Journal of Pharmaceutical Analysis 14 (2024) 101012

Contents lists available at ScienceDirect

Journal of Pharmaceutical Analysis

journal homepage: www.elsevier.com/locate/jpa

Review paper

Epigenetic regulation of targeted ferroptosis: A new strategy for drug development

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ARTICLE INFO

Article history:
Received 28 January 2024
Received in revised form
20 May 2024
Accepted 23 May 2024
Available online 28 May 2024

Keywords:
Treatment strategies
Epigenetics
Ferroptosis
Epigenetic modifiers

ABSTRACT

Ferroptosis is a newly discovered form of cell death that is influenced by iron levels and is triggered by cellular metabolism and excessive lipid peroxidation. Epigenetic regulation plays a crucial role in the development and progression of diseases, making it essential to understand these mechanisms in order to identify potential targets for drug development and clinical treatment. The intersection of ferroptosis and epigenetics has opened up new avenues for research in drug development, offering innovative strategies for combating diseases. Recent studies have shown that epigenetic modifications can impact pathways related to ferroptosis, potentially leading to organ dysfunction. Despite the increasing focus on this relationship, the role of epigenetic regulation in drug development remains largely unexplored. This article explores current research on the interplay between epigenetic regulation and ferroptosis, delving into their regulatory mechanisms and discussing the effects of existing epigenetic modification regulators on diseases. Additionally, we highlight ongoing research on epigenetic factors involved in targeting ferroptosis in cancer, providing new insights for the development of cancer treatments.

1. Introduction

Ferroptosis, as a new non-apoptotic form of cell death, was defined by Dixon et al. [1], in 2012. Different from apoptosis, necrosis, and autophagy, ferroptosis is dependent on the content of iron in cells, which leads to changes in cell morphology, biochemistry, and genetics that cause cell death. This type of death is often catalyzed by unsaturated fatty acids on the cell membrane, leading to the development of lipid peroxidation, in which ferrous ions or lipoxygenase play a crucial role. Therefore, cell metabolism, regulation of reactive oxygen species (ROS), and iron metabolism are important directions for ferroptosis research [2]. Endogenous or enzyme regulatory pathways and exogenous or transfer protein dependent pathways are two common regulatory pathways of ferroptosis, often manifested as imbalanced oxidative recovery, caused by abnormal expression and activity changes of various oxidative recovery enzymes that produce or detoxify free radicals and detoxify, leading to lipid peroxidation. The epigenetic, transcriptional, post-transcriptional, and post-translational levels of ferroptosis can be regulated under this mechanism, thereby affecting cell death [3].

It is precisely because epigenetics has been studied and developed that genetic changes in cell phenotypes can be described. These changes were not related to DNA sequence changes. For example, without altering the DNA sequence, a series of epigenetic modifications (such as DNA methylation, histone modifications, and microRNA (miRNA)) can induce heritable phenotypic changes in cells. It may lead to autoimmune diseases, cancer, and various other diseases after affecting the gene expression pattern controlled by epigenetics [4]. Therefore, in the study of the relationship between ferroptosis and disease, epigenetic regulation is an important direction. Moreover, the continuous elucidation of the epigenetic regulatory mechanism of ferroptosis has deepened our understanding of the disease and provided new directions for drug development. At present, epigenetic modifications such as DNA methylation, RNA methylation, noncoding RNA (ncRNA), histone methylation, acetylation, ubiquitination, transcription factors, and chromatin have been found to affect the occurrence of ferroptosis. This also indicates that these modification methods have value for drug development. For example, in the chromatin direction, genetic lesions in its associated modifiers and global changes in the epigenetic landscape affect the pathogenic role of these proteins in cancer, and these proteins can provide potential targets for therapeutic intervention. Moreover, the study of epigenetic regulation of ferroptosis can provide a new solution to the problem of drug

Peer review under responsibility of Xi'an Jiaotong University.
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https://doi.org/10.1016/j.jpha.2024.101012

resistance in related diseases, as well as epigenetic-specific targeted therapy. However, the study of the epigenetic regulation of ferroptosis still faces many challenges. As in the study of common ferroptosis and tumors, hematopoietic malignancies are more susceptible to epigenetic intervention than solid malignancies, making not all cancers equally susceptible to epigenetic treatment. In addition, epigenetic regulators are ubiquitous, and it is difficult to correctly find effective selective targets [5].

Drug resistance has always been the most challenging treatment issue in clinical practice. Taking the drug resistance of tumors as an example, studies have found that tumors are more prone to ferroptosis. Because the level of oxidative stress in tumor cells increases with an increase in proliferation ability, disrupting the antioxidant defense mechanism of tumors can serve as a new method to address drug resistance issues [6]. Although ferroptosis has developed rapidly in recent years, the epigenetic mechanism of ferroptosis has not yet formed a system and is still in the accumulation stage. Therefore, our aim is to sort out the connection between the two and lay the foundation for the formation of the theory. In addition, the research and application of drugs are the driving force behind our continuous exploration. Therefore, we have also collected information on the application of ferroptosis epigenetic regulatory drugs in related diseases, providing new directions for drug development (Fig. 1).

2. Mechanism and regulation of ferroptosis

The regulatory mechanism of ferroptosis has gradually improved through continuous exploration in recent years, and its fundamental role is to balance and regulate oxidation and antioxidation. Common driving factors include free iron and lipid peroxides. Under continuous research, more and more genes and proteins have been discovered to be involved in the regulation of ferroptosis, leading to the discovery of new pathways that can regulate ferroptosis. Here, we summarize the current regulatory mechanisms and important regulatory pathways of ferroptosis (Fig. 2).

2.1. Oxidative stress and ferroptosis

Ferroptosis is a type of cell death induced by oxidative stress that is characterized by the generation of ROS and lipid peroxidation [7]. Oxidative stress is an imbalance between oxidant production and antioxidant defense, which can affect cellular redox homeostasis and alter molecular structure, thereby leading to cell damage. ROS is the product of the normal aerobic metabolism of the body. It is a general term for a class of substances that are composed of oxygen or contain oxygen and have active properties, including superoxide anion (O^{2-}), hydrogen peroxide (H_2O_2), hydroxyl radical (OH^-), etc. Intracellular ROS originates from a variety of pathways, such as mitochondria, nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX), enzymatic reactions, and Fenton reactions [8].

Under normal circumstances, ROS is at a low level in the body and acts as a “redox messenger” involved in intracellular signaling and regulation. When the body is stimulated by factors such as ultraviolet rays, and radiation, the ROS level will increase sharply, exceeding the body's own scavenging and processing capacity, and

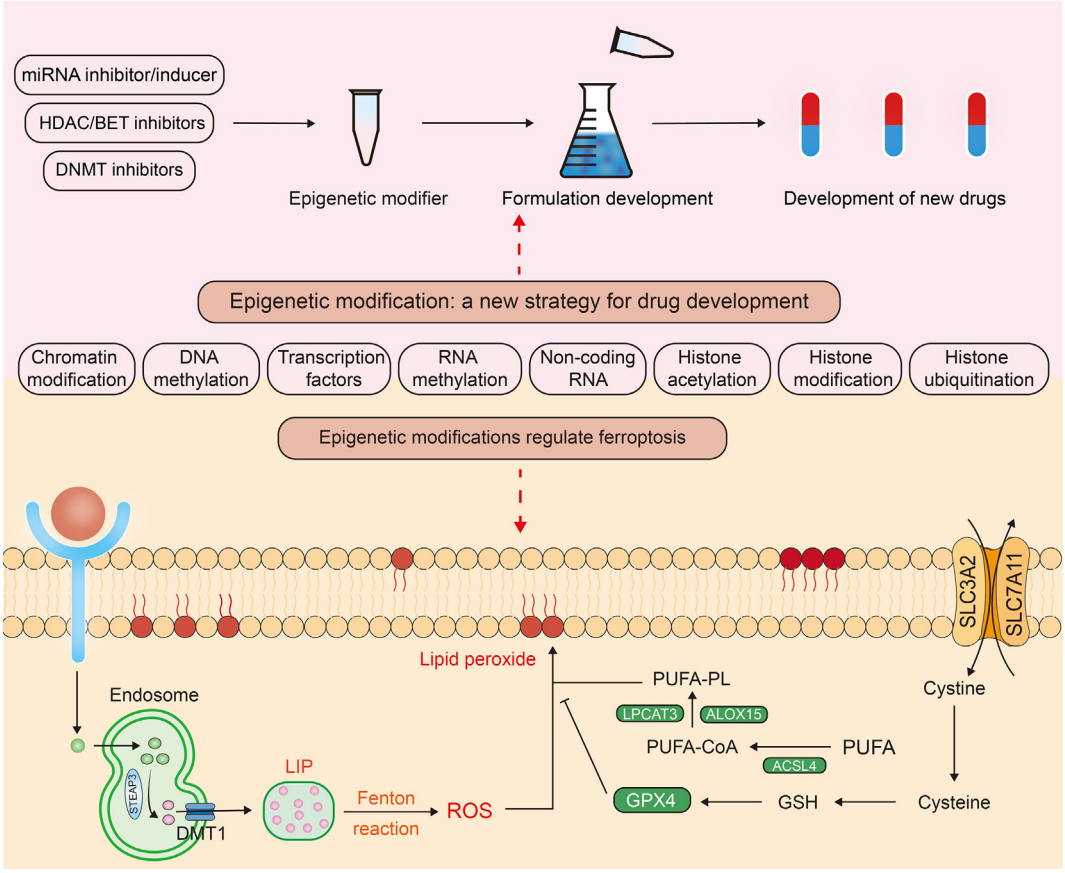

Fig. 1. Exploration of epigenetic drugs based on ferroptosis. miRNA: microRNA; HDAC: histone deacetylase; BET: bromodomain and extra-terminal motif; DNMT: DNA methyltransferase; ACSL4: acyl-CoA synthetase long-chain family 4; ALOX15: arachidonic acid 15-lipoxygenase; DMT1: divalent metal transporter 1; GSH: glutathione; GPX4: glutathione peroxidase 4; LPCAT3: lysophosphatidylcholine acyltransferase 3; LIP: labile iron pool; PUFA: polyunsaturated fatty acid; PUFA-PL: PUFA-containing phospholipid; ROS: reactive oxygen species; SLC7A11: solute carrier family 7 member 11; SLC3A2: solute carrier family 3 member 2; STEAP3: six-transmembrane epithelial antigen of prostate 3.

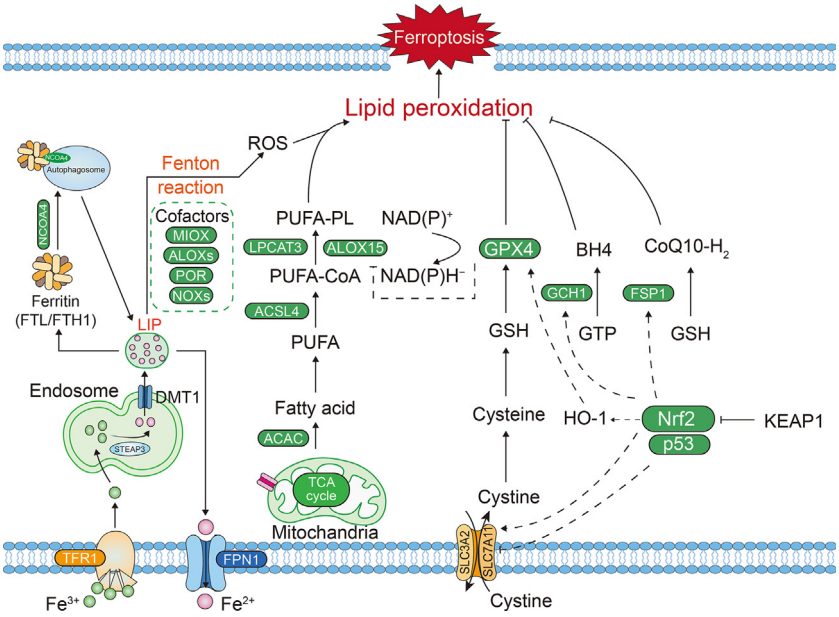

Fig. 2. The important mechanisms and pathways regulating ferroptosis. ALOX15: arachidonic acid 15-lipoxygenase; ACSL4: acyl-CoA synthetase long-chain family 4; BH_4: tetrahydrobiopterin; DMT1: divalent metal transporter 1; POR: cytochrome p450 oxidoreductase; ACAC: acetyl CoA carboxylase; FSP1: ferroptosis suppressor protein 1; GTP: guanosine triphosphate; GSH: glutathione; GPX4: glutathione peroxidase 4; GCH1: GTP cyclohydrolase 1; HO-1: heme oxygenase-1; KEAP1: Kelch-like ECH-associated protein 1; LPCAT3: lysophosphatidylcholine acyltransferase 3; LIP: labile iron pool; Nrf2: nuclear factor erythroid 2-related factor 2; PUFA: polyunsaturated fatty acid; PUFA-PL: PUFA-containing phospholipid; p53: tumor protein p53; ROS: reactive oxygen species; SLC7A11: solute carrier family 7 member 11; SLC3A2: solute carrier family 3 member 2; TFR1: transferrin receptor 1; STEAP3: six-transmembrane epithelial antigen of prostate 3; TCA cycle: tricarboxylic acid cycle.

the oxidation-antioxidant imbalance of the body causes oxidative stress within cells, leading to DNA damage, lipid peroxidation, changes in protein structure and function, as well as membrane disruption, ultimately resulting in cell death.

The process of ferroptosis involves the peroxidation of polyunsaturated fatty acids (PUFA) containing phospholipids (PUFA-PLs) and the formation of the lipid H_2O_2. PUFA-PLs promote the fluidity and deformability of the cell membrane, which is conducive to the exchange of substances and signal transmission. But an excess of PUFA-PLs also increases the susceptibility of cells to ferroptosis [9]. ROS can react with PUFA in the lipid membrane and induce lipid peroxidation to form lipid reactive oxygen species (L-ROS). High concentrations of L-ROS can trigger oxidative stress in cells and cause oxidative damage [7]. Arachidonic acid lipoxygenase (ALOX) is the enzyme that catalyzes the oxidation of PUFA, thereby initiating lipid peroxidation by introducing hydroperoxyl groups (−OOH) into the fatty acid chain [8]. Redox homeostasis also depends on the status of many redox pairs in the internal environment, such as reduced glutathione (GSH)/oxidized GSH (GSSG) [7].

2.2. Intracellular iron

Iron is an important cofactor in many proteins and plays a crucial role in the normal operation of organelles, especially mitochondria, within cells [10]. When the homeostasis of intracellular iron is affected, ferrous iron (Fe^{2+}) no longer converts to ferritin but reacts with H_2O_2 to form OH^-, which can react with PUFA to form lipid peroxides, making a large amount of free iron an inducing factor for ferroptosis [11].

In vivo, transferrin (TF) can bind to extracellular ferric iron (Fe^{3+}) to participate in iron transport and then combine with TF receptor 1 (TFR1) to enter cells [12]. The TF-Fe^{3+}-TFR1 complex is reduced to Fe^{2+} by the action of six-transmembrane epithelial antigen of prostate 3, and ferrous ions finally enter the cytoplasm through divalent metal transporter 1 (DMT1), participating in the formation of labile iron pool (LIP) [13]. The formation of LIP is related to catalytic free radicals through the Fenton reaction [14]. The Fenton reaction is the reaction of Fe^{2+} and H_2O_2 to form hydroxide and OH^-. Therefore, increasing free iron in cells can increase the occurrence of the Fenton reaction and then increase the production of ROS, thereby inducing ferroptosis [15].

Iron is mainly present in the body, while it is stored in mitochondria within cells. The stored form is often ferritin, including ferritin light chain (FTL) and ferritin heavy polypeptide 1 (FTH1) [16], while others are exported back into circulation by ferroportin. When ferritin-selective autophagy turnover occurs, nuclear receptor coactivator 4 (NCOA4) typically acts as a selective cargo receptor [17]. The release of ferritin is due to the transport of ferritin from autophagy to lysosomes, a process that requires NCOA4 to interact directly with FTH1 [18].

The synthesis of cofactors requires iron to be transported to mitochondria. Therefore, iron plays a crucial role in DNA synthesis and repair, redox reactions, and various other cellular processes [10].

