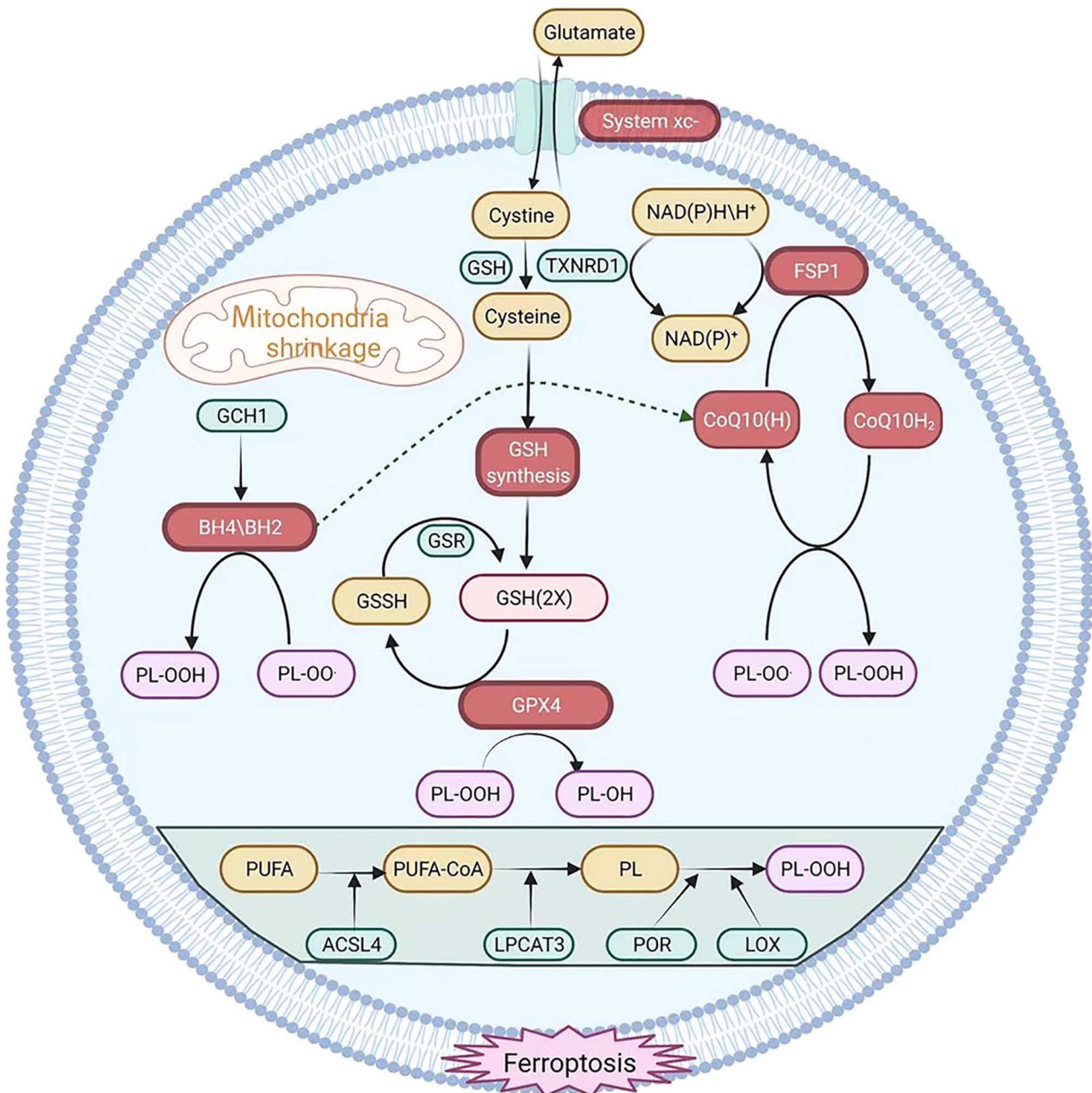


Figure 1. Iron death as an adaptive process is key for eradication of oncogenic cells in malignant tumors. The mechanisms of iron death in cancer involve three primary systems (Xc<sup>-</sup>/GSH/GPX4 system, NADPH/FSP1/coenzyme Q10, GTP cyclohydrolase 1 (GCH1)-tetrahydrobiopterin (BH<sub>4</sub>). Glutathione (GSH), thioredoxin reductase 1(TXNRD1), ferroptosis suppressor protein 1(FSP1), Coenzyme Q10(COQ10), GTP-CH1(GCH1), biopterin(BH<sub>4</sub>), Glutathione Disulfide Reductase(GSR), glutathione(GSSH), phospholipid(PL), Glutathione Peroxidase(GPX), polyunsaturated fatty acid(PUFA), acyl-CoA synthetase long chain family member 4(ACSL4), Lysophosphatidylcholine Acyltransferase(LPCAT), (cytochrome P450 oxidoreductase)POR, Lipoxygenase(LOX).

