# Non-coding RNA-mediated epigenetic modification of ferroptosis in non-small cell lung cancer (Review)

YUMIN WANG[1*], JOSHUA S. FLEISHMAN[2*], YULIN LI[1*], YUWEI CAO[1], HAIDONG WEI[3], ZHE ZHANG[1], JICHAO CHEN[1] and MINGCHAO DING[4]

[1]Department of Respiratory and Critical Care Medicine, Aerospace Center Hospital, Peking University Aerospace School of Clinical Medicine, Beijing 100049, P.R. China; [2]Department of Pharmaceutical Sciences, College of Pharmacy and Health Sciences, St. John's University, New York, NY 11439, USA; [3]Department of Emergency, Aerospace Center Hospital, Peking University Aerospace School of Clinical Medicine, Beijing 100049, P.R. China; [4]Department of Peripheral Vascular Intervention, Aerospace Center Hospital, Peking University Aerospace School of Clinical Medicine, Beijing, Beijing 100049, P.R. China

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**Abstract.** Ferroptosis is a novel form of regulated cell death that plays a key role in inhibiting tumor malignancy. The ferroptosis signalling cascade provides new opportunities for lung cancer therapy. Non-coding RNA (ncRNA)-mediated epigenetic modification can influence the vulnerability of cancer cells to ferroptosis in non-small-cell lung cancer (NSCLC). The present review describes the core molecular mechanisms underlying ferroptosis and the role of epigenetic mechanisms in regulating ferroptosis in NSCLC, as well as developments in understanding the ncRNA-induced mechanisms that affect ferroptosis in NSCLC. The present review aimed to enhance understanding of the epigenetic mechanisms mediated by ncRNAs that modulate ferroptosis in NSCLC, highlighting a novel therapeutic strategy for NSCLC via the ncRNA-ferroptosis axis.

*Correspondence to:* Professor Mingchao Ding, Department of Peripheral Vascular Intervention, Aerospace Center Hospital, Peking University Aerospace School of Clinical Medicine, 15 Yuquan Road, Haidian, Beijing 100049, P.R. China
E-mail: dmc_zxl@vip.sina.com

Professor Jichao Chen, Department of Respiratory and Critical Care Medicine, Aerospace Center Hospital, Peking University Aerospace School of Clinical Medicine, 15 Yuquan Road, Haidian, Beijing 100049, P.R. China
E-mail: chen_htzxyy@sina.com

*Contributed equally

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**Contents**



## 1. Introduction

Cancer is the second leading cause of mortality worldwide after cardiovascular disease (1). Among men, the most common cancers include lung, liver, prostate, colorectal and gastric cancers (2). Lung cancer, broadly classified into small-cell (SC) and non-SC lung cancer (NSCLC), remains the leading cause of cancer-related mortality in males and the second highest cause in female patients, following breast cancer globally (3). NSCLC represents the major histological subtype of lung cancer (4-7), accounting for >80% of all cases. It comprises two primary subtypes: Lung squamous cell carcinoma (LUSC) and lung adenocarcinoma (LUAD) (8). The global incidence of lung cancer is projected to increase from 1.7 million new cases in 2018 to 3.8 million/year by 2070 (9,10).

Although multiple approaches have decreased lung cancer mortality, the 5-year overall survival (OS) rate remains low, at 4-17%, depending on the disease stage and geographical factors (10). Surgery, targeted therapy, immunotherapy and radiotherapy are recommended therapeutic regimens for patients with NSCLC. For advanced NSCLC and earlier stages, the standard first-line treatment remains systemic platinum-based chemotherapy (11). Platinum-based chemotherapy is often combined with pemetrexed, vinorelbine/taxanes and gemcitabine as a first-line regimen for NSCLC. However, the effectiveness of platinum-based chemotherapy is limited by chemoresistance, which varies between individuals (12,13). Therefore, novel therapeutic mechanisms are needed (14,15).

Ferroptosis is a recently discovered type of regulated cell death (RCD) characterized by iron-dependent toxic

accumulation of lipid peroxides on cellular membranes (16-18). Conventional therapies, including chemotherapy, radiotherapy, immunotherapy, and targeted cancer therapy, exert anti-tumor effects by inducing ferroptosis (16,19-22). Thus, targeting ferroptosis offers a promising therapeutic strategy, especially for cancer resistant to conventional treatments, including NSCLC (13,23). Understanding the molecular mechanisms that regulate ferroptosis in NSCLC may enable development of more effective therapeutic strategies for this disease.