2.3. GSH peroxidase 4 (GPX4)

GPX4, the only enzyme that can convert lipid hydroperoxides to non-toxic lipids and reduce lipid hydroperoxides within biological membranes, is the top protein target of the (1S,3R)-GPX4 inhibitor (RSL3) [19]. GPX4 requires GSH as an essential cofactor for its enzyme activity, which can inhibit lipid peroxidation, inhibit antitumor immunity, and maintain Treg cell activation [19,20]. Therefore, the decrease in GPX4 expression level leads to a deepening of intracellular lipid peroxidation. The accumulation of peroxidation products such as 4-hydroxynonenal (4-HNE) promotes the occurrence of ferroptosis [21].

Sirtuin-1 (SIRT1) has been found to be associated with cell death. As a nicotinamide adenine dinucleotide phosphate (NAD(P)+) dependent protein deacetylase, it plays an important regulatory role in the oxidative stress and reduction response of ferroptosis. Its substrate, tumor protein p53 (p53), also plays an important role in the redox regulation of ferroptosis [22]. In addition to SIRT1, nuclear

factor erythroid 2-related factor 2 (Nrf2) and heme oxygenase-1 (HO-1) play important roles in the balance between ferroptosis oxidation and antioxidant activity, mediating the production of various antioxidants [23]. The most important thing is that Nrf2 can affect the synthesis of GPX4 [24]. In addition, research has found that arachidonic acid 15-lipoxygenase (ALOX15), as an oxygenase, can inhibit the expression of GPX4. Therefore, the accumulation of peroxidized lipids in cells induces the occurrence of ferroptosis [25].

2.4. Solute carrier family 7 member 11 (SLC7A11)

SLC7A11, a multi-pass transmembrane protein, is one of the two subunits combining into a cystine and glutamate antiporter system (system Xc^-), which acts as the cystine/glutamate antiporter [26,27]. It is capable of promoting both GSH biosynthesis and GPX4-mediated lipid peroxide detoxification. These functional dependencies are associated with the SLC7A11 introduction of cystine [28].

On the transcription level, there are many factors involved in SLC7A11 mediation. Under various stress conditions, activating transcription factor 4 (ATF4) and Nrf2 may partly be the major mediators, which interact with each other on the SLC7A11 promoter and cooperatively regulate SLC7A11 transcription [29]. The amino acid reaction element can bind to ATF4 when cysteine and amino acids are lacking, leading to the transcription of SLC7A11 [30]. Mediating transcription processes that respond to oxidative stress, binding to the antioxidant response element (ARE) in the gene promoter, and controlling the transcription of SLC7A11 are the main functions of Nrf2 [29]. Nowadays, many genes have been demonstrated to mediate SLC7A11 expression through Nrf2 or ATF4.

Besides, under basal conditions, p53 and ATF3, a transcription factor and a member of the ATF/cyclic adenosine monophosphate (cAMP)-response element binding protein family of transcription factors, both repress SLC7A11 expression by targeting its promoter, respectively [31].

2.5. Nrf2

Nrf2 is considered as a master regulator of the antioxidant response that has been mentioned above. Here we give a summary of its function.

As an important factor in the antioxidant system, Nrf2 is normally at a low level and is inhibited by the E3 ubiquitin ligase complex. When the complex is disrupted, Nrf2 enters the nucleus, and the transcription of ARE is activated, thereby activating the cellular antioxidant system. GSH and NADPH, key donors for the reduction of oxidized substrates, whose synthesis is under the control of Nrf2, are utilized by various redox enzymes to reduce oxidized substrates. What's more, GPX4 and system Xc^-, targets of traditional ferroptosis inducers (RSL3 and erastin), are also downstream targets of Nrf2 [11]. Knocking down Nrf2 notably decreases the expression of SLC7A11 and HO-1 [32]. Nrf2 plays a role in regulating iron metabolism by controlling the light and heavy chains (key iron storage proteins) of iron transporters (Solute carrier family 40 member 1) and ferritin (FTL/FTH1) in iron efflux cells [33,34]. In addition, Nrf2 has an impact on enzymes that catalyze the conversion, synthesis, and transport of heme, thereby regulating intracellular iron content [11]. Phosphorylated signal transducer and activator of transcription 3 (pSTAT3) is often present in inflammatory reactions and has been found to be associated with the ferroptosis regulatory factor Nrf2. The transcription and phosphorylation of STAT3 are promoted by Nrf2. STAT3 has the effect of enhancing lysosomal membrane permeability. And in the study of breast cancer, it was found that it can promote ferroptosis induced by erastin and reduce the expression of SLC7A11 [35–37]. Active lipids such as 4-HNE, as negative regulators of Nrf2, can bind to the Kelch-like ECH-associated protein 1 (KEAP1) adduct cysteine, thereby activating the cellular antioxidant system and promoting the expression of NRF2 target genes [38].

KEAP1 is a common negative regulator of Nrf2. As a stress-induced cell protein, protein sequestosome 1/p62 (p62) has been found to promote KEAP1 degradation, accumulate nuclear Nrf2, and prevent Nrf2 degradation. This is what we call the p62/KEAP1/Nrf2 pathway. When this pathway is activated, it upregulates the expression of HO-1 and FTH1, leading to ferroptosis resistance in cancer cells such as liver cancer cells and malignant brain tumors [39]. Moreover, activation of the Nrf2-KEAP1 signaling upregulates SLC7A11 in glioma cells [40], which fosters the expression of the antioxidant protein HO-1, cooperating to promote resistance to ferroptosis [41]. Besides, the increased expression of glycogen synthase kinase 3β, a multifunctional serine/threonine kinase, can foster the levels of KEAP1 while decreasing the levels of Nrf2 and HO-1 in nobiletin-treated melanoma cells, reversing ferroptosis resistance in human melanoma cells [23].

2.6. Acyl-CoA synthetase long-chain family 4 (ACSL4) and lysophosphatidylcholine acyltransferase 3 (LPCAT3)

ACSL4, a member of the ACSL family, catalyzes the linkage of PUFAs to CoA to generate fatty acyl CoA esters (PUFA-CoA). Under the action of LPCAT3, PUFA-CoA is mainly incorporated into PLs in the endoplasmic reticulum (ER) and re-esterified to form PLs [42,43]. Thus, ACSL4 and LPCAT3 are significant promoters of ferroptosis. In lung adenocarcinoma cell lines undergoing lipid peroxidation, LPCAT3 and ACSL4 levels are positively correlated with ferroapoptotic sensitivity [44]. Knockdown of LPCAT3 confers resistance to RSL3-induced ferroptosis in mouse lung epithelial cells and mouse embryonic cells, whereas ACSL4-deficient cells show resistance to ferroptosis induced by GPX4 deletion or RSL3 treatment. This suggests that the loss of ACSL4 and LPCAT3 may inhibit ferroapoptosis by limiting the membrane-resident pool of oxidation-sensitive fatty acids [43,45].

2.7. Ferroptosis suppressor protein 1 (FSP1)/coenzyme Q10 (CoQ10) pathway

A single lipophilic antioxidant, CoQ10, plays an important role in electron transport during mitochondrial respiration [46]. FSP1 can reduce CoQ10 at the plasma membrane, reducing lipid peroxides. This antioxidant pathway does not affect the GPX4 pathway [47].

More importantly, FSP1 is a transcriptional target of Nrf2. A recent study has shown that the absence of KEAP1 in lung cancer cells inhibits Nrf2 degradation and promotes its accumulation, leading to upregulation of FSP1 expression [48].

2.8. Guanosine triphosphate cyclohydrolase 1 (GCH1)/tetrahydrobiopterin (BH4) pathway

BH4, as an important cofactor, plays a crucial role in the production of hormones such as serotonin and norepinephrine in the body, while GCH1 is the rate-limiting enzyme for BH4 biosynthesis [49], and various products of BH4 metabolism can regulate the function of GCH1. For example, high or low levels of BH4 can reduce the enzyme activity of guanosine triphosphate (GTP), but high phenylalanine concentrations can increase the enzyme activity [50,51].

Recently, some research has shown that the GCH1/BH4 pathway plays a vital role in ferroptosis resistance. GCH1 can reduce BH4 and has been proven to enhance erastin-induced lipid peroxidation and

Fe^{2+} accumulation, leading to ferroptosis in cells [52]. In addition, GCH1/BH4 plays an important role in the immune function of the body and can regulate the proliferation of T cells. Therefore, research has found that overexpression of GCH1 enhances the generation of BH4 by CD4 and CD8 T cells, thereby enhancing *in vivo* anti-tumor activity [53].

More importantly, BH4 not only participates in the synthesis of CoQ10 to inhibit cell lipid peroxidation but also directly acts as an antioxidant to inhibit cell ferroptosis. Interestingly, GCH1 can also affect the synthesis of CoQ10 and inhibit the degradation of PUFA-PLs [54]. In addition, GCH1 is also a regulatory factor for Nrf2, which has been found to be able to treat radiation-induced skin damage. This effect is achieved by inhibiting the production of ROS [55].

3. Epigenetic regulation of ferroptosis

As mentioned above, epigenetic-related proteins play an important role in ferroptosis. Therefore, it is necessary to further understand the mechanism of epigenetic factors that determines the degree of gene expression and plays a key role in cell survival (including protein methylation, acetylation, and ubiquitination, as well as DNA methylation, RNA methylation, and ncRNA). It is reported that many epigenetic drugs have shown exciting results in the prevention and treatment of diseases caused by ferroptosis. Therefore, here we introduce the epigenetic regulation mechanism of ferroptosis in detail.

3.1. DNA methylation

Among numerous gene regulation mechanisms, DNA methylation is the most common epigenetic modification and is typically mediated by DNA methyltransferase (DNMT) [56]. When establishing a connection with ferroptosis, we find that iron plays multiple key regulatory roles in the functional process of DNA methylation modification in eukaryotic cells [57,58], and oxidative stress and abnormal changes in intracellular iron concentration can directly affect DNA methylation [59] (Fig. 3). For example, epigenetic modifications of the colon and intestinal mucosa in mice were significantly altered under an *in vitro* high-iron diet. This is due to the abundant epigenetic changes in the high-speed rail environment, such as the low methylation of NAD(P)H: quinone oxidoreductase 1 (NQO1) and GPX2 occurring at the CG site of the Nrf2 target. This indicates that dietary iron overload can cause changes in the methylation of the ferroptosis regulatory factor Nrf2, thereby regulating the occurrence of ferroptosis [60]. The study of establishing a mouse model of brain iron accumulation using H67D mutant mice consistently indicates that brain iron overload disrupts the cellular redox environment and causes damages overall DNA methylation. Among them, excessive iron disrupts DNA methylation through two possible mechanisms, including S-adenosylmethionine (SAM)/S-adenosylhomocysteine cycle and direct inhibition of DNMT activity, respectively [61]. In addition, ectopic expression of iron metabolism genes in cancer, such as TFR2, may be associated with abnormal DNA methylation. Its upregulation may be controlled by low methylation of the corresponding promoter [62]. Therefore, direct or indirect DNA methylation may play an important role in regulating iron metabolism in ferroptosis and various diseases.

At present, besides iron metabolism, GPX, which can participate in GSH oxidation and H_2O_2 reduction, is an important mechanism regulating ferroptosis. Studies have found that DNA methylation can regulate GPX and participate in the regulation of ferroptosis. GPX1 is a highly expressed member of the GPX family, widely present in various cells. Studies have found that it can reduce oxidative DNA mutations, which possess guiding significance for the prevention of cancer in the initial stage. And studies have also confirmed that the high expression level of GPX1 in kidney renal papillary cell carcinoma may be caused by lower promoter DNA methylation. However, the relationship between GPX1 and ferroptosis remains to be studied, so it is worth exploring whether there is a connection between DNA methylation and the regulatory mechanism [63]. Hyperhomocysteinemia (HHcy) is an independent risk factor for intervertebral disc degeneration, and it has been reported that HHcy is particularly closely associated with DNA methylation [64,65]. Some studies have explored its association with ferroptosis GPX4 methylation and found that the ferroptosis caused by HHcy is related to the increase in methylating enzymes (DNA methyltransferase 1 (DNMT1), DMNT3a, and DMNT3b) stimulated by HHcy, which leads to GPX4 methylation. The enhancement of GPX4 methylation levels leads to a decrease in GPX4 expression, which promotes ferroptosis in cells [66]. Similarly, Nrf2 promoter hypermethylation, which can regulate the expression of GPX4, also induces ferroptosis, and this regulation has been confirmed in chronic obstructive pulmonary disease [67].

At present, it has been confirmed that the peroxidation of PUFA can cause ferroptosis, and research has found that DNA methylation can regulate lipid metabolism and ferroptosis [68]. The research has found that the extremely long-chain fatty acid protein 5 (ELOVL5) and fatty acid desaturase 1 (FADS1) involved in PUFA biosynthesis are upregulated in mesenchymal gastric cancer cells, leading to ferroptosis and sensitization. However, the enhanced DNA methylation of ELOVL5 and FADS1 enables it to inhibit the occurrence of ferroptosis, as the occurrence of DNA methylation reduces the expression of ELOVL5 and FADS1, affecting the synthesis of PUFA and participating in the regulation of ferroptosis.

In addition to being directly associated with ferroptosis, many studies have found that inhibitors and inducers of ferroptosis can mediate the occurrence of DNA methylation. Ferroptosis inhibitor, ferrostatin-1, enhances ten-eleven translocation activity with DNA demethylation ability and inhibits homocysteine-induced DNA methylation, indicating that ferrostatin-1 has a potential mechanism for regulating ferroptosis through DNA methylation [69]. Multiple myeloma is an incurable adult blood cancer, and its pathogenesis is related to DNA methylation. And research has found that the ferroptosis inducer RSL3 can cause local DNA methylation changes [70]. Whether RSL3 will affect the methylation of GPX4 and regulate ferroptosis remains to be studied.

Further exploration is needed for the development of drugs related to DNA methylation regulation of ferroptosis, and current research is still in the validation stage of DNMT inhibitors for ferroptosis regulation. For example, studies have found that 6-thioguanine (6-TG) can downregulate the expression of GPX4 and cause ferroptosis by regulating the system Xc^-, but its specific mechanism has not been elucidated. However, this is likely related to the downregulation of DNMT1 caused by 6-TG, but further validation is needed [71]. Another DNMT1 inhibitor, 5-azacitidine, can prevent epithelial-mesenchymal transition (EMT) due to its downregulation of cadherin 1 (CDH1) methylation levels. And this inhibitory effect on methylation can reduce the sensitivity of head and neck cancer (HNC) cells to ferroptosis inducers, but the specific mechanism has not yet been demonstrated [72].

Overall, research on the regulation of ferroptosis by DNA methylation is increasing, but progress in clinical drug development is still slow. However, as research continues, the development of DNA methylation-related drugs can provide new treatment strategies and research ideas for various diseases.

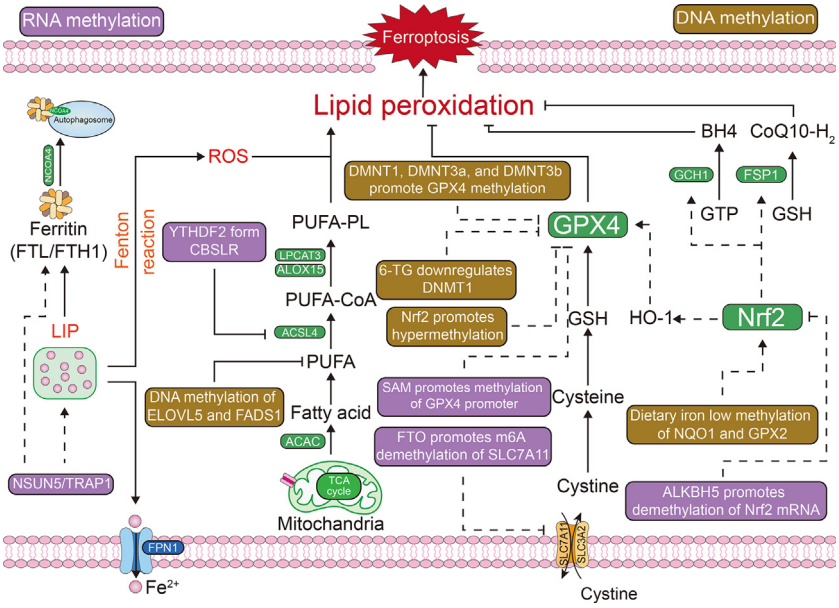

Fig. 3. Regulation of ferroptosis by DNA methylation and RNA methylation. NCOA4: nuclear receptor coactivator 4; FTL: ferritin light chain; FTH1: ferritin heavy polypeptide 1; ACAC: acetyl CoA carboxylase; ALOX15: arachidonic acid 15-lipoxygenase; ACSL4: acyl-CoA synthetase long-chain family 4; ALKBH5: alkylation repair homolog protein 5; BH_4: tetrahydrobiopterin; CBSLR: hypoxia-induced CBS mRNA-destabilizing lncRNA; mRNA: messenger RNA; DNMT1: DNA methyltransferase 1; ELOVL5: extremely long-chain fatty acid protein 5; FADS1: fatty acid desaturase 1; FTO: fat mass and obesity-associated protein; FPN1: ferroportin 1; FSP1: ferroptosis suppressor protein 1; GTP: guanosine triphosphate; GSH: glutathione; GPX4: glutathione peroxidase 4; GPX2: glutathione peroxidase 2; GCH1: GTP cyclohydrolase 1; HO-1: heme oxygenase-1; LIP: labile iron pool; NQO1: NAD(P)H quinone oxidoreductase 1; NSUN5: NOP2/Sun RNA methyltransferase 5; Nrf2: nuclear factor erythroid 2-related factor 2; PUFA: polyunsaturated fatty acid; PUFA-PL: PUFA-containing phospholipid; ROS: reactive oxygen species; SAM: S-adenosylmethionine; SLC7A11: solute carrier family 7 member 11; SLC3A2: solute carrier family 3 member 2; TCA cycle: tricarboxylic acid cycle; TRAP1: tumor necrosis factor receptor-associated protein 1; YTHDF2: YTH domain family protein 2; 6-TG: 6-thioguanine.