acetylated at lysine 27 (H3K27ac) at the GPX4 transcriptional start site. Patients with cancer have a poor prognosis when epigenetic modifications of GPX4 are present; thus, elevated expression of GPX4 in tumor tissue may be due to epigenetic modifications (74). In addition, the activation of autophagy degrades intracellular ferritin and directly induces ferroptosis in tumor cells. Autophagy is a lysosome-dependent process that promotes ferroptosis by generating lysosomal ROS. Promoting autophagy effectively enhances ferroptosis in tumor cells (75). The autophagy-mediated nuclear receptor coactivator (NCOA4) signaling pathway promotes ferritin degradation and enhances ferroptosis when NCOA4

is overexpressed (76), which demonstrates the association between ferroptosis and apoptosis.

*NADPH/ferroptosis suppressor protein 1 (FSP1)/coenzyme Q10 (COQ10)*. Although GPX4 is a key regulator of ferroptosis, inhibition of GPX4 does not induce ferroptosis in certain cell lines. A previous study identified potential factors that regulate ferroptosis independently of the GPX4 signaling pathway (72). Cells were treated with a ferroptosis initiator [RAS selective lethal 3 (RSL3)], and it was observed that Glutathione Independent Iron Death Inhibitor Protein (FSP1) induced apoptosis. The inhibition of GPX4 leads to ferroptosis

when FSP1 is overexpressed. Therefore, FSP1 may act as a ferroptosis inhibitor (77). However, AIFM1, although homologous to FSP1, does not inhibit ferroptosis (78). FSP1 may inhibit ferroptosis because its N-terminal myristoylated mediates FSP1 localization to the plasma membrane. Furthermore, myristoylation of the N-terminus of FSP1 promotes binding of target proteins to the cell membrane. In the plasma membrane, COQ10 serves as a lipophilic radical scavenger (79), while FSP1 serves as a NADPH-dependent COQ oxidoreductase that regulates COQ10 *in vitro*. FSP1 is a component of the traditional mitochondrial respiratory chain that catalyzes the same reactions as complex I. Extra-mitochondrial ubiquinone is reduced from COQ10 by FSP1, which either directly captures lipid free radicals or indirectly serves as an antioxidant by recycling  $\alpha$ -tocopherol (77). Idebenone, a soluble analog of COQ10, inhibits ferroptosis and lipid peroxidation by catalyzing the first step in the biosynthesis of COQ2 (80). The aforementioned findings showed that FSP1, like GPX4, inhibits ferroptosis by regulating the non-mitochondrial COQ10 antioxidant system (80).

*GTP cyclohydrolase 1 (GCH1)-tetrahydrobiopterin (BH4)*. The redox-active cofactor BH4 serves a role in production of neurotransmitters, carbon monoxide and aromatic amino acids. *In vitro*, BH4 exhibits antioxidant properties and GCH1 limits BH4 synthesis (82). In tumor cells, GCH1 overexpression clears lipid peroxidation and protects cells from ferroptosis. Overexpression of GCH1 protects against RSL3-induced ferroptosis when cells were treated with RSL3 and apoptosis-inducing agents. GCH1 protects cells from ferroptosis (83). Treatment of RSL3-exposed cells with BH4 completely prevents ferroptosis. It has been previously shown that GCH1 acts independently of the ferroptosis and GSH pathways to prevent ferroptosis (84). Notably, BH4 as a cofactor for biosynthetic enzymes does not serve a role in ferroptosis protection (85). In addition, BH4 converts phenylalanine to tyrosine to promote synthesis of COQ10, thereby exerting an antioxidant effect (86).