Non-coding RNAs (ncRNAs) are a class of RNA molecules with no or limited protein-coding potential (24). ncRNAs, which include circular RNAs (circRNAs), long ncRNAs (lncRNAs) and microRNAs (miRNAs or miRs), are key epigenetic regulators of ferroptosis (25-31). ncRNAs regulate tumor malignancy by modulating ferroptosis in various types of cancers, including NSCLC (32,33). However, the mechanism underlying ncRNA-mediated epigenetic regulation of ferroptosis in NSCLC remains unclear. The present review summarizes the core molecular mechanisms of ferroptosis, how epigenetic mechanisms modify ferroptosis in NSCLC and research progress on ncRNA-mediated regulation of ferroptosis in NSCLC to clarify understanding of ncRNA-mediated epigenetic modulation of ferroptosis in NSCLC, highlighting the ncRNA-ferroptosis axis as a potential therapeutic target for NSCLC.

## 2. Core mechanisms of ferroptosis

Ferroptosis was first identified in 2012 as a form of RCD driven by iron-dependent lipid peroxidation (LPO) (34-39) (Fig. 1). This discovery stemmed from studying the mechanisms by which small molecules induce cancer cell death. Research has since identified specific small-molecule inhibitors of ferroptosis, which have revealed additional intermediate nodes in the ferroptosis signaling cascade (40). Three essential elements, reactive oxygen species (ROS), oxidizable lipids and LPO, drive the initiation and induction of ferroptosis (41) (Fig. 2). An imbalance between ferroptosis inhibitors and inducers enhances accumulation of lethal lipid peroxides (lipid hydroperoxides) on cell membranes, leading to membrane rupture and ferroptotic cell death (16,42-44).

*Ferroptosis inducers*. The synthesis and peroxidation of polyunsaturated fatty acid-containing phospholipids (PUFA-PLs), along with iron and mitochondrial metabolism, are the primary inducers that initiate ferroptosis (16,45-47).

*LPO*. Phospholipid peroxidation, a process that depends on transition metal iron, PUFA-PL and ROS, induces ferroptosis (34,48,49). Both LPO and the accumulation of peroxidized lipids trigger ferroptosis (44,50). Iron chelation studies have clarified the link between iron and ferroptosis, highlighting interplay between lipids and iron (48,49,51). PUFA-PLs, which are highly susceptible to peroxidation, serve as effective substrates for LPO via enzymatic and non-enzymatic mechanisms (43). Initiation, propagation and termination constitute the mechanism underlying PUFA-PL-mediated LPO (52,53). The incorporation and formation of peroxidized lipids in membrane phospholipids trigger ferroptosis (54,55). In the first step of PUFA-PL synthesis, acyl-CoA synthetase long-chain family member 4 (ACSL4) ligates coenzyme A (CoA) to fatty acids, with a high preference for arachidonic acid (AA) (54,55). Arachidonoyl-CoA is then esterified in membranes by lysophosphatidylcholine acyltransferase 3, which preferentially binds lysophosphatidylethanolamine and lysophosphatidylcholine to produce phospholipids in the endoplasmic reticulum (ER) (56).

Lipoxygenases (LOXs), NADPH oxidases (NOXs), oxidoreductase cytochrome P450 reductase (POR) and NADH-cytochrome b5 reductase (CYB5R1) are enzymes that generate oxidants to initiate and induce LPO (57-64). LOXs, including 15-, 12- and 5-LOX, are a class of enzymes that catalyze reactions through the involvement of iron and other metals. LOXs facilitate double oxidation of PUFAs, exacerbating cell membrane instability and triggering ferroptosis (64,65). Specifically, 15-LOX, which has a high selectivity for PUFA-PLs, oxidizes PUFA-PLs to PL-PUFA-OOH (PL-OOH). POR and CYB5R1 induce ferroptosis by transferring electrons to oxygen to produce hydrogen peroxide ($H_2O_2$), which damages cell membranes by oxidizing membrane phospholipids via Fenton reaction (57). NOXs directly produce ROS and cause LPO (66). Mitochondria produce substantial amounts of ROS, further contributing to initiation of LPO and promoting ferroptosis (47,67). The interaction of iron with lipids leads to LPO, producing lipid peroxides, PUFA-PL hydroperoxides, peroxidized PUFA-PLs (PUFA-PL-OOH) and derivatives such as 4-hydroxynonenal and malondialdehyde (MDA) (44).