3.2. RNA methylation

Previously, it was difficult to speculate on the function of RNA methylation and the corresponding biological results, but with the upgrading and development of analytical tools, research on RNA methylation gradually rose [73]. It has been found that RNA methylation plays an important role in gene regulation-related modifications. A deep understanding of the characteristics of RNA methylation modification can provide new ideas for the study of many diseases [74]. RNA methylation has been found to be widely present and is considered as the most common RNA modification, thus commonly involved in the epigenetic regulation of various cell death modes [75]. Different kinds of RNA methylation are not uniformly distributed in different species [76]. Among a variety of RNA methylation modifications, we focus on the influence mechanism of N^6-methyladenosine (m^6A), 5-methylcytosine level regulation of FTH1/FTL RNA, and other RNA methylation modifications along with their activity regulation in ferroptosis (Fig. 3).

Among them, m^6A is extensively studied [77]. Among many chemical modifications, m^6A methylation is the most common internal RNA modification, especially in post-transcriptional eukaryotic RNA. The termination codon and three' untranslated regions (3′ UTRs) are the sites where m^6A occurs. The three regulators—writer, reader, and eraser—affect their related physiological functions, respectively [78]. M^6A often occurs in cancer and often occurs as a carcinogenic effect [79,80], but its anticancer or anti-tumor effect remains to be studied. The role of m^6A methylation in cancer has been attached to importance, and research involving ferroptosis also occupies a place. They are mainly associated with m^6A regulators, namely readers (YTH domain family), erasers (fat mass and obesity-associated protein (FTO), and alkylation repair homolog protein 5 (ALKBH5). YTH domain family protein 2 (YTHDF2) can form a complex with hypoxia-induced CBS messenger RNA (mRNA)-destabilizing long-chain ncRNA (lncRNA) (CBSLR). This complex can lead to a decrease in the stability of CBS mRNA. CBS expression can promote the methylation of ACSL4 protein and improve the stability of ACSL4 protein. Therefore, YTHDF2 can affect the stability of the ACSL4 protein and thus affect ferroptosis [81]. FTO has the function of m^6A demethylation and can promote the demethylation of m^6A in the ferroptosis suppressor gene SLC7A11. Ferroptosis occurs due to the inhibition of SLC7A11 expression [82]. ALKBH5 is also a m^6A demethylase. ALKBH5 can regulate ferroptosis by acting on the key anti-oxidative factor Nrf2. This regulation of ALKBH5 induces ferroptosis by demethylating Nrf2 mRNA, leading to a decrease in Nrf2 expression [83].

In addition, we also found other methylation modifications besides m^6A methylation, such as NOP2/Sun RNA methyltransferase 5 (NSUN5). NSUN5 can enhance the level of 5-methylcytosine in FTH1 RNA by binding to tumor necrosis factor receptor-associated protein 1 (TRAP1) and FTH1. The intracellular iron concentration will decrease as a result, and the knocking down of NSUN5 will lead to a decrease in the expression of GPX4, ROS, and lipid peroxidation products. This indicates that NSUN5 is closely related to ferroptosis [84]. The study also found that under the action of SAM, the methylation of the GPX4 promoter increased, promoting the occurrence of ferroptosis [85].

Overall, RNA methylation provides a new perspective on the relationship between ferroptosis and disease, and the gradual expansion of this perspective represents a new direction in drug development. Diseases such as gastric cancer, papillary thyroid cancer, nasopharyngeal squamous cell carcinoma, and rheumatoid arthritis have been found to be associated with this association. For example, a deeper understanding of reversible mRNA m^6A methylation and its regulatory factors can provide new strategies for the treatment of cancer, especialy nasopharyngeal squamous cell carcinoma and gastric cancer. However, research on related drugs and inhibitors is not yet available. Therefore, strengthening the development and demonstration of RNA methylation modifiers and

regulatory drugs can bring more directions for disease treatment and research.

3.3. ncRNA

ncRNA, as a very important epigenetic regulatory pattern, plays an important role in regulating transcription, RNA processing, and translation levels. Therefore, ncRNA is essential for exploring the epigenetics of ferroptosis. There are many kinds of ncRNAs. In this paper, we mainly introduce the types of ncRNAs related to the apparent regulation of ferroptosis, including lncRNA, miRNA, and circular RNA (circRNA) (Fig. 4).

lncRNA is composed of transcripts containing over 200 nucleotides and plays a role in regulating gene expression and local chromatin structure. With the development of technology, more and more related studies are emerging. For example, lncRNA has the functions of influencing the transcription mode, regulating the activity of protein-binding chaperone, acting as the precursor of small RNA, and influencing the processing of other RNA to specific genomic sites. These effects provide more ideas for researchers to study the specific mechanisms of related diseases and also lay the foundation for the pharmacological effects of drugs [86]. Many studies have shown that many lncRNAs can mediate the expression of factors related to ferroptosis regulation. For example, lncRNA H19 can enhance the transcriptional activity of FTH1 related to iron metabolism, thereby increasing the expression level of FTH1 and inhibiting ferroptosis. Therefore, lncRNA H19 can enhance the expression level of FTH1, thus inhibiting ferroptosis [87]. lncRNA LINC01606 was found to enhance the expression of stearyl-CoA desaturase 1 (SCD1) in colon cancer, which could promote an increase in the concentration of monounsaturated fatty acids (MUFAs) in cells while the concentration of saturated fatty acids (SFAs) and PUFAs decreased significantly, thus improving the resistance of cells to ferroptosis [88]. In the regulation of ferroptosis by system Xc^{-}, it was found that the expression of nuclear paraspeckle assembly transcript 1 (NEAT1) increases due to the binding of the promoter of lncRNA NEAT1 to p53. NEAT1 can promote myo-inositol oxygenase (MIOX) expression, which is generated by NEAT1's competitive binding to miR-362-3p. This ultimately induces ferroptosis in cells, as MIOX can increase intracellular ROS levels and reduce intracellular NADPH and GSH levels [89]. In addition, it was found that lncRNA PVT1 can also regulate p53 gene-induced ferroptosis, and the downstream molecule SLC7A11 of p53 can be regulated by lncRNA OIP5-AS1 and lncRNA SLC16A1-AS1 [90–92]. Therefore, the study of lncRNA promotes the exploration of the mechanism of ferroptosis and provides a theoretical basis for the development of clinical drugs.

miRNAs, as a large class of RNA about 21 nucleotides long, are key post-transcriptional regulators of gene expression, and the research on miRNAs has greatly deepened our understanding of post-transcriptional regulation of gene expression [93]. Because of its function in gene transcription regulation, miRNA has been widely studied in the mechanism exploration of various types of diseases. miRNA is also widely studied in the epigenetic regulation of ferroptosis. For example, in melanoma cells, miR-137 can bind to the glutamine transporter solute carrier family 1 member 5 (SLC1A5), reducing the mRNA and protein levels of SLC1A5 and inducing ferroptosis. Because L-glutamine (Gln) metabolism can promote the formation of oxidizable lipids, the lower expression level of SLC1A5 will inhibit the metabolism of Gln and reduce the uptake of glutamine and the accumulation of malondialdehyde, thus inhibiting ferroptosis [94]. miR-182-5p and miR-378a-3p can directly bind GPX4 and SLC7A11 mRNA, which can reduce the expression of GPX4 and SLC7A11, leading to the activation of cell ferroptosis [95]. Exosome-miR-522 can inhibit the occurrence of cell ferroptosis, as it inhibits the synthesis of ALOX15 and reduces the production of lipid ROS [96]. The regulatory mechanism of miRNA on ferroptosis mentioned above indicates that miRNA, as a deeper regulatory factor, can provide new directions for in-depth research on ferroptosis as well as directions for clinical drug development and precise treatment.

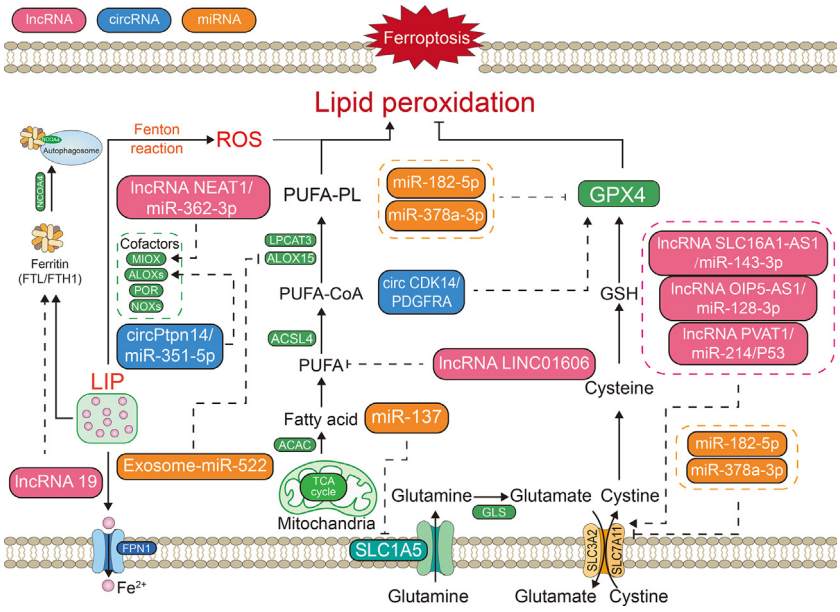

Fig. 4. The regulation of ferroptosis by non-coding RNA (ncRNA). lncRNA: long-chain ncRNA; circRNA: circular RNA; miRNA: microRNA; NCOA4: nuclear receptor coactivator 4; ALOX15: arachidonic acid 15-lipoxygenase; NEAT1: nuclear paraspeckle assembly transcript 1; ACAC: acetyl CoA carboxylase; ACSL4: acyl-CoA synthetase long-chain family 4; FPN1: ferroportin 1; GSH: glutathione; GPX4: glutathione peroxidase 4; GLS: glutaminase; LIP: labile iron pool; PUFA: polyunsaturated fatty acid; PUFA-PL: PUFA-containing phospholipid; POR: cytochrome p450 oxidoreductase; PDGFRA: platelet-derived growth factor receptor; ROS: reactive oxygen species; SLC7A11: solute carrier family 7 member 11; SLC3A2: solute carrier family 3 member 2; LPCAT3: lysophosphatidylcholine acyltransferase 3; FTL: ferritin light chain; FTH1: ferritin heavy polypeptide 1; MIOX: myo-inositol oxygenase; ALOX: Arachidonic acid lipoxygenase; NOX: nicotinamide adenine dinucleotide phosphate (NADPH) oxidase; TCA cycle: tricarboxylic acid cycle.

circRNA has the function of binding or separating proteins, as well as protein translocation or redistribution. It has gradually become a new hotspot in the study of ncRNA [97]. Therefore, circRNA in the field of ferroptosis research on ncRNA has attracted people's attention. circCDK14 can promote the expression of platelet-derived growth factor receptor alpha (PDGFRA), regulate lipid peroxidation, and increase the expression of GPX4 to regulate cell sensitivity to ferroptosis. This effect occurs under the mutual influence of circCDK14 and miR-3938 [98]. circPtpn14 also indirectly regulates the expression of 5-lipoxygenase (5-LOX) under the action of miR-351-5p. Because 5-LOX can resist lipid peroxidation, circPtpn14 enhances cell ferroptosis resistance through the circPtpn14/miR-351-5p/5-LOX axis [99]. circRHOT1 can combine with miRNA 106a-5p (miR-106a-5p), leading to a reduction of the expression of miR-106a-5p. circRHOT1 can indirectly inhibit the mRNA and protein expression of STAT3, thereby regulating the occurrence of ferroptosis, because circRHOT1 can bind to miR-106a-5p and inhibit its expression, while miR-106a-5p can target and regulate STAT3 [100].

The regulation of ferroptosis by ncRNA is often explored as a mechanism, with limited achievements in clinical applications and drug development. At present, research has shown that miR-101-3p, which can activate cell ferroptosis, can be made into nanomedicines through nanotechnology for cancer treatment. *In vitro* experimental results have shown clear promotion of ferroptosis and tumor-killing effects. This is based on the fact that nanodrug carriers can effectively transport nucleic acid-based drugs and small-molecule drugs and achieve tumor tissue distribution through the enhanced permeability and retention effect [101]. The development of this nanomedicine provides a new direction for the treatment of diseases and the resolution of drug resistance.

Overall, it is believed that with the continuous development of technology, the network mechanism of ncRNA-regulating ferroptosis will continue to improve. Not only at the level of mechanism exploration, but research achievements related to nanomedicines and targeted therapeutic drugs will also continue to emerge, injecting new vitality into the research of new cancer drugs.

3.4. Histone modifications

The chromatin of eukaryotic cells is composed of DNA tightly bound to factors such as histones (nucleosomes). As a fundamental component of chromatin, nucleosomes consist of approximately 150 bp of DNA wrapped around an octamer of histone proteins. Among them, the histone octamer is composed of the two-fold core histones H2A, H2B, H3, and H4, respectively [102]. Basic lysine and arginine residues are densely distributed in the tails of histones and work together to regulate the chromatin state through extensive covalent post-translational modifications [103]. Compared with many epigenetic modifications, such as DNA methylation, the function of histone modification is more complex. The same type of modification or different combinations of modifications on different histone residues can lead to completely different functions of gene expression regulation [104]. Cell homeostasis and development are influenced by epigenetic regulation of gene transcription, and diseases such as cancer can occur due to abnormal regulation. Among them, the regulation of histone modification in ferroptosis has attracted the attention of most people in the research of tumor treatment, and related studies emerge in an endless stream (Fig. 5).

3.4.1. Histone acetylation

Histone acetylation is closely related to transcriptional activity, especially in enhancers, promoters, and genomes. Histone acetylation neutralizes the positive charge of histones, which prevents their ability to bind to DNA [105]. This process is usually mediated by factors such as histone deacetylase (HDAC), histone acetyltransferase (HAT), and the brominated domain protein (BRD) family, but with continuous research, more and more regulatory factors have emerged.

For HDAC, studies have found that Class I HDAC inhibitors can selectively protect neurons from erastin-induced cytotoxicity caused by system Xc^--cysteine transport inhibition, but they can also enhance ferroptosis in other cancer cells. This opposite effect is thought-provoking, but the specific mechanism of action remains to be studied [106]. Under the action of HDAC (such as SIRT1), ferroptosis is inhibited due to the inhibition of EMT [72]. In addition, HDAC (such as SIRT3) can also induce ACSL4 expression, leading to ferroptosis, but this regulation depends on the protein kinase B pathway [107]. HDAC inhibitors (such as BEBT-908) can cause excessive acetylation of p53, and acetylated p53 can mediate the expression of SLC7A11 and GPX4, thereby regulating ferroptosis [108]. Other HDAC inhibitors, such as quisinostat and vorinostat, also regulate ferroptosis through similar mechanisms [109,110]. These results indicate a close relationship between HDAC and ferroptosis, but currently, the specific mechanism of HDAC's role in ferroptosis has not been elucidated, and their targets are still unclear. Therefore, further research is highly worthwhile to explore.