#### 4. Epigenetic regulation of ferroptosis in cancer

Alterations in DNA methylation, histone modifications and ncRNA regulation are characteristic of epigenetic regulation, which determines gene transcription, cell proliferation, developmental processes and immune function (87). Epigenetic regulation is important for ferroptosis.

*DNA methylation and ferroptosis*. There are numerous roles for DNA methylation in cancer, including suppression of DNA methylation at transcriptional start sites of key gene regulatory elements, such as enhancers and promoters (88). In DNA methylation, a methyl group is typically inserted at the carbon 5 position of the cytosine base (5mC) via DNA methylation mediated by CpG transferase DNMTs (89). DNA methylation primarily regulates mitotic gene expression, centromere stability and chromatin segregation. In addition, 5-hydroxymethylcytosine (5hmC) has been demonstrated to be produced by 5mC oxidation. 5hmC has been widely studied in relation to its potential role in modifying methylation landscapes by ten-eleven translocation (TET)

enzymes (90,91). The ability of TET proteins to oxidize 5hmC to 5-formylcytosine and 5-carboxycytosine indicates utilization of the base excision repair pathway, while thymine DNA glycosylase excises cytosine and replaces it with an unmodified cytosine (92). CpG sites are found at ~28 million sites in the human genome. The distribution of CpG sites in somatic cells is uneven and ~70% of CpG sites are oxidized in normal somatic cells (93). Clusters of CpG sites are known as CGIs; CpG sites in CGIs tend not to be methylated in somatic cells. Chromosomes are their primary medium. Unmethylated CpG sites are found in promoter CGIs, where transcription factors bind to control gene expression. The CpG coast is ~2 kb pairs away from the CGI and has a lower density of CpGs than the CGI (94). Normal cells also contain these unmethylated regions that regulate gene activity (95). During tumorigenesis, normal epigenetic processes such as DNA methylation are disrupted. Tumor development is primarily accompanied by genome-wide hypomethylation and DNA hypermethylation in the promoter regions of CGIs (96). Cell proliferation and tumor suppressor genes and downstream signaling pathways are primarily silenced by the hypermethylation of CGIs (97). Moreover, tumors also abnormally express DNMT enzymes, resulting in aberrant DNA methylation across the genome, potentially causing mutations in genomic sequences (98). Aneuploidy and genomic instability are associated with genome-wide hypomethylation in cancer (99). The abnormal expression of transposable elements and oncogenes is also associated with genome-wide DNA hypomethylation, which disrupts cellular pathways and changes chromatin structure, as chromatin structure and DNA methylation are associated and a nucleosome is required before 5mC can be obtained (100). To anchor the DNMT enzyme, abnormal DNA methylation must disrupt chromatin structure (101). The most studied (102) epigenetic modification is DNA methylation (103). However, the mechanism of this process is unclear and the number of cancer-associated genes that are silenced and targeted is unknown. A recent study on the association between DNA methylation, ferroptosis and cancer has led to novel targeted therapy for cancer (104). Hydrase, lymphoid specific (HELLS/LSH) is a chromatin remodeling enzyme that inhibits ferroptosis by activating metabolic genes such as stearyl-coenzyme A desaturase (SCD). HELLS induces epigenetic silencing of the long non-coding RNA (lncRNA) LINC00472. LINC00472, as a tumor suppressor, is downregulated in tumors and can inhibit ferroptosis (105). Egl nine homolog 1 and c-Myc in tumor cells activate LSH expression by inhibiting hypoxia inducible factor 1. LSH inhibits iron dynamics by activating GLUT1, SCD1 and fatty acid desaturase 2, which are involved in lipid metabolism, by interacting with WD repeat domain 76. Several types of cancer tissue (pancreatic and lung cancer) express high levels of SCD1, an enzyme that catalyzes fatty acid synthesis at the rate-limiting step. Through inhibition of SCD1, COQ10 activity is decreased, resulting in lipid oxidation and cell death (106). GPX4 DNA methylation in the nucleus pulposus is induced by homocysteine treatment, resulting in ferroptosis (107). Furthermore, DNA hypermethylation of the cadherin 1 (CDH1) gene promoter increases ferroptosis by suppressing expression of E-cadherin, which is encoded by CDH1 (108). DNA methylation contributes to

ferroptosis-associated gene silencing, as demonstrated by the aforementioned studies. There is, however, a need for further research to determine whether DNA methylation also affects other ferroptosis-associated genes. Notably, TET proteins also catalyze DNA demethylation by oxidizing 5mC (109).