*Iron in ferroptosis*. Iron induces ferroptosis by directly driving LPO via a non-enzymatic Fenton reaction and serving as an essential cofactor for iron-dependent peroxidases (the enzymatic LPO pathway) (16,50,53,68,69). Iron exists in two states: Ferric ($Fe^{3+}$) and ferrous iron ($Fe^{2+}$) (70). PUFA-PLs can react with ROS, such as lipid peroxyl ($LO^{\bullet}$) or hydroxyl radicals ($HO^{\bullet}$), via the Fenton reaction to produce PUFA-PL-OOH, triggering LPO (71-73). When PUFA-PL-OOH is not neutralized promptly, it can propagate peroxidation to neighboring PUFA-PLs in the presence of labile iron. Inhibiting the iron exporter ferroportin (74-76), promoting transferrin uptake (77) or inducing autophagic degradation of ferritin (78,79) increase the labile iron pool in cells, enhancing cellular sensitivity to ferroptosis (50). In the enzymatic LPO pathway, $Fe^{2+}$ serves as a key cofactor for iron-dependent peroxidases, initiating dioxygenation of membrane PUFA-PLs (80,81). In this pathway, LOXs and POR use labile iron and $O_2$ to peroxidize PUFA-PLs, forming PUFA-PL-OOH (43,58,62). Previous reviews provide further details on lipid resources involved in ferroptosis: ACSL4 that activates long-chain fatty acids by converting them into acyl-CoA esters, lysophosphatidylcholine acyltransferase 3 (LPCAT3) that incorporates PUFA into phosphatidylethanolamines (PEs), whereas the other activates sterol O-acyltransferase 1-producing PUFA-cholesteryl esters instead of PUFA-PEs), proxisomes that is involved in fatty acid breakdown, hydrogen peroxide production and PUFA plasmalogen biosynthesis, and lipophagy that selectively degrades lipid droplets, releasing lipids for peroxidation (41,53,82).

*Ferroptosis inhibitors*. Specific ferroptosis inhibitors typically suppress LPO to prevent unwanted ferroptosis (69).