For HAT-mediated ferroptosis, KAT6B can be enriched on the STAT3 promoter in glioma cells. Hemolytic deficiency of KAT6B prevented the enrichment of histone H3 lysine 23 acetylation (H3K23ac) and RNA polymerase II (RNA pol II) at the STAT3 promoter in cells. Through epigenetics, KAT6B can induce STAT3 inhibition of ferroptosis, resulting in glioma progression, as demonstrated by these phenomena [111]. Acting as a blocker of lysine acetyltransferase 5 (KAT5), ketamine can suppress KAT5 on GPX4, curtailing histone H3 lysine 27 acetylation (H3K27ac), resulting in reduced GPX4 levels and fostering ferroptosis [112].

The current research results on the regulation of ferroptosis by the BRD family are limited. $^{(+)}$-JQ1 (JQ1) is a bromodomain-containing protein 4 (BRD4) inhibitor, which has been found to enhance ferritin autophagy by inhibiting BRD4 and downregulating the expression of GPX4, SLC7A11, and solute carrier family 3 member 2 (SLC3A2) to promote ferroptosis. JQ1's inhibition of BRD4 depends on the mediation of SIRT1 [113]. BRD4 regulates ferroptosis by promoting the expression of acyl-CoA synthetase long-chain 3 [114].

In addition to the common ways of regulating histone acetylation mentioned above, studies have found that hydroxymethylglutaryl CoA lyase (HMGCL) induces β-hydroxybutyric acid (β-OHB) production and reduces susceptibility to ferroptosis mediated by dipeptidyl peptidase 4 (DPP4) in hepatocellular carcinoma (HCC). Mechanistically speaking, HMGCL enhances β-OHB levels, induces H3K9 acetylation, promotes DPP4 transcription, leads to ferroptosis in HCC cells, and effectively weakens sorafenib and erastin resistance [115].

Overall, epigenetic histone acetylation has shown great potential in regulating ferroptosis in treating diseases and tumor resistance, but research in this field is scarce and the specific mechanisms need to be clarified. Therefore, strengthening research in this field is crucial for understanding the specific molecules of ferroptosis and exploring useful prognostic biomarkers and intervention therapy targets.

3.4.2. Histone methylation

Compared to histone acetylation, the methylation of lysine and arginine residues at the tail of histones is more complex. The alteration of histone methylation is stringently controlled by numerous methyltransferase writers and demethylase erasers. The addition or removal of specific methyl marks by these enzymes is critical for gene expression, cell fate, and even genome stability [103]. Up to this point, numerous alterations in histone methylation

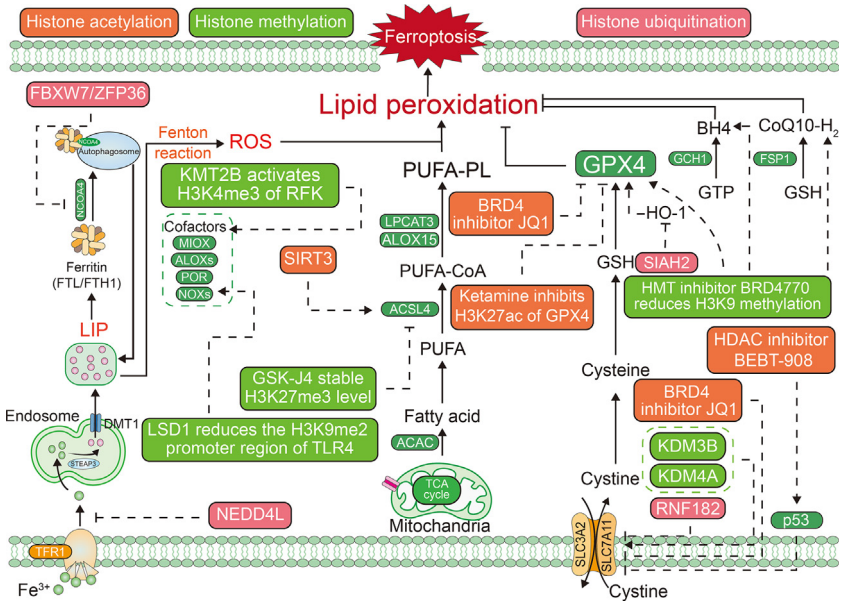

Fig. 5. The regulation of ferroptosis by histone modification. ACAC : acetyl CoA carboxylase; ALOX15: arachidonic acid 15-lipoxygenase; ACSL4: acyl-CoA synthetase long-chain family 4; BH_4: tetrahydrobiopterin; FPN1: ferroportin 1; FSP1: ferroptosis suppressor protein 1; FBXW7: F-Box and WD Repeat Domain Containing 7; GSK-J4: an effective H3K27me3/me2 demethylase; GTP: guanosine triphosphate; GSH: glutathione; GPX4: glutathione peroxidase 4; GCH1: GTP cyclohydrolase 1; HO-1: heme oxygenase-1; KDM3B: lysine Demethylase 3B; KDM4A: lysine Demethylase 4A; KMT2B: Lysine-specific methyltransferase 2B; LSD1: lysine-specific demethylase 1; LPCAT3: lysophosphatidylcholine acyltransferase 3; LIP: labile iron pool; NEDD4L: NEDD4-like the E3 ubiquitin protein ligase gene; POR: cytochrome p450 oxidoreductase; PUFA: polyunsaturated fatty acid; PUFA-PL: PUFA-containing phospholipid; RFK: riboflavin kinase; ROS: reactive oxygen species; p53: tumor protein p53; SIAH2: Siah E3 ubiquitin protein ligase 2; SIRT3: sirtuin-3; SLC7A11: solute carrier family 7 member 11; SLC3A2: solute carrier family 3 member 2; TFR1: transferrin receptor 1; TLR4: toll-like receptor 4; ZFP36: zinc finger protein 36; TCA cycle: tricarboxylic acid cycle.

have been recognized. It has been discovered that specific gene transcription patterns correlate with distinct histone modifications. The methylation of arginine in H3 and H4 links to the activation of transcription, while the methylation of lysine in histones can either stimulate or inhibit transcription, contingent on the location of methylation. As an illustration, transcription is initiated by monomethylated and trimethylated H3 lysine 4 (H3K4me1 and H3K4me3). However, trimethylated histones H3, lysine 9, and lysine 27 (H3K9me3 and H3K27me3) have inhibitory effects on transcription [29,102].

For histone methylation modifications that regulate ferroptosis, they are commonly associated with histone methyltransferase (HMT) and histone demethylase (HDM). For HMT, methylation of H3K4 and H3K9 is its main target. A study has found that the high expression of GPX4 in cancer may be the result of epigenetic regulation by a decrease in upstream DNA methylation sites of GPX4 and an increase in H3K4me3 or H3K27ac levels [116]. Therefore, the corresponding HMT inhibitors are worth exploring. Some studies have also found that HMT inhibitors (such as BRD4770) can regulate smooth muscle cell ferroptosis and aortic dissection (AD), due to increased H3K9 methylation in AD patients' aortic smooth muscle cells inhibiting the expression of SLC7A11, GPX4, FSP1, and GCH1, resulting in an unresponsive antioxidant system related to ferroptosis system Xc^--GPX4, FSP1 CoQ10, and GCH1-BH4. BRD4770 can reduce H3K9 methylation and reactivate these antioxidant systems, thereby alleviating lipid peroxidation and ferroptosis in smooth muscle cells. BRD4770 can alleviate the release of pro-inflammatory cytokines induced by ferroptosis and ultimately prevent the development of AD [117]. In addition, the expression of Snapi1 is downregulated by HMT called SET domain bifurcated 1 (SETDB1), which is based on SETDB1 catalyzing Snapi1's H3K9me3, regulating the ferroptosis pathway, and inhibiting transforming growth factor-β (TGF-β)-induced pulmonary fibrosis EMT [118]. Lysine-specific methyltransferase 2B (KMT2B), as an H3K4 methyltransferase, may activate its transcription by inducing H3K4me3 of the riboflavin kinase (RFK) gene and mediating tumor necrosis factor (TNF)-α/the leukocyte NADPH oxidase 2 (NOX2) axis, which induces ROS accumulation disorders. Cell damage and ferroptosis are caused by myocardial ischemia/reperfusion injury stimulation [119]. DPP4 can promote lipid peroxidation because it is located on the plasma membrane and can bind with NADPH oxidase 1 to form a complex, thereby inducing ferroptosis. According to reports, the deficiency of suppressor of variegation 3–9 homolog 1 encoding histone H3K9 methyltransferase can regulate the H3K9me3 state of the DPP4 gene promoter, leading to its upregulation and induction of ferroptosis [120].

For HDM that regulates ferroptosis, lysine demethylase 3B (KDM3B) can activate the transcriptional activity of SLC7A11 to inhibit erastin-induced ferroptosis, thus determining KDM3B as a potential epigenetic regulator of ferroptosis [121]. In addition, studies have also found that lysine-specific demethylase 4A (KDM4A) can mediate ferroptosis by regulating the transcription of SLC7A11. KDM4A has the capability to regulate H3K9me3 within the SLC7A11 promoter area, thereby managing the transcription and ferroptosis of SLC7A11 [122]. The enzyme histone lysine demethylase KDM6A shows high expression in cardiomyocytes induced by palmitic acid (PA), triggering ACSL4 transcription and leading to ferroptosis. GSK-J4, as a specific inhibitor of KDM6A, can stabilize H3K27me3 levels and inhibit ACSL4 transcription, protecting myocardial cells from ferroptosis under PA stimulation [123]. In addition, lysine-specific demethylase 1 (LSD1) can activate the toll-like receptor 4 (TLR4)/NADPH oxidase 4 (NOX4) pathway by reducing the enrichment of H3K9me2 in the TLR4 promoter region, thereby exacerbating oxidative stress and ferroptosis caused by renal I/R injury in mice [124]. LSD1 has been shown to primarily inhibit transcription through H3K4me2 demethylation, and LSD1 inhibitors maintain SLC7A11 expression through this epigenetic modification to prevent ROS-related oxidative stress.

This neuroprotective effect may effectively protect cochlear spiral ganglion neurons from damage caused by cisplatin [125].

Based on the above research conclusions, we found that the regulation of ferroptosis by histone methylation modification is mostly in the exploratory stage, but the development of related inhibitors and the feasibility of clinical disease treatment have not yet been studied. Therefore, it is necessary to strengthen related research and exploration, which is of great significance for the further development of ferroptosis and histone methylation modification.

3.4.3. Histone ubiquitination

Protein ubiquitination is a crucial component of cellular activity. Ubiquitin modifies target proteins, especially ligases, through a series of activating enzymes, binding enzymes, and ligases.

At present, the regulation of ferroptosis by histone ubiquitination mainly focuses on ligases. For example, the E3 ubiquitin ligase RNF182 can mediate the ubiquitination of p65 and accelerate the degradation of the p65 protein. P65's ability to bind to the SLC7A11 promoter can lead to increased SLC7A11 expression. Therefore, RNF182 can downregulate the expression of SLC7A11 and regulate ferroptosis [126]. F-Box and WD repeat domain containing 7 (FBXW7) is a well-known ligase that promotes ferroptosis through various pathways. It downregulates the expression of zinc finger protein 36 (ZFP36) related to ferritin and NCOA4, thereby promoting ferroptosis in hepatic stellate cells [16]. In addition, it can reduce protein levels rich in AU-binding factor 1 (AUF1) and voltage-dependent anion channel 3 through ubiquitination to achieve its function in acute lymphoblastic leukemia (ALL) cells [127,128]. As a member of the E3 ligase family in the homologous E6-associated protein C-terminus domain of eukaryotes, neuronally expressed developmentally downregulated 4 (NEDD4) ubiquitinates and mediates protein degradation of voltage-dependent anion channel 2/3 in melanoma, which can be promoted by the typical ferroptosis inducer erastin [129]. In addition, lactoferrin (LF) is degraded under the action of NEDD4-like the E3 ubiquitin protein ligase gene (NEDD4L), leading to reduced intracellular iron accumulation and enhanced oxidative damage, thereby promoting ferroptosis [130]. At the same time, NEDD4L promotes the ubiquitination and degradation of TRF1, and estrogen receptor 1 in breast cancer cells can accelerate the ubiquitination and degradation of TRF1, thus accelerating IR-induced ferroptosis [131]. In Siah E3 ubiquitin protein ligase 2 (SIAH2), downgrading HO-1 transcription by inhibiting Nrf2 can prevent ferroptosis in specific organs, such as the heart, kidney and skeletal muscle [132]. In addition, knocking out SIAH2 will also increase the level of HO-1, thereby regulating ferroptosis. In addition to ligases, BRCA1-associated protein 1 and polycomb inhibit complex 1, and a nuclear deubiquitinase removes histone 2A mono-ubiquitination, both of which are known for their opposite functions but both inhibit SLC7A11 expression [29].

It is not difficult to find that current research mainly focuses on the regulation of ubiquitin ligase in ferroptosis, and the main research is still focused on exploring the mechanism. When research on the development and application of related inhibitors has not yet emerged, this is a large gap that has great research value and clinical significance. In addition, exploring other ubiquitination mechanisms is also of great significance.

3.5. Transcription factors

Several transcription factors play a role in ferroptosis regulation.

Transcription factor EB can promote quercetin-induced ferroptosis, which promotes the expression of lysosome-related gene lysosomal-associated membrane protein 1 and finally induces ROS and lysosome-dependent ferritin, resulting in lipid peroxidation ferroptosis in breast cancer cells [133]. BTB domain and CNC homolog1 are also transcription factors that regulate heme and iron metabolism, repressing genes like SLC7A11 and FTH1 that are involved in the synthesis of GSH and stimulating ferroptosis at the transcription level [134]. The ATF3 suppresses system Xc^-, represses the expression of SLC7A11 and GPX4, depletes intracellular GSH, and promotes lipid peroxidation and ferroptosis through the Nrf2/KEAP1/system Xc^- pathway [31].

Nonetheless, yes-associated protein/transcriptional co-activator with PDZ-binding motif is the key driver of Sorafenib resistance. Mechanically, it can upgrade SLC7A11 at the protein level to maintain intracellular GSH homeostasis. Besides, it can sustain the protein stability, nuclear location, and transcription vitality of ATF4, which participates in SLC7A11 expression promotion [135]. Nuclear protein 1, a stress-inducible transcription factor, targets and transactivates the expression of the gene encoding lipocalin 2, an iron transporter ferrying Fe^{2+} into the extracellular space, which plays an important role in ferroptosis resistance in two human pancreatic ductal adenocarcinomas [136].

3.6. Chromatin modification

Chromatin can be modified by a lot of factors. Here we put an emphasis on lymphoid-specific helicase (LSH), a chromatin remodeling protein that inhibits ferroptosis by enhancing the transcription of SLC7A11 after the recruitment to the promoter regions of SLC7A11 in human leukemia and activating lipid metabolism-associated genes, including glucose transporter type 1, and ferroptosis-related genes SCD1 and FADS2 in lung cancer [137,138]. LSH also interacts with lncRNA. As it is known to us, p53 plays a dual role in regulating ferroptosis [139]. Among them, p53 inhibits cystine uptake and sensitizes cells to ferroptosis by repressing the expression of SLC7A11 [140]. By silencing the cytosolic P53RRA, which displaces p53 from a GTPase-activating protein SH3 domain-binding protein 1 complex, LSH promotes ferroptosis and apoptosis in cancer cells [141]. Reversely, it can also be attenuated by LINC00618, another lncRNA [137].

4. Clinical significance: targeting epigenetic factors to mediate ferroptosis as a new strategy to combat cancer resistance

In this review, we describe how alterations in epigenetic factors mediate ferroptosis-related gene abnormalities that are critical for triggering ferroptosis in many cancers. Although many drugs regulating ferroptosis have been used in the clinical treatment of tumors, more and more studies have found that complex gene metabolic changes in tumors promote their drug resistance. Targeting epigenetic regulation to combat tumor drug resistance and further developing drug and treatment combinations are new strategies for effective cancer treatment. Truly, a significant number of epigenetic medications prove beneficial in cancer treatment through the control of ferroptosis. Here, we illustrate the potential of epigenetic drugs targeting ferroptosis in the treatment of tumor resistance with HDAC inhibitors, DNMT inhibitors, and bromodomain and extra-terminal motif (BET) inhibitors (Table 1) [71,72,108,109,112,116,122,142].