*ncRNAs and ferroptosis.* RNA is a key biological macromolecule in cells and it can be classified into two categories according to its function, namely, coding RNA and ncRNA. RNA is responsible for gene regulation and information transmission and is involved in disease. For example, nc-RNAs encode tumor peptides or proteins (110,111). The following subsections review ncRNAs in the context of microRNAs (miRNAs or miRs), lncRNAs and circular RNAs (circRNAs) involved in ferroptosis.

*miRNAs and ferroptosis.* miRNAs are the most well-studied (112) ncRNAs in tumor biology (113). Endogenous genes encode a class of RNA molecules known as miRNAs, which are single-stranded ncRNA molecules with a length of 20-24 nucleotides. miRNAs regulate translational and transcriptional activities that control metabolic pathways, tumor growth and cell migration and invasion and induce resistance to chemotherapeutic agents (113). During post-transcriptional processing, miRNAs bind to the 3' untranslated region of target mRNAs and regulate gene expression. miRNAs that bind to specific mRNAs directly inhibit translation by suppressing translation or decreasing mRNA stability post-transcriptionally (114). In addition to controlling cell differentiation, proliferation, drug resistance and lipid metabolism, miRNAs also participate in several other biological processes. For example, miRNAs prevent translation by inactivating or inducing mRNA degradation, which is a key step in post-transcriptional gene regulation (115). Cancer cells are genetically or epigenetically altered as a result. Furthermore, miRNAs inhibit tumor cell proliferation by altering ferroptosis (116). For example, miR-9 interferes with the catalytic efficacy of glutamic-oxaloacetic transaminase 1 in melanoma cells, thus inhibiting its ability to transaminate  $\alpha$ -ketoglutarate. By contrast, miR-9 inhibition causes lipid ROS accumulation, thereby increasing ferroptosis (117). Upregulation of miR-137 protects melanoma cells against ferroptosis by inhibiting the glutamine transporter SLC1A5 (118). By decreasing ferrous iron levels in the cytoplasm, miR-7-5p also decreases tumor cell migration and invasion (119). By decreasing tumor cell susceptibility to ferroptosis induced by treatment with RSL3 and erastin, activating transcription factor 4 knockout increases inhibition of tumor cell proliferation (120). In addition, GPX4 is inhibited by miR-4715-3p and cisplatin sensitivity is enhanced by miR-4715-3p. As a result of inhibition of the intracellular aurora kinase A, a key serine-threonine kinase in mitosis, the expression of miR-4715-3p is suppressed (121). In addition, inhibition of miR-4715-3p results in decreased levels of intracellular GSH, thereby preventing ferroptosis (122). Human colon adenocarcinoma cells are protected from oxidative damage by miR-185, which increases GPX2 levels in cells (123). Furthermore, specific transcriptional targets of miRNAs are involved in GSH metabolism, which is associated with ferroptosis and tumorigenesis (124,125). miRNAs

serve both tumor-suppressive and -promotive functions in ferroptosis. Additionally, miRNAs modulate gene transcription at the mRNA level to decrease tumorigenesis, ferroptosis or degraded exon production (126). To determine the roles of miRNAs in tumor resistance mechanisms, it is imperative to understand the molecular mechanisms of miRNAs.