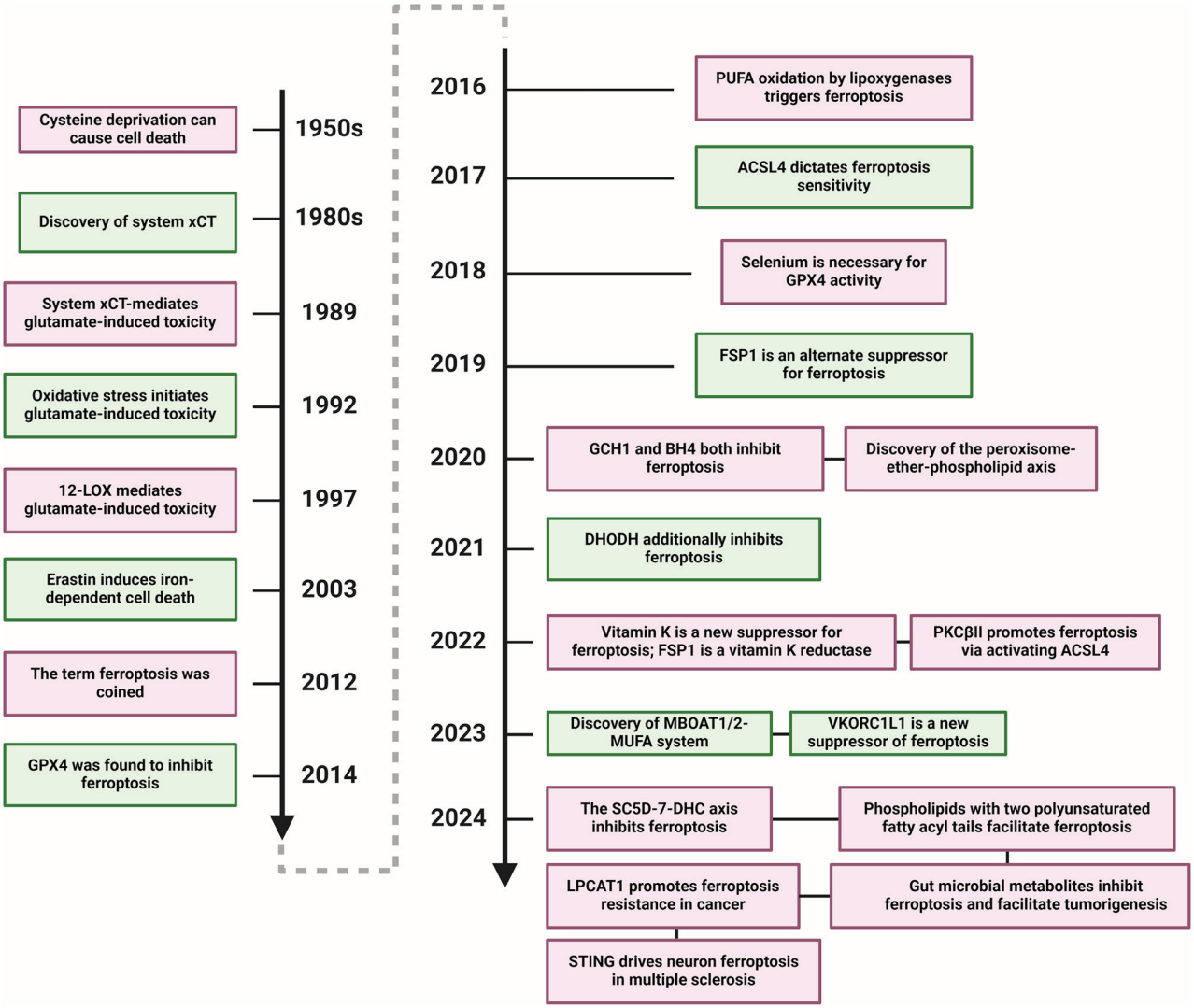


Figure 1. Key milestones in ferroptosis research. 7-DHC,7-dehydrocholesterol; 2-LOX, 12-Lipoxygenases; ACSL4,acyl-CoA synthetase long-chain family member 4; $BH_4$,tetrahydrobiopterin; DHODH, Dihydroorotate dehydrogenase; FSP1, Ferroptosis suppressor protein 1;GPX4,glutathione peroxidase 4; GCH1,GTP cyclohydrolase 1; LPCAT3, lysophosphatidylcholine acyltransferase 3; MBOAT1/2, membrane-bound O-acyltransferase domain-containing 1/2; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; SC5D,lathosterol oxidase; SLC7A11, solute carrier family 7 member 11; STING, stimulator of interferon genes;VKORC1L1,vitamin K epoxide reductase complex subunit 1 like 1.

Ferroptosis inhibitors or defense systems that directly neutralize lipid peroxides comprise GPX4-dependent or -independent surveillance mechanisms with specific subcellular localization (35).

*Solute carrier family 7 member 11-glutathione peroxidase 4 (SLC7A11-GPX4) axis*. SLC7A11-GPX axis is a ferroptosis inhibitors (16,83). As a lipid repair enzyme (84,85), GPX4 converts reactive PUFA-PL-OOH to non-reactive PUFA-PL alcohols while concurrently oxidizing two reduced GSH molecules to oxidized glutathione (GSSG) (86,87). GPX4 has distinctive subcellular localizations, including mitochondrial, nuclear and cytosolic isoforms, and functions as a key ferroptosis inhibitor (34,88-91). Both mitochondrial and cytosolic GPX4 are key for ferroptosis (40). GPX4 works with the cystine/glutamate antiporter system $Xc^-$, which consists of SLC7A11 and SLC3A2 (49). SLC7A11 exports intracellular glutamate and imports extracellular cysteine to biosynthesize reduced GSH (92,93).

*Ferroptosis suppressor protein 1 (FSP1)-ubiquinol ($CoQH_2$) system*. In the FSP1-$CoQH_2$ system, plasma membrane-localized FSP1 catalyzes the reduction of ubiquinone ($CoQ_{10}$) to its reduced form, $CoQH_2$, which functions as a lipid-soluble antioxidant to trap $LO^{\bullet}$, thereby preventing LPO and suppressing ferroptosis in cellular membranes (94-96). FSP1 inhibits ferroptosis by activating the endosomal sorting complex required for transport III complex, which causes plasma membrane damage (97,98).