4.1. HDAC inhibitors

HDAC inhibitors enhance the efficacy of chemotherapy by promoting ferroptosis in tumors while inhibiting ferroptosis in neurons by regulating system Xc^- transporters [106]. The pharmacological inhibition of SIRT1 is the direct cause of the EMT inhibition caused by EX527, thereby inhibiting cell ferroptosis. Similarly, the enhancement of ferroptosis occurs due to SIRT1 inducers, SRT1720, and resveratrol [72]. Vorinostat, a clinically

Table 1
Epigenetic drugs regulate ferroptosis in clinical treatment of diseases.

Drug type	Drug	Molecular mechanism	Association with ferroptosis	Cancer/disease types	Refs.
DNMT inhibitors	6-TG	Inhibiting the regulation of the system Xc^- and downregulating the expression of GPX4	Promotion	Gastric cancer	[71]
HDAC inhibitors	EX527	Downregulation of HDAC SIRT1 inhibits EMT	Inhibition	Head and neck cancer	[72]
DNMT inhibitors	5-aza-CdR	Decreased CDH1 hypermethylation, resulting in increased E-cadherin expression	Inhibition	Head and neck cancer	[72]
HDAC inhibitors	BEBT-908	Hyperacetylated p53 upregulates its expression and represses SLC7A11 transcription	Promotion	Colon adenocarcinoma	[108]
HDAC inhibitors	Quisinostat	Activation of GPX4 and p53 protein related signaling pathways, the specific mechanism is unknown	Promotion	Tongue squamous cell carcinoma	[109]
HAT inhibitors	Ketamine	Inhibition of GPX4 expression	Promotion	Breast cancer	[112]
HDM inhibitors	2PCPA/S2101/CBB1007	Increase SLC7A11 expression	Inhibition	Injury of spiral ganglion n5-eurons	[116]
HMT inhibitors	BRD4770	Activate antioxidant system	Inhibition	Aortic dissection	[122]
DNMT inhibitors	5-aza-CdR	Unknown	Inhibition	Diabetes myocardial ischemia/ reperfusion injury	[142]

GPX4: glutathione peroxidase 4; BEBT-908: a selective pi3kα inhibitor; BRD4770: a histone methyltransferase G9a inhibitor; CBB1007: an inhibitor of histone demethylase; DNMT: DNA methyltransferase; CDH1: Cadherin 1; EX527: An inhibitor of SIRT1; HDAC: histone deacetylase; EMT: epithelial-mesenchymal transition; HAT: histone acetyltransferase; HDM: histone demethylase; SLC7A11: solute carrier family 7 member 11; HMT: histone methyltransferase; S2101: a lysine specific demethylase 1 inhibitor; 2PCPA: a monoamine oxidase inhibitor; 5-aza-CdR: specific inhibition of DNA methylation; 6-TG: a type of anti-leukemia and immunosuppressive agent.

approved class I HDAC inhibitor, significantly enhances the antiproliferative effect of the ferroptosis inducer erastin in non-small-cell lung cancer cell therapy, which may be related to the ROS-related cell death effect induced in lung cancer cells [143]. In addition, vorinostat can further promote ferroptosis by inhibiting SLC7A11 expression, leading to a significant increase in endogenous or acquired hydroperoxidases resistant to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors in EGFR-mutant lung cancer cells, showing the promise of epigenetic modifiers against tumor drug resistance [110]. Importantly, the ROS detoxification system associated with GSH leads to resistance to several antineoplastic agents, and SLC7A11 inhibition increases sensitivity to vorinostat in a ROS-dependent manner [144], showing promise for combination therapy with epigenetic and ferroptosis-inducing drugs. Another HDAC inhibitor, BEBT-908, has been found to sensitize a variety of cancer cells to ferroptosis by inducing the hyperacetylation of lysine 370 of p53 to up-regulate the expression of p53, thereby inhibiting the transcription of its downstream gene SLC7A11 [108]. As an HDAC inhibitor, quinostat induces ferroptosis in tongue squamous cell carcinoma by activating the GPX4 and p53 protein signaling pathways, but the specific mechanism has not been elucidated [109]. In addition, Oliveira et al. [145] experimentally found that treatment with the potent HDAC inhibitor FK228 can enhance the ferroptosis susceptibility of SW13 cells by inducing EMT and altering intracellular iron levels, and these results can be used to develop iron-targeted tumor therapy strategies to improve clinical outcomes in a variety of diseases.

4.2. DNMT inhibitors

5-azacytidine (5-AZA), a classical DNMT inhibitor, is widely used in epigenetic studies. For example, 5-AZA alleviates ferroptosis by inhibiting DNMT1 in the treatment of diabetic myocardial ischemia-reperfusion injury, and NCOA4-mediated ferritin autophagy may be involved. Since DNMT1 can mediate the methylation of a variety of genes to regulate their expression, whether DNMT1 interacts with the NCOA4 promoter region needs to be further identified [142]. Lee et al. [72] found that the hypermethylation of CDH1 is inhibited by the action of 5-AZA, increasing the expression of E-cadherin and thereby enhancing cell ferroptosis resistance. Suggesting that epigenetic reprogramming of EMT helps to promote ferroptosis sensitivity in HNC cells may be a promising novel approach for the fight against ferroptosis-resistant cancers. Consistently, homocysteine induces oxidative stress and ferroptosis in the nucleus pulposus through DNA methylation-mediated epigenetic silencing of GPX4, which could be rescued by 5-AZA [66]. 6-TG has been found to downregulate DNMT1, suggesting its involvement as a demethylating agent in epigenetic regulation [146], and it has also been found to promote ferroptosis by reducing the expression level of GPX4 [71].

In addition, more and more studies have found strategies for dual inhibition of DNMT and HDAC to treat tumors. A multifunctional DNMT and HDAC inhibitor, C02S, modulates multiple cancer markers in breast cancer therapy [147]. The novel G9a/DNMT dual reversible DNMT and HDAC inhibitors have a strong anti-tumor effect on bladder cancer cells [148]. Whether dual inhibition of DNMT and HDAC can regulate ferroptosis more effectively and exert a greater anticancer effect may be a new direction for future research.

4.3. BET inhibitors

Medications known as BET inhibitors are used to stop BET from engaging with acetylated histone [56]. Studies have found that the epigenetic BRD4/miR-29 system may play an important role in regulating the progression of neurodegenerative diseases by promoting SLC7A11 and reducing ferritin autophagy to counter ferroptosis [149], showing the potential of BET inhibitors in the treatment of tumor progression mediated by ferroptosis. Currently, BET inhibitors are shown to limit the progression of several cancers, making this protein a popular pharmacological target [149]. Research has found that JQ1, an inhibitor that can inhibit methyltransferase and HDAC, is an inhibitor of BRD4, which inhibits enzymes G9a and SIRT1, respectively. It is interesting that JQ1's epigenetic modification inhibits the expression of BRD4, while downregulating ferroptosis regulatory factors such as GPX4, SLC7A11, and SLC3A2, inducing the occurrence of ferroptosis [113]. In addition, the inhibitory effect of the ferroptosis inducer RSL3 on cancer can be significantly enhanced under the action of JQ1. Qiao et al. [150] also found that nuclear receptor subfamily 5, group A, member 2, and NCOA3 inhibitors were combined with BET inhibitors to induce ferroptosis in breast cancer resistant to BET inhibitors. These results hold promise for BRD4 inhibitors in combination with ferroptosis-inducing agents and ferroptosis-related gene inhibitors to enhance cancer therapy. At present, there are few studies on BET inhibitors that regulate epigenetic-

mediated ferroptosis in the treatment of cancer, and further research is needed.

In fact, many epigenetic regulatory drugs have been studied and entered clinical trials, showing exciting prospects. Here, we propose that multi-targeted inhibitors targeting multiple epigenetic regulators may be a more effective approach to cancer therapy, especially in the regulation of ferroptosis [147,148].

4.4. Other medications

The epigenetic regulation of ferroptosis in drug development is explored. In addition to directly studying epigenetic modifiers, many drugs have also been found to regulate the occurrence of ferroptosis through epigenetic modifications for disease treatment (Table 2) [151–159].

For example, by promoting the ubiquitination of ferroptosis regulatory factors to regulate ferroptosis, drugs that promote Nrf2 ubiquitination in liver cancer include tiliroside [151], while drugs that promote GSH synthetase (GSS) ubiquitination in liver cancer include corosolic acid [152]. The drugs that promote GPX4 ubiquitination are bufotalin and DMOCPTL, which have been proven in the research of lung cancer and breast cancer, respectively [153,154]. In addition to directly regulating important ferroptosis regulatory factors, some upstream targets have also been found to indirectly regulate ferroptosis through epigenetic modifications. The ubiquitination of hypoxia-inducible factor 1 alpha (HIF1α) proteins and the ubiquitination of poly (ADP-ribose) polymerase-1 (PARP1) have been found in studies of neurological diseases and lung cancer, respectively, to regulate ferroptosis through the regulation of streptococcin and proteolysis-targeting chimera (PROTAC) [155,156].

In addition to drugs that regulate protein ubiquitination, there are also drugs that can participate in disease treatment by modifying methylation and ncRNA to regulate the occurrence of ferroptosis. Sodium selenite can downregulate DNMT1 and upregulate ten-eleven translocation protein 1 (TET1) in lung cancer, while doxorubicin can promote enzymatic methylation of Nrf2 by protein arginine methyltransferase 4 in cardiomyopathy [157,158]. Melatonin and isoleucine regulate the occurrence of traumatic brain injury and ferroptosis after cerebral hemorrhage through circRNA and miRNA, respectively [99,159].

Overall, most of these drugs have been found to regulate the occurrence of ferroptosis through epigenetic modification pathways, which is of great significance for drug development in related diseases. After comparing it with the direct study of epigenetic drugs for the treatment of diseases, we conclude that direct epigenetic modifiers can purposefully conduct drug research on diseases from the perspective of epigenetic modifications. There is already a wealth of research on the mechanism, which represents a clear direction for drug development. Starting from the drug itself, exploring its mechanism of treating diseases and proving its correlation with epigenetic regulation can be strong or weak, but we can screen for more epigenetic modifiers through this connection. Searching for drugs to regulate epigenetic structures, as well as pruning and synthesizing them, provides direction for the search for epigenetic modifiers.

5. Clinical stages of epigenetic drugs

Epigenetic drugs, as a new treatment method, can be used to treat various diseases, especially cancer or neurological disorders [160–162]. At present, the development of epigenetic drugs is still under continuous exploration. It is known that epigenetic drugs such as 5-AZA, decitabine (DAC), vorinostat, valproic acid, and belinostat have been approved or are currently undergoing clinical trials, and some drugs have been found to regulate ferroptosis. This provides an important reference for the development of drugs related to the epigenetic regulation of ferroptosis (Table 3) [117,151,159,163–182].

The drugs that regulate DNA methylation currently in clinical trials are 5-AZA, DAC, and 6-TG. 5-AZA is currently used for the treatment of various diseases such as acute myeloid leukemia (AML), peripheral T-cell lymphoma, and myelodysplastic syndromes (MDS) [163–165]. And studies have found that 5-AZA can promote ferroptosis in HNC cells [72]. DAC has been found to be able to treat MDS [166], and it can inhibit the expression of GPX4 and promote ferroptosis in AML cells [183]. 6-TG can be used to treat ALL [167], and it inhibits the expression of GPX4, inducing ferroptosis in gastric cancer cells [71].

For drugs that regulate histone modification, the main drugs currently used are those that regulate histone acetylation, including vorinostat, belinostat, valproic acid, and others. Among them, vorinostat can be used to treat hematological and neurological diseases such as cutaneous T-cell lymphoma, ALL, and glioblastoma [168–170]. Vorinostat can increase intracellular ROS accumulation and induce ferroptosis in cells [144]. Belinostat has certain therapeutic effects on diseases such as peripheral T-cell lymphoma and HCC [171,172]. Valproic acid can be used for the treatment of AML and advanced solid tumors [173,174], and it has also been found to promote the expression of GPX4 and improve cisplatin-induced ferroptosis [184].

In addition to drugs that directly modify epigenetics, many drugs have also been found to regulate the ubiquitination and methylation of ferroptosis histones. However, except for some that have been used in clinical trials, most of them are still under experimental research. Examples such as berberine, recombinant fibroblast growth factor 21 (FGF21), and ginkgolide B have been used in clinical trials and have been found to regulate histone ubiquitination in ferroptosis. Berberine increases intracellular ROS production and promotes ferroptosis in hepatic stellate cells through the ubiquitin proteasome pathway [185]. Currently,

Table 2
Drugs regulate ferroptosis through epigenetic modification to treat diseases.

Modification	Drug	Molecular mechanism	Association with ferroptosis	Cancer/disease types	Refs.
Ubiquitination	Tiliroside	Promote NRF2 ubiquitination and degradation	Promotion	Hepatocellular carcinoma	[151]
Ubiquitination	Corosolic acid	Promote GSS ubiquitination	Promotion	Liver cancer	[152]
Ubiquitination	DMOCPTL	Promote GPX4 ubiquitination	Promotion	Breast cancer	[153]
Ubiquitination	Bufotalin	Promote GPX4 ubiquitination	Promotion	Lung cancer	[154]
Ubiquitination	Streptococcin	HIF1α ubiquitination	Inhibition	Neurological diseases	[155]
Ubiquitination	PROTAC	PARP1 ubiquitination	Promotion	Lung cancer	[156]
Methylation	Sodium selenite	Downregulate DNMT1 and upregulate TET1	Inhibition	Lung cancer	[157]
Methylation	Doxorubicin	Promote enzymatic methylation of Nrf2	Promotion	Cardiomyopathy	[158]
ncRNA	Isorhynchophylline	miR-122-5p/p53/SLC7A11	Inhibition	Cerebral hemorrhage	[159]

Nrf2: nuclear factor erythroid 2-related factor 2; GSS: glutathione synthetase; DMOCPTL: a derivative of natural product parthenolide; GPX4: glutathione peroxidase 4; HIF1α: hypoxia-inducible factor 1 alpha; PROTAC: proteolysis-targeting chimera; PARP1: poly (ADP-ribose) polymerase-1; DNMT1: DNA methyltransferase 1; TET1: ten-eleven translocation protein 1; ncRNA: noncoding RNA; p53: tumor protein p53; SLC7A11: solute carrier family 7 member 11.

Table 3
Clinical stages of epigenetic drugs.

Modification	Drug	Association with ferroptosis	Clinical stage	Refs.
Histone methylation	BRD4770	Inhibition	Experimental testing	[117]
Histone ubiquitination	Tiliroside	Promotion	Experimental testing	[151]
ncRNA	Lsorhynchophylline	Inhibition	Experimental testing	[159]
DNA methylation	5-AZA	Promotion	Phase II	[163–165]
DNA methylation	DAC	Promotion	Phase II	[166]
DNA methylation	6-TG	Promotion	Phase II/III	[167]
Histone acetylation	Vorinostat	Promotion	Phase III	[168–170]
Histone acetylation	Belinostat	Unclear	Phase II	[171,172]
Histone acetylation	Valproic acid	Inhibition	Phase I	[173,174]
Histone ubiquitination	Berberine	Promotion	Phase IV	[175]
Histone ubiquitination	Recombinant FGF21	Inhibition	Phase II	[176]
Histone ubiquitination	Ginkgolide B	Inhibition	Experimental testing	[177]
Histone methylation	UNC0642	Promotion	Experimental testing	[178]
ncRNA	Ketamine	Promotion	Phase II	[179]
ncRNA	Melatonin	Inhibition	Phase IV	[180]
Histone ubiquitination	Paeonol	Inhibition	Phase II	[181]
Histone ubiquitination	Obacunone	Inhibition	Experimental testing	[182]

The reference for each drug only represents the application. The clinical stage data comes from the website: https://pubchem.ncbi.nlm.nih.gov/. BRD4770: a histone methyltransferase G9a inhibitor; ncRNA: noncoding RNA; 5-AZA: 5-azacytidine; DAC: decitabine; 6-TG: 6-thioguanine; FGF21: fibroblast growth factor 21; UNC0642: a selective inhibitor of lysine methyltransferase G9a and GLP.

berberine has been used for the treatment of type 2 diabetes [175]. Recombinant FGF21 was found to promote the ubiquitination and degradation of HO-1 and inhibit the occurrence of ferroptosis [186]. Recombinant FGF21 was used in clinical trials for the treatment of non-alcoholic steatohepatitis [176]. Ginkgolide B has been found to have certain therapeutic effects on asthma in clinical trials [177]. In addition, studies have found that Ginkgolide B can inhibit the ubiquitination of GPX4 and protect the kidneys from ferroptosis [187]. However, although UNC0642 and BRD4770 have been found to regulate ferroptosis histone methylation, they are still under experimental research. As a histone methyltransferase G9a, UNC0642 can reduce intracellular GSH levels and induce ferroptosis in cells [178].