*lncRNAs and ferroptosis.* RNA molecules >200 nucleotides in length are known as lncRNAs and influence gene expression at different levels, including transcription and post-transcriptional translation. lncRNAs have also been reported to be key for a variety of biological processes, such as cell differentiation, regulation of the cell cycle and maintenance of stem cell pluripotency (127). Via downregulation of membrane receptors and inhibition of necroptosis-associated proteins, overexpression of lncRNAs inhibits the extrinsic apoptotic pathway in tumor cells (128). lncRNAs are important regulators of ferroptosis. A number of them affect miRNAs, while others bind to specific enzymes. Wang *et al* (129) reported that the lncRNAs LINC00336 and embryonic lethal, abnormal vision, *Drosophila*-like 1 (ELAVL1) inhibit ferroptosis by interacting with each other. In addition, ELAVL1 increases LINC00336 expression by stabilizing its post-transcriptional levels when RSL3 is used to activate ferroptosis in lung cancer cell lines. Overexpression of LINC00336 inhibits ferroptosis caused by RSL3 treatment, as well as protein kinase-induced ferroptosis. Furthermore, overexpression of LINC00336 decreases intracellular  $\text{Fe}^{2+}$  and mitochondrial superoxide concentrations, as well as ROS production, demonstrating that LINC00336 overexpression inhibits ferroptosis (129). Urothelial cancer associated 1 (UCA1) sponges miR-16 and increases expression of glutaminase 2 (GLS2) in bladder cancer cells. There are two mechanisms by which lncRNAs affect ferroptosis (130). GLS2 enzyme catalyzes conversion of glutamine to glutamate and subsequent synthesis of GSH. NADPH is produced when glutamine enters the tricarboxylic acid cycle. Glutathione is reduced to GSH in the presence of NADPH (131). Therefore, UCA1 regulates GSH and NADPH expression, thereby enhancing the antioxidant effects of GPX4 and inhibiting ferroptosis in tumor cells by decreasing ROS production (132). The transcription factor NRF2 also has antioxidant properties and can activate downstream antioxidant factors. NRF2 can promote the production of NADPH via the pentose phosphate pathway, thereby enhancing antioxidant activity. Additionally, NRF2 activates transcription of GSH and GPX family genes, while GPX4 is activated to exert antioxidant effects during ferroptosis (133). The balance of intracellular iron levels is key for cell survival. The co-function of transferrin and transferrin receptor is required for the absorption of  $\text{Fe}^{3+}$  by cells. Subsequently,  $\text{Fe}^{3+}$  becomes  $\text{Fe}^{2+}$  through a redox reaction and it is then stored in the iron pool (134). Ferroptosis occurs when  $\text{Fe}^{2+}$  donates electrons to oxygen in the Fenton reaction to form ROS, which catalyzes generation of lipid free oxygen radicals (135). In HCC, for example, expression of the ncRNA plasmacytoma variant translocation 1 (PVT1) is increased; PVT1 binds to miR-150 and regulates the target hypoxia-inducible gene (HIG2) (136). HIG2 is involved in ferroptosis and iron uptake via hypoxia-induced protein expression. Decreased transferrin receptor and increased ferritin light chain expression

are observed when PVT1 is silenced, thereby decreasing iron uptake and affecting ferroptosis (137). The induction of ferroptosis by erastin results in upregulation of the lncRNA GA binding protein subunit  $\beta 1$  (GABPB1)-antisense RNA 1, blocking of the transcription and translation of GABPB1 and the inhibition of peroxidase 5 (PRDX5) expression. PRDX5 is less effective than non tumor tissue at preventing ROS production from  $H_2O_2$ , which ultimately impairs the antioxidant capacity of tumor cells, resulting in increased cell death (138). Melanoma glucose-6-phosphate dehydrogenase (G6PD) may stimulate NADPH production, thereby activating NADPH oxidase 4 (NOX4) (139). Superoxide and ROS are produced by NOX4, a transmembrane protein. When growth arrest specific 5 is silenced, G6PD and NOX4 activity is increased (140). Furthermore, ferroptosis is induced by G6PD and NOX4 in tumor cells (141). Inhibition of iron-induced cell death by targeting the miR-106B-5p/acyl-coenzyme A synthetase long chain family member 4 axis is a mechanism by which H19 promotes cancer progression (142). Iron-induced death is also regulated by PVT1 via activation of TFR1 and TP53 by miR-214. The PVT1/miR-214-3p/GPX4 signaling pathway activates ketamine and inhibits the proliferation of HCC cells both *in vitro* and *in vivo*, leading to iron-induced cell death (143). In addition, lncRNA ZNF8 antisense RNA 1 acts as a competing endogenous RNA for iron-induced death via the miR-150-5p/SLC38A1 axis (144). Multiple other lncRNAs are involved in iron-induced tumor cell death. Further studies are needed to investigate the specific mechanism by which lncRNA regulates iron-related cell death.