*GTP cyclohydrolase 1 (GCH1)-tetrahydrobiopterin ($BH_4$) axis*. GCH1-$BH_4$ system is an inhibitor of ferroptosis independent of GPX4 (99,100). GCH1 inhibits ferroptosis by generating $BH_4$, an endogenous metabolite and radical-trapping antioxidant. $BH_4$ serves as a cofactor for aromatic amino acid hydroxylases and is analogous to $CoQ_{10}$ in preventing LPO (99,100). Alternatively, GCH1 inhibits ferroptosis by remodeling the lipid membrane environment by increasing the abundance of $CoQH_2$ and decreasing PUFA-PL levels (37).

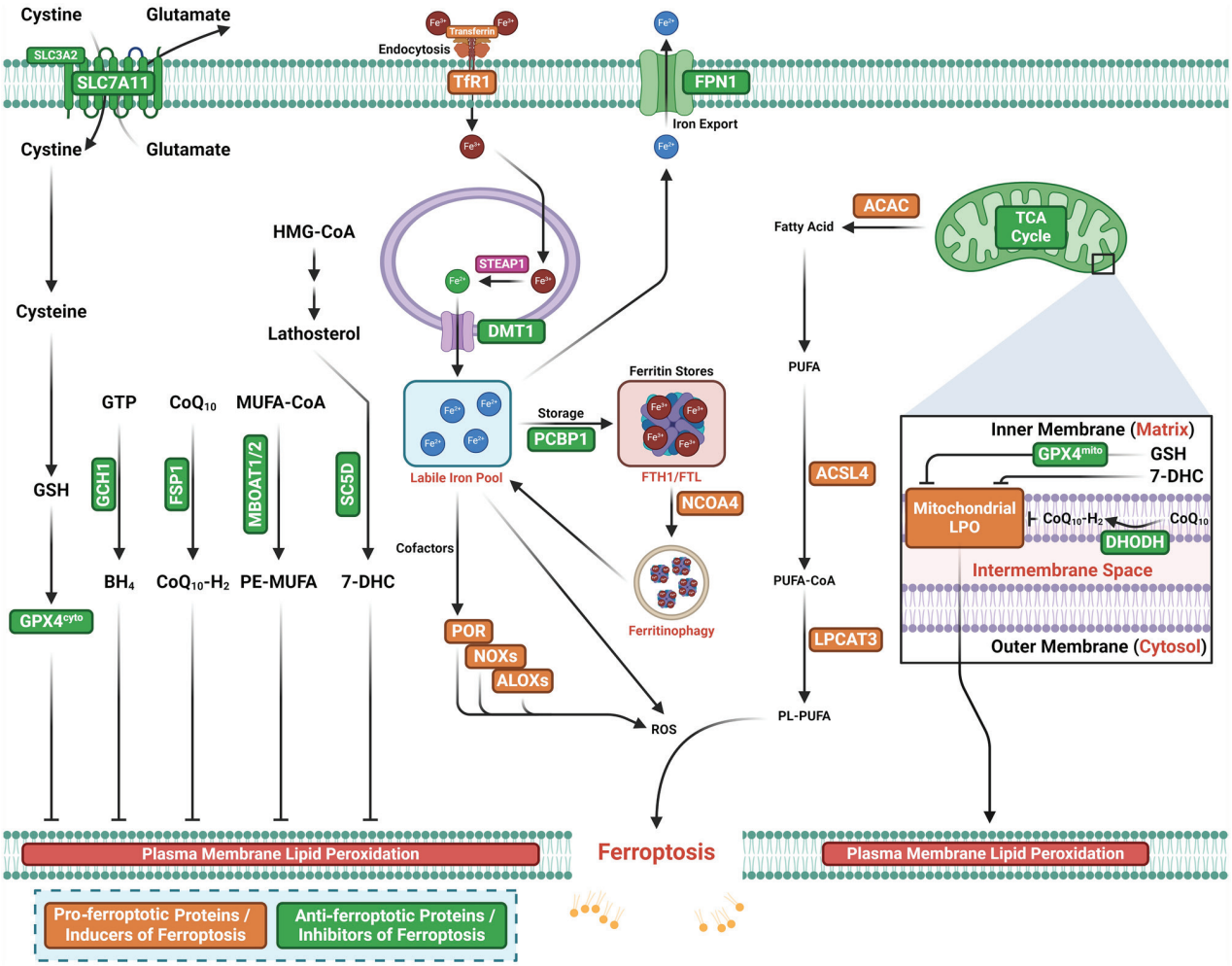


Figure 2. Core mechanisms of ferroptosis. Ferroptosis is induced by an imbalance of pro-ferroptotic factors and anti-ferroptotic defense mechanisms. SLC7A11/SLC3A2 system imports cystine for GSH synthesis to quench lipid peroxides, along with other endogenous antioxidants GCH1, FSP1, MBOAT1/2 and SC5D. Iron import and mobilization via POR/NOX/ALOX catalyzes ROS synthesis, which, alongside the Fenton reaction, induces synthesis of lipid peroxides. Lipid peroxides accumulate in the plasma membrane and lead to cell lysis. ALOX, arachidonate lipoxygenase;FSP1, Ferroptosis suppressor protein 1; GCH1, GTP cyclohydrolase 1; GSH, glutathione; MBOAT1/2, membrane-bound O-acyltransferase domain-containing 1/2; NOX, NADPH oxidase; POR, cytochrome P450 oxidoreductase; ROS, reactive oxygen species; SC5D, lathosterol oxidase; SLC7A11, solute carrier family 7 member 11; SLC3A2, solute carrier family 3 member 2.

*Dihydroorotate dehydrogenase (DHODH)-dihydroubiquione ($CoQH_2$) axis*. The DHODH-$CoQH_2$ pathway is a ferroptosis inhibitor independent of GPX4, with mitochondrial localization that inhibits LPO (101). DHODH is a mitochondrial enzyme in the inner mitochondrial membrane that enhances pyrimidine biosynthesis and converts $CoQ_{10}$ to $CoQH_2$, thereby decreasing mitochondrial $CoQ_{10}$, analogous to FSP1, which functions in extra-mitochondrial membranes.