Drugs that regulate ncRNA include ketamine and melatonin. Ketamine is commonly used to treat depression [179], but studies have found that it can reduce the expression of lncPVT1 and GPX4 and induce ferroptosis in liver cancer cells [188]. Melatonin can reduce the level of circ-Ptpn 14, regulate the level of 5-LOX, and inhibit the occurrence of ferroptosis [99]. It has been used in clinical trials for the treatment of gastroesophageal reflux disease [180].

Overall, epigenetic drugs have gradually entered clinical practice, bringing new strategies for the treatment of various diseases. However, epigenetic drugs based on ferroptosis have not yet emerged, but the epigenetic regulation of ferroptosis by many drugs proves that this drug development path has broad prospects.

6. Conclusions and perspectives

The discovery of ferroptosis has sparked a research boom in this field, and the discovery of this new mode of cell death provides new directions for disease treatment and drug development. Firstly, a large number of ferroptosis regulatory factors have been gradually discovered, and the regulatory mechanism of ferroptosis has been gradually improved. After the continuous discovery and improvement of the mechanism of ferroptosis, relevant inducers and inhibitors began to emerge. These reagents can be derived from chemical synthesis that directly regulates the levels of ferroptosis-inducing or inhibiting factors, or they can be extracted from plants that can induce or inhibit ferroptosis. They are all believed to be able to treat certain diseases related to ferroptosis due to their ability to regulate the occurrence of ferroptosis. Therefore, they all have the potential to become candidate drugs for treating diseases. We know that developing a new drug requires identifying the disease and its target. Ferroptosis has been found to be associated with the occurrence of various diseases, and inducing cell ferroptosis can treat and reduce the occurrence and development of diseases.

Here, we focus on the epigenetic regulation of ferroptosis, which includes various modifications such as DNA methylation, RNA methylation, ncRNA, histone methylation, acetylation, ubiquitination, transcription factors, and chromatin. These modifications can induce or inhibit the occurrence of ferroptosis, which means that these epigenetic modifications have the potential to participate in disease treatment by regulating ferroptosis. Therefore, we have summarized the role of epigenetic regulation of ferroptosis in drug development. The epigenetic regulation of ferroptosis can provide a clear pathway for drug development. With the continuous development of bioinformatics analysis and network pharmacology technology, the most tedious and difficult screening work for epigenetic modifications has been solved. With the continuous improvement of databases, the screening of genes and their association with ferroptosis has become simpler. For example, the microarray analysis can be performed on normal tissue and cancerous tissue to identify target genes with significant changes, further confirm the role of these genes, and validate them. In addition, by conducting bioinformatics analysis on extracts of potential anti-cancer drugs such as natural derivatives, effective targets are screened and their mechanisms of action are explored to determine their association with ferroptosis. After identifying the target gene, developing corresponding inhibitors or inducers becomes the focus of the next step. Currently, many studies have shown that epigenetic modifiers such as HDAC inhibitors and DNMT inhibitors are involved in the treatment of diseases through ferroptosis. Therefore, the development of epigenetic modifiers will be the focus of future research. The research and development of nanomedicine and traditional herbal medicine may take two different directions for future development. For example, preliminary observations of nanomedicines regulating ferroptosis through miRNA revealed differences in miRNA expression between cancer tissue and normal tissue. This has led to the discovery that controlling the levels of these miRNAs can effectively control the proliferation of tumor cells. Next, while exploring its mechanism of action, the author will apply nanotechnology to select suitable gene carriers to prepare nanomedicines and determine their therapeutic effects through *in vivo*

and *in vitro* experiments to improve the level of drug development [101]. However, the development of nanomedicines is limited by the development of new technologies such as protein hydrolysis-targeted chimeras, monomer-targeted protein degradation agents, and molecular gels. Compared to the development of nanomedicines, the application of traditional herbs is more universal and accessible to the public. Due to the continuous development of bioinformatics technology, the screening of effective small-molecule compounds in traditional herbs has become easier and faster. With the assistance of network pharmacology and other technologies, binding verification between molecules and targets is made faster. For example, a study using bioinformatics technology analysis found that the expression level of CYP2E1 in solid cancer is lower than that in normal tissues and then verified its correlation with the cancer prognosis. Network pharmacology was then used to search for traditional Chinese medicine that could be combined with it [189]. After determining the lead compound, its structure is optimized to make the ferroptosis epigenetic modifier a candidate drug. Therefore, the epigenetic regulation of ferroptosis provides new strategies and directions for drug development, especially in situations where traditional drug therapies face limitations and resistance.

While the future looks promising, it is important to focus on the present and address the current shortcomings and challenges. Currently, research on epigenetic regulators is primarily focused on pathological models, and it is crucial to consider the various factors that can impact therapeutic effectiveness. For example, when targeting lncRNA, there is a risk of off-target effects leading to unpredictable consequences, so feasibility must be thoroughly verified. Additionally, it has been observed that the same epigenetic modifications can have opposite effects in different tissues or diseases, indicating potential side effects and complicating clinical drug development. To address this, a deeper understanding of the unique biological effects of different tissue cells is necessary. Technological limitations also present a challenge, particularly in verifying the function and therapeutic effects of epigenetic modifications related to ferroptosis *in vivo*. The development and validation of corresponding drugs also require technical maturity and support.

Overall, the epigenetic regulation of ferroptosis has important value for drug development. However, due to the limitations of current technology, research depth, and applicability, continuous research and exploration are still needed. However, its enormous application value deserves our continuous investment.

CRediT authorship contribution statement

Shengli Ouyang: Writing – original draft, Visualization, Methodology, Investigation. **Zeyao Zeng:** Writing – original draft, Visualization, Software, Resources. **Jieyi He:** Writing – original draft, Methodology, Investigation. **Lianxiang Luo:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that there are no conflicts of interest.

References

[1] S.J. Dixon, K.M. Lemberg, M.R. Lamprecht, et al., Ferroptosis: An iron-dependent form of nonapoptotic cell death, Cell 149 (2012) 1060–1072.
[2] B.R. Stockwell, Ferroptosis turns 10: Emerging mechanisms, physiological functions, and therapeutic applications, Cell 185 (2022) 2401–2421.
[3] D. Tang, X. Chen, R. Kang, et al., Ferroptosis: Molecular mechanisms and health implications, Cell Res. 31 (2021) 107–125.
[4] L. Zhang, Q. Lu, C. Chang, Epigenetics in health and disease, Adv. Exp. Med. Biol. 1253 (2020) 3–55.
[5] M.A. Dawson, T. Kouzarides, Cancer epigenetics: From mechanism to therapy, Cell 150 (2012) 12–27.
[6] A. Cort, T. Ozben, L. Saso, et al., Redox control of multidrug resistance and its possible modulation by antioxidants, Oxid. Med. Cell. Longev. 2016 (2016), 4251912.
[7] L. Rochette, G. Dogon, E. Rigal, et al., Lipid peroxidation and iron metabolism: Two corner stones in the homeostasis control of ferroptosis, Int. J. Mol. Sci. 24 (2022), 449.
[8] E. Dai, X. Chen, A. Linkermann, et al., A guideline on the molecular ecosystem regulating ferroptosis, Nat. Cell Biol. (2024) 1447–1457.
[9] D. Liang, A.M. Minikes, X. Jiang, Ferroptosis at the intersection of lipid metabolism and cellular signaling, Mol. Cell 82 (2022) 2215–2227.
[10] B.T. Paul, D.H. Manz, F.M. Torti, et al., Mitochondria and Iron: Current questions, Expert Rev. Hematol. 10 (2017) 65–79.
[11] M. Dodson, R. Castro-Portuguez, D.D. Zhang, NRF2 plays a critical role in mitigating lipid peroxidation and ferroptosis, Redox Biol. 23 (2019), 101107.
[12] K. Pantopoulos, S.K. Porwal, A. Tartakoff, et al., Mechanisms of mammalian iron homeostasis, Biochemistry 51 (2012) 5705–5724.
[13] G.J. Anderson, D.M. Frazer, Current understanding of iron homeostasis, Am. J. Clin. Nutr. 106 (2017) 1559S–1566S.
[14] F. Zolea, A.M. Battaglia, E. Chiarella, et al., Ferritin heavy subunit silencing blocks the erythroid commitment of K562 cells via miR-150 up-regulation and GATA-1 repression, Int. J. Mol. Sci. 18 (2017), 2167.
[15] J. Liu, R. Kang, D. Tang, Signaling pathways and defense mechanisms of ferroptosis, FEBS J. 289 (2022) 7038–7050.
[16] Z. Zhang, M. Guo, Y. Li, et al., RNA-binding protein ZFP36/TTP protects against ferroptosis by regulating autophagy signaling pathway in hepatic stellate cells, Autophagy 16 (2020) 1482–1505.
[17] J.D. Mancias, L. Pontano Vaites, S. Nissim, et al., Ferritinophagy via NCOA4 is required for erythropoiesis and is regulated by iron dependent HERC2-mediated proteolysis, elife 4 (2015), e10308.
[18] W.E. Dowdle, B. Nyfeler, J. Nagel, et al., Selective VPS34 inhibitor blocks autophagy and uncovers a role for NCOA4 in ferritin degradation and iron homeostasis *in vivo*, Nat. Cell Biol. 16 (2014) 1069–1079.
[19] C. Xu, S. Sun, T. Johnson, et al., The glutathione peroxidase Gpx4 prevents lipid peroxidation and ferroptosis to sustain Treg cell activation and suppression of antitumor immunity, Cell Rep. 35 (2021), 109235.
[20] W.S. Hambright, R.S. Fonseca, L. Chen, et al., Ablation of ferroptosis regulator glutathione peroxidase 4 in forebrain neurons promotes cognitive impairment and neurodegeneration, Redox Biol. 12 (2017) 8–17.
[21] W.S. Yang, R. SriRamaratnam, M.E. Welsch, et al., Regulation of ferroptotic cancer cell death by GPX4, Cell 156 (2014) 317–331.
[22] C.K. Singh, G. Chhabra, M.A. Ndiaye, et al., The role of sirtuins in antioxidant and redox signaling, Antioxid. Redox Signal. 28 (2018) 643–661.
[23] C. Biswas, N. Shah, M. Muthu, et al., Nuclear heme oxygenase-1 (HO-1) modulates subcellular distribution and activation of Nrf2, impacting metabolic and anti-oxidant defenses, J. Biol. Chem. 289 (2014) 26882–26894.
[24] X. Song, D. Long, Nrf2 and ferroptosis: A new research direction for neurodegenerative diseases, Front. Neurosci. 14 (2020), 267.
[25] M. Conrad, A. Sandin, H. Förster, et al., 12/15-lipoxygenase-derived lipid peroxides control receptor tyrosine kinase signaling through oxidation of protein tyrosine phosphatases, Proc. Natl. Acad. Sci. U.S.A. 107 (2010) 15774–15779.
[26] H. Sato, M. Tamba, T. Ishii, et al., Cloning and expression of a plasma membrane cystine/glutamate exchange transporter composed of two distinct proteins, J. Biol. Chem. 274 (1999) 11455–11458.
[27] P. Koppula, Y. Zhang, L. Zhuang, et al., Amino acid transporter SLC7A11/xCT at the crossroads of regulating redox homeostasis and nutrient dependency of cancer, Cancer Commun. (Lond) 38 (2018), 12.
[28] B.R. Stockwell, J.P. Friedmann Angeli, H. Bayir, et al., Ferroptosis: A regulated cell death nexus linking metabolism, redox biology, and disease, Cell 171 (2017) 273–285.
[29] P. Koppula, L. Zhuang, B. Gan, Cystine transporter SLC7A11/xCT in cancer: Ferroptosis, nutrient dependency, and cancer therapy, Protein Cell 12 (2021) 599–620.
[30] M.S. Kilberg, J. Shan, N. Su, ATF4-dependent transcription mediates signaling of amino acid limitation, Trends Endocrinol. Metab. 20 (2009) 436–443.
[31] L. Wang, Y. Liu, T. Du, et al., ATF3 promotes erastin-induced ferroptosis by suppressing system Xc, Cell Death Differ. 27 (2020) 662–675.
[32] H. Dong, Z. Qiang, D. Chai, et al., Nrf2 inhibits ferroptosis and protects against acute lung injury due to intestinal ischemia reperfusion via regulating SLC7A11 and HO-1, Aging 12 (2020) 12943–12959.
[33] A.S. Agyeman, R. Chaerkady, P.G. Shaw, et al., Transcriptomic and proteomic profiling of KEAP1 disrupted and sulforaphane-treated human breast epithelial cells reveals common expression profiles, Breast Cancer Res. Treat. 132 (2012) 175–187.
[34] N. Harada, M. Kanayama, A. Maruyama, et al., Nrf2 regulates ferroportin 1-mediated iron efflux and counteracts lipopolysaccharide-induced ferroportin 1 mRNA suppression in macrophages, Arch. Biochem. Biophys. 508 (2011) 101–109.
[35] Z. Qiang, H. Dong, Y. Xia, et al., Nrf2 and STAT3 alleviates ferroptosis-mediated IIR-ALI by regulating SLC7A11, Oxid. Med. Cell. Longev. 2020 (2020), 5146982.