**circRNAs and ferroptosis.** circRNAs are formed by the 3' and 5' ends of mRNAs. According to their structural features, they are primarily classified into three categories, namely, exonic, circular intronic and exonic intronic circRNAs, and they function as miRNA sponges and protein scaffolds (145). Compared with miRNAs, the abundance, conservation and tissue specificity of circRNAs make them better biomarkers for certain pathological states. For example, circRNA-002178 is abnormally expressed in lung cancer, which is of great help in the diagnosis of lung cancer (146). The majority of circRNAs are highly stable and specific. Cancer cells express abnormal levels of circRNAs, which are involved in cell proliferation, autophagy and apoptosis, among other aspects of programmed cell death (147). circRNAs affect the post-transcriptional stability of miRNAs by altering their target gene expression. In tumor cells, circRNAs serve as sponges and regulate ferroptosis (148). Furthermore, they enhance tumor cell proliferation and invasion by sponging miR-761 and activating integrin  $\beta 8$  (ITGB8) in glioma, inhibit ferroptosis by activating ITGB8 and inhibit apoptosis by targeting MET, while knockdown of circ-tubulin kinase 2 promotes erastin-induced ferroptosis (149). In addition, 526 circRNAs are dysregulated in cervical cancer cells according to a previous high-throughput microarray-based study (150). circRNAs are predominantly involved in GSH metabolism according to a previous bioinformatics analysis (151). However, associated downstream factors and miRNAs have not been screened (152). Therefore, further studies on regulation of circRNAs in ferroptosis are needed (Fig. 2).

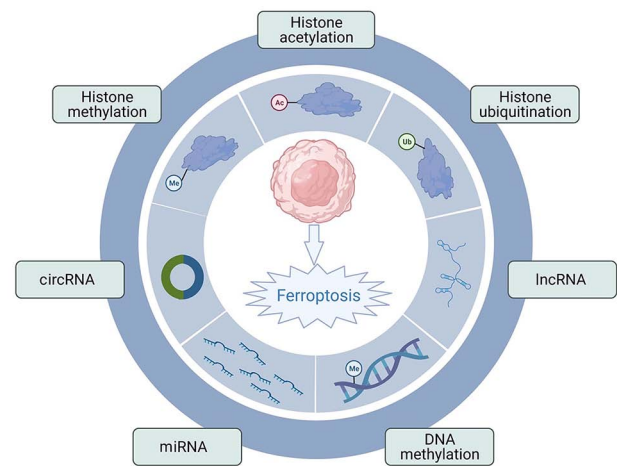


Figure 2. In tumor cells, epigenetic regulation primarily includes DNA methylation and ncRNA and histone modification regulation, which regulate cell proliferation, developmental processes and immune function by promoting or inhibiting ferroptosis. lnc, long non-coding; miRNA, microRNA; circ, circular.

## 5. Histone modifications and ferroptosis

Chemical modifications of the tails of four core histone proteins (H2A, H2B, H3 and H4) alter the interactions between histones and other nuclear proteins, according to a recent study (153). Consequently, histone modification modifies expression of target genes. For example, the ferroptosis-associated genes GPX4 and SLC7A11 are regulated by histone modifications in non-Hodgkin lymphoma (154,155). Therefore, regulation of ferroptosis is dependent on histone modification.

**Histone methylation and ferroptosis.** The histone H3 lysine 9 demethylase that regulates SLC7A11 expression in response to erastin-induced ferroptosis is lysine demethylase 3B (156). E1A binding protein p300-CREB binding protein (CREBBP), which is involved in transactivation of genes, acetylates nuclear factor erythroid-derived 2-like 2 (NFE2L2) (157). Mouse double minute 2 homolog is a proto-oncogene associated with TP53 stability and activation, while cyclin-dependent kinase inhibitor 2A/ARF promotes its degradation. Ferroptosis is promoted by ARF independently of TP53 (158). Cancer is frequently caused by TP53 inactivation or mutations. A number of genes controlled by TP53 serve key roles in various cellular processes such as cell proliferation, cell cycle progression, cell death and response to DNA damage. Cancer cells, when activated by TP53, not only promote tumor growth but also inhibit ferroptosis (159). ARF protein disrupts CREBBP-NFE2L2 interaction, resulting in attenuated acetylation of NFE2L2 and the decreased expression of SLC7A11 mediated by NFE2L2 (160). Furthermore, members of the bromodomain (BRD) family are epigenetic regulators that recognize acetylated lysine residues on histones. JQ1, an inhibitor of the BRD4 complex, induces ferroptosis in breast and lung cancer cells by decreasing expression of GPX4, SLC7A11 and SLC3A2. Other anti-ferroptotic genes are also regulated by BRD4 (161).