*Membrane-bound O-acyltransferase domain-containing 1/2 (MBOAT1/2)-monounsaturated fatty acid (MUFA) system*. MBOAT1/2-MUFA system is a newly identified ferroptosis inhibitor independent of GPX4 and FSP1 (102). MBOAT1/2 inhibits ferroptosis in this system (102). Phosphatidylethanolamine (PE)-PUFAs are the preferred substrates for LPO and dictate the ferroptosis sensitivity (103,104). MBOAT2 is a lyso-PL acyltransferase that selectively transfers MUFAs to lyso-PE, resulting in increased cellular PE-MUFA levels and decreased cellular PE-PUFAs, thereby suppressing ferroptosis induction (102).

*Lathosterol oxidase (SC5D)-7-dehydrocholesterol (7-DHC) axis*. The SC5D-7-DHC axis is a recently identified ferroptosis inhibitor, with 7-DHC serving as a natural inhibitor of ferroptosis (105,106). 7-DHC, generated in the ER, is found in mitochondria and cell membranes along the cholesterol synthesis pathway. It diverts the LPO pathway from phospholipids and traps radicals, suppressing LPO and subsequent ferroptosis in both mitochondria and the plasma membrane.

## 3. ncRNA-mediated epigenetic modification of ferroptosis in NSCLC

Increasing evidence indicates that dysregulated epigenetic modifications contribute to cancer initiation and progression through aberrant gene expression, protein alteration and malignant transformation (107-109). ncRNAs have recently emerged as key regulators of ferroptosis (28). Studies suggest that epigenetic modifications modulate ferroptosis at transcriptional, post-transcriptional and post-translational levels (39,110). Targeting epigenetic and post-translational