[36] E.J. Hillmer, H. Zhang, H.S. Li, et al., STAT3 signaling in immunity, Cytokine Growth Factor Rev. 31 (2016) 1–15.
[37] B. Zhou, J. Liu, R. Kang, et al., Ferroptosis is a type of autophagy-dependent cell death, Semin. Cancer Biol. 66 (2020) 89–100.
[38] A.L. Levonen, A. Landar, A. Ramachandran, et al., Cellular mechanisms of redox cell signalling: Role of cysteine modification in controlling antioxidant defences in response to electrophilic lipid oxidation products, Biochem. J. 378 (2004) 373–382.
[39] X. Sun, Z. Ou, R. Chen, et al., Activation of the p62-Keap1-NRF2 pathway protects against ferroptosis in hepatocellular carcinoma cells, Hepatology 63 (2016) 173–184.
[40] Z. Fan, A.K. Wirth, D. Chen, et al., Nrf2-Keap1 pathway promotes cell proliferation and diminishes ferroptosis, Oncogenesis 6 (2017), e371.
[41] Y. Sun, L. He, T. Wang, et al., Activation of p62-Keap1-Nrf2 pathway protects 6-hydroxydopamine-induced ferroptosis in dopaminergic cells, Mol. Neurobiol. 57 (2020) 4628–4641.
[42] Q. Dang, Z. Sun, Y. Wang, et al., Ferroptosis: A double-edged sword mediating immune tolerance of cancer, Cell Death Dis. 13 (2022), 925.
[43] J.-Y. Lee, W.K. Kim, K.-H. Bae, et al., Lipid metabolism and ferroptosis, Biology 10 (2021), 184.
[44] J. Cui, Y. Wang, X. Tian, et al., LPCAT3 is transcriptionally regulated by YAP/ZEB/EP300 and collaborates with ACSL4 and YAP to determine ferroptosis sensitivity, Antioxid. Redox Signal. 39 (2023) 491–511.
[45] S.J. Dixon, G.E. Winter, L.S. Musavi, et al., Human haploid cell genetics reveals roles for lipid metabolism genes in nonapoptotic cell death, ACS Chem. Biol. 10 (2015) 1604–1609.
[46] T. Grenier-Larouche, A. Galinier, L. Casteilla, et al., Omental adipocyte hypertrophy relates to coenzyme Q10 redox state and lipid peroxidation in obese women, J. Lipid Res. 56 (2015) 1985–1992.
[47] K. Bersuker, J.M. Hendricks, Z. Li, et al., The CoQ oxidoreductase FSP1 acts parallel to GPX4 to inhibit ferroptosis, Nature 575 (2019) 688–692.
[48] P. Koppula, G. Lei, Y. Zhang, et al., A targetable CoQ-FSP1 axis drives ferroptosis-and radiation-resistance in KEAP1 inactive lung cancers, Nat. Commun. 13 (2022), 2206.
[49] A. Latremoliere, M. Costigan, GCH1, BH4 and pain, Curr. Pharm. Biotechnol. 12 (2011) 1728–1741.
[50] T. Harada, H. Kagamiyama, K. Hatakeyama, Feedback regulation mechanisms for the control of GTP cyclohydrolase I activity, Science 260 (1993) 1507–1510.
[51] T. Yoneyama, J.M. Brewer, K. Hatakeyama, GTP cyclohydrolase I feedback regulatory protein is a pentamer of identical subunits. Purification, cDNA cloning, and bacterial expression, J. Biol. Chem. 272 (1997) 9690–9696.
[52] Q. Hu, W. Wei, D. Wu, et al., Blockade of GCH1/BH4 axis activates ferritinophagy to mitigate the resistance of colorectal cancer to erastin-induced ferroptosis, Front. Cell Dev. Biol. 10 (2022), 810327.
[53] S.J.F. Cronin, C. Seehus, A. Weidinger, et al., The metabolite BH4 controls T cell proliferation in autoimmunity and cancer, Nature 563 (2018) 564–568.
[54] V.A.N. Kraft, C.T. Bezjian, S. Pfeiffer, et al., GTP cyclohydrolase 1/tetrahydrobiopterin counteract ferroptosis through lipid remodeling, ACS Cent. Sci. 6 (2020) 41–53.
[55] J. Xue, C. Yu, W. Sheng, et al., The Nrf2/GCH1/BH4 axis ameliorates radiation-induced skin injury by modulating the ROS cascade, J. Invest. Dermatol. 137 (2017) 2059–2068.
[56] Y. Pei, Y. Qian, H. Wang, et al., Epigenetic regulation of ferroptosis-associated genes and its implication in cancer therapy, Front. Oncol. 12 (2022), 771870.
[57] K.M. Schachtschneider, Y. Liu, L.A. Rund, et al., Impact of neonatal iron deficiency on hippocampal DNA methylation and gene transcription in a porcine biomedical model of cognitive development, BMC Genomics 17 (2016), 856.
[58] L.M. Iyer, S. Abhiman, L. Aravind, Natural history of eukaryotic DNA methylation systems, Prog. Mol. Biol. Transl. Sci. 101 (2011) 25–104.
[59] K. Kawai, Y.-S. Li, M.-F. Song, et al., DNA methylation by dimethyl sulfoxide and methionine sulfoxide triggered by hydroxyl radical and implications for epigenetic modifications, Bioorg. Med. Chem. Lett. 20 (2010) 260–265.
[60] R.D. Hornblow, P. Pathak, D.L. Balacco, et al., Iron-mediated epigenetic activation of NRF2 targets, J. Nutr. Biochem. 101 (2022), 108929.
[61] Q. Ye, M. Trivedi, Y. Zhang, et al., Brain iron loading impairs DNA methylation and alters GABAergic function in mice, FASEB J. 33 (2019) 2460–2471.
[62] S. Zhang, W. Chang, H. Wu, et al., Pan-cancer analysis of iron metabolic landscape across the Cancer Genome Atlas, J. Cell. Physiol. 235 (2020) 1013–1024.
[63] R. Wei, H. Qiu, J. Xu, et al., Expression and prognostic potential of GPX1 in human cancers based on data mining, Ann. Transl. Med. 8 (2020), 124.
[64] N.A.B. Schumann, A.S. Mendonça, M.M. Silveira, et al., Procaine and S-adenosyl-l-homocysteine affect the expression of genes related to the epigenetic machinery and change the DNA methylation status of *in vitro* cultured bovine skin fibroblasts, DNA Cell Biol. 39 (2020) 37–49.
[65] W. Shen, C. Gao, R. Cueto, et al., Homocysteine-methionine cycle is a metabolic sensor system controlling methylation-regulated pathological signaling, Redox Biol. 28 (2020), 101322.
[66] X. Zhang, Z. Huang, Z. Xie, et al., Homocysteine induces oxidative stress and ferroptosis of nucleus pulposus via enhancing methylation of GPX4, Free Radic. Biol. Med. 160 (2020) 552–565.
[67] Z. Zhang, C. Fu, J. Liu, et al., Hypermethylation of the Nrf2 promoter induces ferroptosis by inhibiting the Nrf2-GPX4 axis in COPD, Int. J. Chron. Obstruct. Pulmon. Dis. 16 (2021) 3347–3362.
[68] J.-Y. Lee, M. Nam, H.Y. Son, et al., Polyunsaturated fatty acid biosynthesis pathway determines ferroptosis sensitivity in gastric cancer, Proc. Natl. Acad. Sci. U.S.A. 117 (2020) 32433–32442.
[69] Q. Shi, R. Liu, L. Chen, Ferroptosis inhibitor ferrostatin-1 alleviates homocysteine-induced ovarian granulosa cell injury by regulating TET activity and DNA methylation, Mol. Med. Rep. 25 (2022), 130.
[70] E. Logie, B. Van Puyvelde, B. Cuypers, et al., Ferroptosis induction in multiple myeloma cells triggers DNA methylation and histone modification changes associated with cellular senescence, Int. J. Mol. Sci. 22 (2021), 12234.
[71] J. Zhang, M. Gao, Y. Niu, et al., From DNMT1 degrader to ferroptosis promoter: Drug repositioning of 6-thioguanine as a ferroptosis inducer in gastric cancer, Biochem. Biophys. Res. Commun. 603 (2022) 75–81.
[72] J. Lee, J.H. You, M.S. Kim, et al., Epigenetic reprogramming of epithelial-mesenchymal transition promotes ferroptosis of head and neck cancer, Redox Biol. 37 (2020), 101697.
[73] K.D. Meyer, Y. Saletore, P. Zumbo, et al., Comprehensive analysis of mRNA methylation reveals enrichment in 3' UTRs and near stop codons, Cell 149 (2012) 1635–1646.
[74] X. Chen, Y.-Z. Sun, H. Liu, et al., RNA methylation and diseases: Experimental results, databases, Web servers and computational models, Brief. Bioinform. 20 (2019) 896–917.
[75] P. Boccaletto, F. Stefaniak, A. Ray, et al., MODOMICS: A database of RNA modification pathways. 2021 update, Nucleic Acids Res. 50 (2022) D231–D235.
[76] P.V. Sergiev, N.A. Aleksashin, A.A. Chugunova, et al., Structural and evolutionary insights into ribosomal RNA methylation, Nat. Chem. Biol. 14 (2018) 226–235.
[77] Y. Pan, P. Ma, Y. Liu, et al., Multiple functions of m^{6}A RNA methylation in cancer, J. Hematol. Oncol. 11 (2018), 48.
[78] L. He, H. Li, A. Wu, et al., Functions of N6-methyladenosine and its role in cancer, Mol. Cancer 18 (2019), 176.
[79] J. Han, J.-Z. Wang, X. Yang, et al., METTL3 promote tumor proliferation of bladder cancer by accelerating pri-miR221/222 maturation in m6A-dependent manner, Mol. Cancer 18 (2019), 110.
[80] M. Cheng, L. Sheng, Q. Gao, et al., The m^{6}A methyltransferase METTL3 promotes bladder cancer progression via AFF4/NF-κB/MYC signaling network, Oncogene 38 (2019) 3667–3680.
[81] H. Yang, Y. Hu, M. Weng, et al., Hypoxia inducible lncRNA-CBSLR modulates ferroptosis through m6A-YTHDF2-dependent modulation of CBS in gastric cancer, J. Adv. Res. 37 (2021) 91–106.
[82] F.-H. Ji, X.-H. Fu, G.-Q. Li, et al., FTO prevents thyroid cancer progression by SLC7A11 m6A methylation in a ferroptosis-dependent manner, Front. Endocrinol. 13 (2022), 857765.
[83] J. Ye, X. Chen, X. Jiang, et al., RNA demethylase ALKBH5 regulates hypopharyngeal squamous cell carcinoma ferroptosis by posttranscriptionally activating NFE2L2/NRF2 in an m^6 A-IGF$_2$BP$_2$-dependent manner, J. Clin. Lab. Anal. 36 (2022), e24514.
[84] J. Liu, Z. Ren, L. Yang, et al., The NSUN5-FTH1/FTL pathway mediates ferroptosis in bone marrow-derived mesenchymal stem cells, Cell Death Discov. 8 (2022), 99.
[85] H. Ling, M. Li, C. Yang, et al., Glycine increased ferroptosis via SAM-mediated GPX4 promoter methylation in rheumatoid arthritis, Rheumatology (Oxford) 61 (2022) 4521–4534.
[86] J.E. Wilusz, H. Sunwoo, D.L. Spector, Long noncoding RNAs: Functional surprises from the RNA world, Genes Dev. 23 (2009) 1494–1504.
[87] R. Zhang, T. Pan, Y. Xiang, et al., Curcumenol triggered ferroptosis in lung cancer cells via lncRNA H19/miR-19b-3p/FTH1 axis, Bioact. Mater. 13 (2021) 23–36.
[88] Y. Luo, S. Huang, J. Wei, et al., Long noncoding RNA LINC01606 protects colon cancer cells from ferroptotic cell death and promotes stemness by SCD1-Wnt/β-catenin-TFE3 feedback loop signalling, Clin. Transl. Med. 12 (2022), e752.
[89] Y. Zhang, M. Luo, X. Cui, et al., Long noncoding RNA NEAT1 promotes ferroptosis by modulating the miR-362-3p/MIOX axis as a ceRNA, Cell Death Differ. 29 (2022) 1850–1863.
[90] J. Lu, F. Xu, H. Lu, LncRNA PVT1 regulates ferroptosis through miR-214-mediated TFR1 and p53, Life Sci. 260 (2020), 118305.
[91] Y. Zhang, S. Guo, S. Wang, et al., LncRNA OIP5-AS1 inhibits ferroptosis in prostate cancer with long-term cadmium exposure through miR-128-3p/SLC7A11 signaling, Ecotoxicol. Environ. Saf. 220 (2021), 112376.
[92] Y.Z. Li, H.C. Zhu, Y. Du, et al., Silencing lncRNA SLC16A1-AS1 induced ferroptosis in renal cell carcinoma through miR-143-3p/SLC7A11 signaling, Technol. Cancer Res. Treat. 21 (2022), 15330338221077803.
[93] J. Krol, I. Loedige, W. Filipowicz, The widespread regulation of microRNA biogenesis, function and decay, Nat. Rev. Genet. 11 (2010) 597–610.
[94] M. Luo, L. Wu, K. Zhang, et al., miR-137 regulates ferroptosis by targeting glutamine transporter SLC1A5 in melanoma, Cell Death Differ. 25 (2018) 1457–1472.
[95] C. Ding, X. Ding, J. Zheng, et al., miR-182-5p and miR-378a-3p regulate ferroptosis in I/R-induced renal injury, Cell Death Dis. 11 (2020), 929.
[96] H. Zhang, T. Deng, R. Liu, et al., CAF secreted miR-522 suppresses ferroptosis and promotes acquired chemo-resistance in gastric cancer, Mol. Cancer 19 (2020), 43.
[97] W. Zhou, Z. Cai, J. Liu, et al., Circular RNA: Metabolism, functions and interactions with proteins, Mol. Cancer 19 (2020), 172.