Table I. Epigenetic regulatory mechanisms associated with ferroptosis in cancer.

A, DNA modification					
Molecular mechanism	Effect on ferroptosis	First author	Year of publication	Country	(Refs.)
HELLS induce epigenetic silencing of the lncRNA LINC00472	Inhibition	Mao <i>et al.</i> ,	2018	China	(105)
EGLN1 and c-Myc in tumor cells activate LSH expression by inhibiting HIF-1	Inhibition	Jiang <i>et al.</i> ,	2017	China	(106)
DNA methylation modifier LSH interacts with WDR76 by activating lipid metabolism-related genes GLUT1, SCD1, and FADS2	Inhibition	Jiang <i>et al.</i> ,	2017	China	(106)
Inhibition of SCD1 leads to a decrease in coenzyme Q10 activity	Promotion	Jiang <i>et al.</i> ,	2017	China	(106)
Homocysteine treatment induces DNAmethylation of GPX4 gene in the nucleus pulposus	Promotion	Zhang <i>et al.</i> ,	2020	China	(107)
DNA hypermethylation of the CDH1 gene promoter suppresses expression of E-cadherin	Promotion	Van,	2014	Belgium	(108)
B, Non-coding RNA					
Molecular mechanism	Effect on ferroptosis	First author	Year of publication	Country	(Refs.)
miR-9 inhibits GOT1 and prevents the transamination of $\alpha$ -ketoglutarate results in accumulation of lipid ROS	Promotion	Lande <i>et al.</i> ,	2020	India	(117)
miR-137 inhibits SLC1A5 expression	Inhibition	Luo <i>et al.</i> ,	2018	China	(118)
miR-7-5p decreases ferrous iron levels	Inhibition	Tomita <i>et al.</i> ,	2021	Japan	(119)
miR-4715-3p inhibits GPX4 expression	Promotion	Gomaa <i>et al.</i> ,	2019	USA	(121)
Inhibition of AURKA expression	Inhibition	Gomaa <i>et al.</i> ,	2019	USA	(121)
inhibiting miR-4715-3p expression reduces depletion of GSH levels					
miR-185 upregulates GPX2 expression	Inhibition	Zhuang <i>et al.</i> ,	2020	China	(123)
lncRNA LINC00336 relates to ELAVI 1 to decrease the intracellular Fe <sup>2+</sup> , ROS level	Inhibition	Wang <i>et al.</i> ,	2019	China	(129)
lncRNA UCA1 upregulates the expression of GSH and NADPH, enabling GPX4 to exert an antioxidant effect and to reduce the production of ROS	Inhibition	Chen <i>et al.</i> ,	2019	China	(132)
lncRNA PVT1 regulates miR-150/HIG2 axis	Promotion	Xu <i>et al.</i> ,	2018	China	(136)
Circ-TTBK2 regulates miR-761/ITGB8 axis	Inhibition	Zhang <i>et al.</i> ,	2020	China	(149)
C, Histone modification					
Molecular mechanism	Effect on ferroptosis	First author	Year of publication	Country	(Refs.)
KDM3B induces H3K9me3 demethylation at the promoter region of SLC7A11 and promotes transcription	Inhibition	Wang <i>et al.</i> ,	2020	China	(156)

Table I. Continued.

C, Histone modification					
Molecular mechanism	Effect on ferroptosis	First author	Year of publication	Country	(Refs.)
Overexpression OTUB1 increase SLC7A11 expression	Inhibition	Liu <i>et al</i> ,	2019	USA	(162)
BAP1 and PRC1 reduces H2A ubiquitination of the SLC7A11 promoter and suppresses its expression	Promotion	Zhang <i>et al</i> ,	2019	USA	(153)
USP7 reduces GPX4 expression	Promotion	Dai <i>et al</i> ,	2020	China	(163)
Ubiquitin ligase HERC2 ubiquitinates and degrades NCOA4	Promotion	Lin <i>et al</i> ,	2021	China	(165)
mutant P533KR inhibits cysteine uptake and reduces GSH, leading to lipid peroxidation	Promotion	Jiang <i>et al</i> ,	2015	USA	(171)