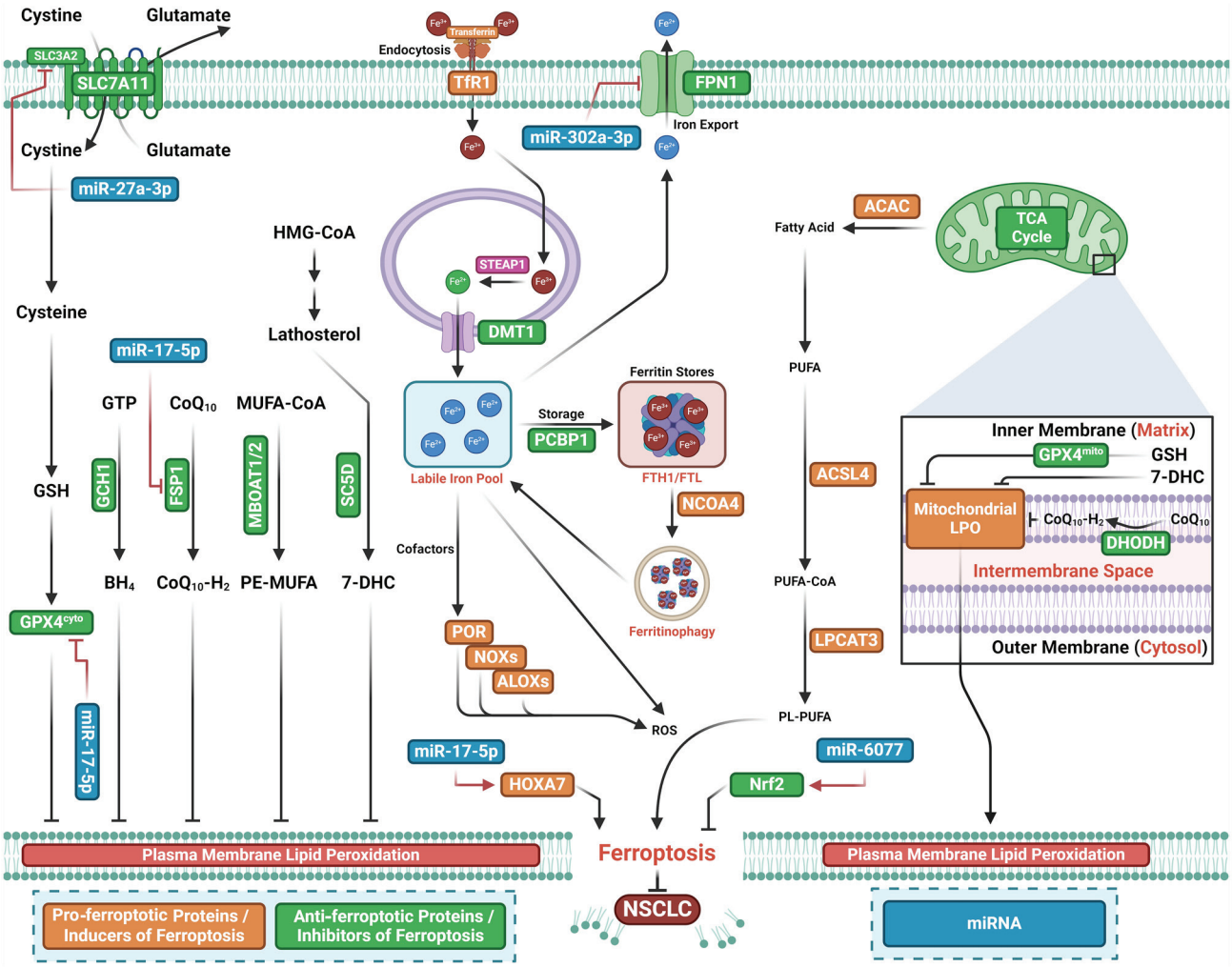


Figure 3. Regulatory miRNA modulation of ferroptosis in NSCLC. miRNAs may modulate the pro/anti-ferroptotic balance, enhancing or suppressing ferroptotic induction. miRNA-mediated silencing of pro-ferroptotic factors suppresses ferroptosis, while miRNA-mediated silencing of anti-ferroptotic factors enhances ferroptosis. miRNA, microRNA; NSCLC, non-small cell lung cancer.

modifications that modulate ferroptosis may offer new directions for cancer treatment (39,110). Recent research has shown that ncRNAs modulate ferroptosis by regulating glutathione metabolism, mitochondria-associated proteins, LPO and iron metabolism, thereby impacting cancer biology (25-31). In cancer, ncRNAs influence ferroptosis by modulating genes associated with ferroptosis inducers or inhibitors, affecting pathways such as the SLC7A11-GPX4 axis, lipid, glutamine and iron metabolism and Nrf2 signaling axis (28).