[98] S. Chen, Z. Zhang, B. Zhang, et al., CircCDK14 promotes tumor progression and resists ferroptosis in glioma by regulating PDGFRA, Int. J. Biol. Sci. 18 (2022) 841–857.
[99] C. Wu, M. Du, R. Yu, et al., A novel mechanism linking ferroptosis and endoplasmic reticulum stress via the circPtpn14/miR-351-5p/5-LOX signaling in melatonin-mediated treatment of traumatic brain injury, Free Radic. Biol. Med. 178 (2022) 271–294.
[100] H. Zhang, Z. Ge, Z. Wang, et al., Circular RNA RHOT1 promotes progression and inhibits ferroptosis via mir-106a-5p/STAT3 axis in breast cancer, Aging 13 (2021) 8115–8126.
[101] Y. Luo, G. Niu, H. Yi, et al., Nanomedicine promotes ferroptosis to inhibit tumour proliferation *in vivo*, Redox Biol 42 (2021), 101908.
[102] M.D. Stewart, J. Li, J. Wong, Relationship between histone H3 lysine 9 methylation, transcription repression, and heterochromatin protein 1 recruitment, Mol. Cell. Biol. 25 (2005) 2525–2538.
[103] J.E. Audia, R.M. Campbell, Histone modifications and cancer, Cold Spring Harb. Perspect. Biol. 8 (2016), a019521.
[104] T. Lan, T.T. Sun, C. Wei, et al., Epigenetic regulation of ferroptosis in central nervous system diseases, Mol. Neurobiol. 60 (2023) 3584–3599.
[105] B.R. Sabari, D. Zhang, C.D. Allis, et al., Metabolic regulation of gene expression through histone acylations, Nat. Rev. Mol. Cell Biol. 18 (2017) 90–101.
[106] M. Zille, A. Kumar, N. Kundu, et al., Ferroptosis in neurons and cancer cells is similar but differentially regulated by histone deacetylase inhibitors, eNeuro 6 (2019) ENEURO.0263-ENEURO.0218.2019.
[107] L. Liu, Y. Li, D. Cao, et al., SIRT3 inhibits gallbladder cancer by induction of AKT-dependent ferroptosis and blockade of epithelial-mesenchymal transition, Cancer Lett. 510 (2021) 93–104.
[108] F. Fan, P. Liu, R. Bao, et al., A dual PI3K/HDAC inhibitor induces immunogenic ferroptosis to potentiate cancer immune checkpoint therapy, Cancer Res. 81 (2021) 6233–6245.
[109] X. Wang, K. Liu, H. Gong, et al., Death by histone deacetylase inhibitor quisinostat in tongue squamous cell carcinoma via apoptosis, pyroptosis, and ferroptosis, Toxicol. Appl. Pharmacol. 410 (2021), 115363.
[110] T. Zhang, B. Sun, C. Zhong, et al., Targeting histone deacetylase enhances the therapeutic effect of Erastin-induced ferroptosis in EGFR-activating mutant lung adenocarcinoma, Transl, Lung Cancer Res. 10 (2021) 1857–1872.
[111] Y. Liu, X. Duan, C. Zhang, et al., KAT6B may be applied as a potential therapeutic target for glioma, J. Oncol. 2022 (2022), 2500092.
[112] H. Li, W. Liu, X. Zhang, et al., Ketamine suppresses proliferation and induces ferroptosis and apoptosis of breast cancer cells by targeting KAT5/GPX4 axis, Biochem. Biophys. Res. Commun. 585 (2021) 111–116.
[113] S. Sui, J. Zhang, S. Xu, et al., Ferritinophagy is required for the induction of ferroptosis by the bromodomain protein BRD4 inhibitor (+)-JQ1 in cancer cells, Cell Death Dis. 10 (2019), 331.
[114] S.-H. Luo, J.-M. Tian, Y. Chu, et al., The BRD4-SRPK2-SRSF2 signal modulates the splicing efficiency of ACSL3 pre-mRNA and influences erastin-induced ferroptosis in osteosarcoma cells, Cell Death Dis. 14 (2023), 760.
[115] X. Cui, X. Yun, M. Sun, et al., HMGCL-induced β-hydroxybutyrate production attenuates hepatocellular carcinoma via DPP4-mediated ferroptosis susceptibility, Hepatol. Int. 17 (2023) 377–392.
[116] X. Zhang, S. Sui, L. Wang, et al., Inhibition of tumor propellant glutathione peroxidase 4 induces ferroptosis in cancer cells and enhances anticancer effect of cisplatin, J. Cell. Physiol. 235 (2020) 3425–3437.
[117] Y. Chen, X. Yi, B. Huo, et al., BRD4770 functions as a novel ferroptosis inhibitor to protect against aortic dissection, Pharmacol. Res. 177 (2022), 106122.
[118] T. Liu, P. Xu, S. Ke, et al., Histone methyltransferase SETDB1 inhibits TGF-β-induced epithelial-mesenchymal transition in pulmonary fibrosis by regulating SNAI1 expression and the ferroptosis signaling pathway, Arch. Biochem. Biophys. 715 (2022), 109087.
[119] Y. Cao, F. Luo, J. Peng, et al., KMT2B-dependent RFK transcription activates the TNF-α/NOX2 pathway and enhances ferroptosis caused by myocardial ischemia-reperfusion, J. Mol. Cell. Cardiol. 173 (2022) 75–91.
[120] J. Wang, X. Yin, W. He, et al., SUV39H1 deficiency suppresses clear cell renal cell carcinoma growth by inducing ferroptosis, Acta Pharm. Sin. B 11 (2021) 406–419.
[121] Y. Wang, Y. Zhao, H. Wang, et al., Histone demethylase KDM3B protects against ferroptosis by upregulating SLC7A11, FEBS Open Bio 10 (2020) 637–643.
[122] M. Chen, Y. Jiang, Y. Sun, KDM4A-mediated histone demethylation of SLC7A11 inhibits cell ferroptosis in osteosarcoma, Biochem. Biophys. Res. Commun. 550 (2021) 77–83.
[123] K. Xu, X. Liu, B. Wen, et al., GSK-J4, a specific histone lysine demethylase 6A inhibitor, ameliorates lipotoxicity to cardiomyocytes *via* preserving H3K27 methylation and reducing ferroptosis, Front. Cardiovasc. Med. 9 (2022), 907747.
[124] R. Feng, Y. Xiong, Y. Lei, et al., Lysine-specific demethylase 1 aggravated oxidative stress and ferroptosis induced by renal ischemia and reperfusion injury through activation of TLR4/NOX4 pathway in mice, J. Cell. Mol. Med. 26 (2022) 4254–4267.
[125] A. Li, Y. He, S. Sun, et al., Lysine-specific demethylase 1 inhibitors protect cochlear spiral ganglion neurons against cisplatin-induced damage, Neuroreport 26 (2015) 539–547.
[126] Y. Liu, L. Ouyang, C. Mao, et al., PCDHB14 promotes ferroptosis and is a novel tumor suppressor in hepatocellular carcinoma, Oncogene 41 (2022) 3570–3583.
[127] T. Zhu, B. Liu, D. Wu, et al., Autophagy regulates VDAC3 ubiquitination by FBXW7 to promote erastin-induced ferroptosis in acute lymphoblastic leukemia, Front. Cell Dev. Biol. 9 (2021), 740884.
[128] Y. Wang, D. Chen, H. Xie, et al., AUF1 protects against ferroptosis to alleviate sepsis-induced acute lung injury by regulating NRF2 and ATF3, Cell. Mol. Life Sci. 79 (2022), 228.
[129] Y. Yang, M. Luo, K. Zhang, et al., Nedd4 ubiquitylates VDAC2/3 to suppress erastin-induced ferroptosis in melanoma, Nat. Commun. 11 (2020), 433.
[130] Y. Wang, Y. Liu, J. Liu, et al., NEDD4L-mediated LTF protein degradation limits ferroptosis, Biochem. Biophys. Res. Commun. 531 (2020) 581–587.
[131] L. Liu, C. Zhang, S. Qu, et al., ESR1 inhibits ionizing radiation-induced ferroptosis in breast cancer cells via the NEDD4L/CD71 pathway, Arch. Biochem. Biophys. 725 (2022), 109299.
[132] S. Chillappagari, R. Belapurkar, A. Möller, et al., SIAH2-mediated and organ-specific restriction of HO-1 expression by a dual mechanism, Sci. Rep. 10 (2020), 2268.
[133] S. An, M. Hu, Quercetin promotes TFEB nuclear translocation and activates lysosomal degradation of ferritin to induce ferroptosis in breast cancer cells, Comput. Intell. Neurosci. 2022 (2022), 5299218.
[134] H. Nishizawa, M. Matsumoto, T. Shindo, et al., Ferroptosis is controlled by the coordinated transcriptional regulation of glutathione and labile iron metabolism by the transcription factor BACH1, J. Biol. Chem. 295 (2020) 69–82.
[135] R. Gao, R.K.R. Kalathur, M. Coto-Llerena, et al., YAP/TAZ and ATF4 drive resistance to Sorafenib in hepatocellular carcinoma by preventing ferroptosis, EMBO Mol. Med. 13 (2021), e14351.
[136] J. Liu, X. Song, F. Kuang, et al., NUPR1 is a critical repressor of ferroptosis, Nat. Commun. 12 (2021), 647.
[137] Z. Wang, X. Chen, N. Liu, et al., A nuclear long non-coding RNA LINC00618 accelerates ferroptosis in a manner dependent upon apoptosis, Mol. Ther. 29 (2021) 263–274.
[138] Y. Jiang, C. Mao, R. Yang, et al., EGLN1/c-Myc induced Lymphoid-specific helicase inhibits ferroptosis through lipid metabolic gene expression changes, Theranostics 7 (2017) 3293–3305.
[139] R. Kang, G. Kroemer, D. Tang, The tumor suppressor protein p53 and the ferroptosis network, Free Radic. Biol. Med. 133 (2019) 162–168.
[140] L. Jiang, N. Kon, T. Li, et al., Ferroptosis as a p53-mediated activity during tumour suppression, Nature 520 (2015) 57–62.
[141] C. Mao, X. Wang, Y. Liu, et al., A G3BP1-Interacting lncRNA promotes ferroptosis and apoptosis in cancer via nuclear sequestration of p53, Cancer Res. 78 (2018) 3484–3496.
[142] W. Li, W. Li, Y. Wang, et al., Inhibition of DNMT-1 alleviates ferroptosis through NCOA4 mediated ferritinophagy during diabetes myocardial ischemia/reperfusion injury, Cell Death Discov. 7 (2021), 267.
[143] H. Yang, L. Zhao, Y. Gao, et al., Pharmacotranscriptomic analysis reveals novel drugs and gene networks regulating ferroptosis in cancer, Cancers 12 (2020), 3273.
[144] K. Miyamoto, M. Watanabe, S. Boku, et al., xCT inhibition increases sensitivity to vorinostat in a ROS-dependent manner, Cancers 12 (2020), 827.
[145] T. Oliveira, E. Hermann, D. Lin, et al., HDAC inhibition induces EMT and alterations in cellular iron homeostasis to augment ferroptosis sensitivity in SW13 cells, Redox Biol. 47 (2021), 102149.
[146] B.K. Flesner, S.R. Kumar, J.N. Bryan, 6-Thioguanine and zebularine down-regulate DNMT1 and globally demethylate canine malignant lymphoid cells, BMC Vet. Res. 10 (2014), 290.
[147] Z. Yuan, S. Chen, C. Gao, et al., Development of a versatile DNMT and HDAC inhibitor C02S modulating multiple cancer hallmarks for breast cancer therapy, Bioorg. Chem. 87 (2019) 200–208.
[148] W.A. Kwon, H.K. Seo, Novel G9a/DNMT first-in-class dual reversible inhibitor has potent antitumor effect in bladder cancer, Transl, Cancer Res. 9 (2020) 1319–1321.
[149] A. Sfera, K.G. Thomas, C.V. Andronescu, et al., Bromodomains in human-immunodeficiency virus-associated neurocognitive disorders: A model of ferroptosis-induced neurodegeneration, Front. Neurosci. 16 (2022), 904816.
[150] J. Qiao, Y. Chen, Y. Mi, et al., NR5A2 synergizes with NCOA3 to induce breast cancer resistance to BET inhibitor by upregulating NRF2 to attenuate ferroptosis, Biochem. Biophys. Res. Commun. 530 (2020) 402–409.
[151] C. Yang, T. Lu, M. Liu, et al., Tiliroside targets TBK1 to induce ferroptosis and sensitize hepatocellular carcinoma to sorafenib, Phytomedicine 111 (2023), 154668.
[152] Y. Peng, N. Li, F. Tang, et al., Corosolic acid sensitizes ferroptosis by upregulating HERPUD1 in liver cancer cells, Cell Death Discov. 8 (2022), 376.
[153] Y. Ding, X. Chen, C. Liu, et al., Identification of a small molecule as inducer of ferroptosis and apoptosis through ubiquitination of GPX4 in triple negative breast cancer cells, J. Hematol. Oncol. 14 (2021), 19.
[154] W. Zhang, B. Jiang, Y. Liu, et al., Bufotalin induces ferroptosis in non-small cell lung cancer cells by facilitating the ubiquitination and degradation of GPX4, Free Radic. Biol. Med. 180 (2022) 75–84.
[155] Y. Liu, L. He, B. Liu, et al., Pharmacological inhibition of sphingolipid synthesis reduces ferroptosis by stimulating the HIF-1 pathway, iScience 25 (2022), 104533.
[156] G. Li, S. Lin, Z. Yu, et al., A PARP1 PROTAC as a novel strategy against PARP inhibitor resistance via promotion of ferroptosis in p53-positive breast cancer, Biochem. Pharmacol. 206 (2022), 115329.

[157] L.S. Chan, J. Liu, M.S.C. Li, et al., Selenite as a dual apoptotic and ferroptotic agent synergizes with EGFR and KRAS inhibitors with epigenetic interference, Clin. Epigenetics 15 (2023), 36.
[158] Y. Wang, S. Yan, X. Liu, et al., PRMT4 promotes ferroptosis to aggravate doxorubicin-induced cardiomyopathy via inhibition of the Nrf2/GPX4 pathway, Cell Death Differ. 29 (2022) 1982–1995.
[159] H. Zhao, X. Li, L. Yang, et al., Isorhynchophylline relieves ferroptosis-induced nerve damage after intracerebral hemorrhage via miR-122-5p/TP53/SLC7A11 pathway, Neurochem. Res. 46 (2021) 1981–1994.
[160] M. Szyf, Prospects for the development of epigenetic drugs for CNS conditions, Nat. Rev. Drug Discov. 14 (2015) 461–474.
[161] S. Moufarrij, M. Dandapani, E. Arthofer, et al., Epigenetic therapy for ovarian cancer: Promise and progress, Clin. Epigenetics 11 (2019), 7.
[162] J.S. Smolen, D. Aletaha, A. Barton, et al., Rheumatoid arthritis, Nat. Rev. Dis. Primers 4 (2018), 18001.
[163] C.D. DiNardo, B.A. Jonas, V. Pullarkat, et al., Azacitidine and venetoclax in previously untreated acute myeloid leukemia, N. Engl. J. Med. 383 (2020) 617–629.
[164] L. Falchi, H. Ma, S. Klein, et al., Combined oral 5-azacytidine and romidepsin are highly effective in patients with PTCL: A multicenter phase 2 study, Blood 137 (2021) 2161–2170.
[165] G. Garcia-Manero, E.A. Griffiths, D.P. Steensma, et al., Oral cedazuridine/decitabine for MDS and CMML: A phase 2 pharmacokinetic/pharmacodynamic randomized crossover study, Blood 136 (2020) 674–683.
[166] M.A. Sekeres, J. Taylor, Diagnosis and treatment of myelodysplastic syndromes: A review, JAMA 328 (2022) 872–880.
[167] L.C. Stork, Y. Matloub, E. Broxson, et al., Oral 6-mercaptopurine versus oral 6-thioguanine and veno-occlusive disease in children with standard-risk acute lymphoblastic leukemia: Report of the children's oncology group CCG-1952 clinical trial, Blood 115 (2010) 2740–2748.
[168] Y.H. Kim, M. Bagot, L. Pinter-Brown, et al., Mogamulizumab versus vorinostat in previously treated cutaneous T-cell lymphoma (MAVORIC): An international, open-label, randomised, controlled phase 3 trial, Lancet Oncol. 19 (2018) 1192–1204.
[169] M.J. Burke, J.K. Lamba, S. Pounds, et al., A therapeutic trial of decitabine and vorinostat in combination with chemotherapy for relapsed/refractory acute lymphoblastic leukemia, Am. J. Hematol. 89 (2014) 889–895.
[170] P. Chinnaiyan, S. Chowdhary, L. Potthast, et al., Phase I trial of vorinostat combined with bevacizumab and CPT-11 in recurrent glioblastoma, Neuro-oncology 14 (2012) 93–100.
[171] O.A. O'Connor, S. Horwitz, T. Masszi, et al., Belinostat in patients with relapsed or refractory peripheral T-cell lymphoma: Results of the pivotal phase II BELIEF (CLN-19) study, J. Clin. Oncol. 33 (2015) 2492–2499.
[172] W. Yeo, H.C. Chung, S.L. Chan, et al., Epigenetic therapy using belinostat for patients with unresectable hepatocellular carcinoma: A multicenter phase I/II study with biomarker and pharmacokinetic analysis of tumors from patients in the mayo phase II consortium and the cancer therapeutics research group, J. Clin. Oncol. 30 (2012) 3361–3367.
[173] H. Fredly, H. Reikvam, B.T. Gjertsen, et al., Disease-stabilizing treatment with all-trans retinoic acid and valproic acid in acute myeloid leukemia: Serum hsp70 and hsp90 levels and serum cytokine profiles are determined by the disease, patient age, and anti-leukemic treatment, Am. J. Hematol. 87 (2012) 368–376.
[174] B.E. Nelson, A.M. Tsimberidou, X. Fu, et al., A phase I trial of bevacizumab and temsirolimus in combination with valproic acid in advanced solid tumors, Oncologist 28 (2023), 1100-e1292.
[175] Y. Zhang, Y. Gu, H. Ren, et al., Gut microbiome-related effects of berberine and probiotics on type 2 diabetes (the PREMOTE study), Nat. Commun. 11 (2020), 5015.
[176] S.A. Harrison, P.J. Ruane, B.L. Freilich, et al., Efruxifermin in non-alcoholic steatohepatitis: A randomized, double-blind, placebo-controlled, phase 2a trial, Nat. Med. 27 (2021) 1262–1271.
[177] K.H. Hsieh, Effects of PAF antagonist, BN52021, on the PAF-, methacholine-, and allergen-induced bronchoconstriction in asthmatic children, Chest 99 (1991) 877–882.
[178] N. Rothammer, M.S. Woo, S. Bauer, et al., G9a dictates neuronal vulnerability to inflammatory stress via transcriptional control of ferroptosis, Sci. Adv. 8 (2022), eabm5500.
[179] E.J. Daly, M.H. Trivedi, A. Janik, et al., Efficacy of esketamine nasal spray plus oral antidepressant treatment for relapse prevention in patients with treatment-resistant depression: A randomized clinical trial, JAMA Psychiatry 76 (2019) 893–903.
[180] Rde S. Pereira, Regression of gastroesophageal reflux disease symptoms using dietary supplementation with melatonin, vitamins and aminoacids: Comparison with omeprazole, J. Pineal Res. 41 (2006) 195–200.
[181] Z.-L. Jin, W.-Y. Gao, S.-J. Liao, et al., Paeonol inhibits the progression of intracerebral haemorrhage by mediating the HOTAIR/UPF1/ACSL4 axis, ASN Neuro 13 (2021), 17590914211010647.
[182] J. Li, S.-H. Deng, J. Li, et al., Obacunone alleviates ferroptosis during lipopolysaccharide-induced acute lung injury by upregulating Nrf2-dependent antioxidant responses, Cell. Mol. Biol. Lett. 27 (2022), 29.
[183] S. Feng, Y. Yuan, Z. Lin, et al., Low-dose hypomethylating agents cooperate with ferroptosis inducers to enhance ferroptosis by regulating the DNA methylation-mediated MAGEA6-AMPK-SLC7A11-GPX4 signaling pathway in acute myeloid leukemia, Exp. Hematol. Oncol. 13 (2024), 19.
[184] Y. Li, K. Li, W. Zhao, et al., VPA improves ferroptosis in tubular epithelial cells after cisplatin-induced acute kidney injury, Front. Pharmacol. 14 (2023), 1147772.
[185] X. Li, J. Chen, W. Feng, et al., Berberine ameliorates iron levels and ferroptosis in the brain of 3 × Tg-AD mice, Phytomedicine 118 (2023), 154962.
[186] A. Wu, B. Feng, J. Yu, et al., Fibroblast growth factor 21 attenuates iron overload-induced liver injury and fibrosis by inhibiting ferroptosis, Redox Biol. 46 (2021), 102131.
[187] J. Chen, Z. Ou, T. Gao, et al., Ginkgolide B alleviates oxidative stress and ferroptosis by inhibiting GPX4 ubiquitination to improve diabetic nephropathy, Biomed. Pharmacother. 156 (2022), 113953.
[188] G.N. He, N.R. Bao, S. Wang, et al., Ketamine induces ferroptosis of liver cancer cells by targeting lncRNA PVT1/miR-214-3p/GPX4, Drug Des. Devel. Ther. 15 (2021) 3965–3978.
[189] L. Ye, Y. Xu, L. Wang, et al., Downregulation of CYP2E1 is associated with poor prognosis and tumor progression of gliomas, Cancer Med 10 (2021) 8100–8113.