**Histone ubiquitination and ferroptosis.** Cancer cells overexpress deubiquitinase OUT deubiquitinase ubiquitin aldehyde binding 1 (OTUB1), which stabilizes cystine transporter SLC7A11, inhibits ferroptosis and promotes tumor growth (162). BRCA1-associated protein 1 (BAP1) decreases SLC7A11 promoter H2A ubiquitination via an H2A deubiquitinase that functions as a tumor suppressor. As a result, ferroptosis is regulated and SLC7A11 expression is inhibited. The H2A ubiquitin ligases BAP1 and protein regulator of cytokinesis 1 inhibit expression of SLC7A11. The tumor suppressor deubiquitinating enzymes (DUB) inactivates P53 and BAP1 by downregulating SLC7A11 expression or enhancing OTUB1 or CD44 expression to stabilize SLC7A11 (153). As a result, tumor growth is suppressed and proteasomal activity and apoptosis are inhibited. The DUB inhibitor ubiquitin-specific protease (USP7) enhances caspase-dependent apoptosis during ferroptosis while degrading GPX4, which results in ubiquitinated protein accumulation and cell death (163). The expression of H2Bub1, which binds to the regulatory region of SLC7A11, is decreased by P53, thereby inhibiting SLC7A11 expression (164). Furthermore, ferritin degradation occurs via lysosomal or proteasomal mechanisms. Via ferritin heavy chain 1, NCOA4 binds to iron-rich ferritin on autophagosomes, thus transporting it to lysosomes for iron release. The ubiquitin ligase HERC2, which affects stability of proteins, ubiquitinates and degrades NCOA4 in environments with high iron concentrations. Therefore, ferroptosis is suppressed by inhibition of NCOA4 (165).

**Histone acetylation and ferroptosis.** The four aforementioned histones are acetylated on specific lysine residues, which is associated not only with gene transcription but also with DNA replication and repair (166). During transcription, histone acetylation induces HAT to acetylate lysine residues in histones, while histone deacetylation inhibits HDAC (167). HAT and HDAC catalyze histone acetylation and deacetylation, respectively (168). Patients with cancer have a poor prognosis when GPX4 expression is higher in tumor than in normal tissue (169). In tumor cells, high GPX4 levels may be

due to epigenetic regulation such as methylation of DNA and histones and acetylation of histones, as reported in a previous study that analyzed upstream regulation of GPX4 (170). Mutant P533KR causes lipid peroxidation and ferroptosis via decreased acetylation and cysteine uptake (171). As a result of hydrolysis of cystinase, GSH is synthesized and GSH metabolism is affected. Cystinase depletion also cause ferroptosis (Table I) (172).

## 6. Conclusion

Iron is a key element and its absorption, transport, storage and excretion are tightly regulated in the human body. Iron promotes formation of free radicals; excessive free radicals can be harm to the body by promoting tumor formation and subsequent metastasis. Study of iron metabolism in tumors has demonstrated that the combined actions of iron transporters and iron efflux regulator hepcidin promote tumorigenesis (173). Ferroptosis is an iron-dependent mechanism involving production of ROS. Mechanisms controlling transcripts that encode iron-regulated proteins, known as epigenetic regulatory mechanisms, have been reported in tumor cells (57). Furthermore, epigenetic changes in gene expression levels are not induced by changes in genomic sequences but DNA methylation, chromatin histone modifications and ncRNA regulation. Thus, abnormal epigenetic mechanisms affect gene transcription, which promotes tumor occurrence and development with certain generality and tissue specificity (174). Epigenetic modifications are key for tumor cell death and ferroptosis. The aforementioned findings may provide new therapeutic insights for the treatment of cancer in the future.

The present review summarizes the research of epigenetic inheritance and ferroptosis. The three main regulatory mechanisms of ferroptosis and ROS were introduced, with emphasis on the association between ROS and ferroptosis and epigenetic inheritance. The process of iron homeostasis metabolism and the association between iron homeostasis and reactive oxygen species were also described, which has not performed in the

other two papers (175,176). In addition, the epigenetic regulation mechanism of ferroptosis was introduced, especially the association between ncRNA, miRNA and circRNA in ferroptosis and histone ubiquitination, methylation and acetylation with ferroptosis. The aforementioned findings may provide novel options for the treatment of tumors in terms of epigenetic regulation of ferroptosis (177).

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## Authors' contributions

JWu, SZ and PW wrote the manuscript. JWa, JH, TW and LG constructed figures and tables. DL, QM and HP performed the literature review. 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

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## Competing interests

The authors declare that they have no competing interests.

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