*miRNAs modulate ferroptosis in NSCLC*. Decreased miR-324-3p expression is observed in cisplatin-resistant A549 human lung cancer cells(DDP-A549) (111) (Fig. 3; Table I). Overexpression of miR-324-3p overcomes DDP resistance by targeting GPX4, where increased GPX4 expression reverses the miR-324-3p-induced sensitivity of DDP-A549 cells to DDP (111). miR-324-3p enhances DDP-triggered ferroptosis in DDP-A549 cells and GPX4 inhibitor RSL3 mimics miR-324-3p by increasing DDP-A549 cell sensitivity to DDP (111). Thus, miR-324-3p overcomes DDP resistance by promoting ferroptosis and suppressing GPX4 expression in NSCLC cells. Upregulation of miR-4443 has also been observed in exosomes derived from DDP-resistant NSCLC tumor tissues (112). Exosomal miR-4443 promotes resistance in recipient cells by inhibiting DDP-mediated ferroptosis through upregulation of FSP1 via $m^6A$ modification mediated by $m^6A$-methylase methyltransferase-like protein 3 (METLL3) *in vitro* and enhancing tumor growth *in vivo* (112). Furthermore, lncRNA HCP5 promotes ferroptosis and limits brain metastasis by upregulating homeobox A7 (HOXA7) through competitive binding to miR-17-5p (113). Overexpression of miR-27a-3p, however, inhibits erastin-induced ferroptosis by suppressing SLC7A11 (114). miR-6077 prevents cisplatin/pemetrexed (CDDP/PEM)-mediated NSCLC cell death through cyclin-dependent kinase inhibitor 1A (CDKN1A)/cyclin-dependent kinase 1 (CDK1)-mediated cell cycle arrest and ferroptosis suppression by inactivating Kelch-like ECH-associated protein 1 (KEAP1), which subsequently increases Nrf2-SLC7A11/NQO1 expression and leads to chemoresistance *in vitro* and *in vivo* (115). Decreased expression of miR-302a-3p has also been observed in human NSCLC cells and tissue. miR-302a-3p inhibits cell proliferation and colony formation by inducing ferroptosis in NSCLC cells (116). Conversely, silencing miR-302a-3p inhibits

Table I. Regulatory role of miRs in modulation of ferroptosis in NSCLC.

| miR | Expression | Function | Targets of ferroptosis | Effect | (Refs.) |
|---|---|---|---|---|---|
| miR-324-3p | Decreased | Tumor suppressor | Decreased GPX4 | Reverses DDP resistance; increases DDP-induced ferroptosis in the A549/DDP cells | (111) |
| miR-4443 | Increased | Oncogene | Increased FSP1 | Exosomal miR-4443 induces cisplatin resistance in cells. miR-4443 overexpression inhibits cisplatin-mediated ferroptosis *in vitro* and enhances tumor growth *in vivo* | (112) |
| miR-17-5p | ND | Tumor suppressor | ND | lncRNA HCP5 upregulates HOXA7 to increase ferroptosis by binding competitively with miR-17-5p and limiting brain cancer metastases | (113) |
| miR-27a-3p | Decreased | Tumor suppressor | SLC7A11 | Overexpressing miR-27a-3p inhibits erastin-caused ferroptosis by suppressing SLC7A11 | (114) |
| miR-6077 | Increased | Oncogene | KEAP1-Nrf2-SLC7A11/NQO1 | miR-6077 inhibits CDDP/PEM-mediated LUAD cell death through CDKN1A-CDK1-mediated cell-cycle arrest and suppressing ferroptosis via inactivating KEAP1, thereby increasing Nrf2-SLC7A11/NQO1 signaling, resulting in chemoresistance *in vitro* and *in vivo* | (115) |
| miR-302a-3p | Decreased | Tumor suppressor | Ferroportin | miR-302a-3p inhibits proliferation and colony formation through inducing ferroptosis in NSCLC cells by directly binding and decreasing ferroportin protein expression | (116) |
| miR-139 | Decreased | Tumor suppressor | KPNA2/Nrf2 | miR-139 overexpression increases radiosensitivity of NSCLC cells *in vitro* and *in vivo*. miR-139 works as a novel radiosensitizer by suppressing Nrf2 in NSCLC | (117) |

CDDP, cisplatin; CDKN1A, cyclin-dependent kinase inhibitor 1A; CDK1, cyclin-dependent kinase 1; FSP1, ferroptosis suppressor protein 1; GPX4, glutathione peroxidase 4; KEAP1, Kelch-like ECH-associated protein 1; KPNA2, Karyopherin-2 alpha; NQO1, NAD (P) H: quinone oxidoreductase; PEM, pemetrexed; SLC7A11, solute carrier family 7a member 11.

erastin- or RSL3-induced ferroptosis and tumor suppression (116). miR-302a-3p binds ferroportin and decreases its protein expression; ferroportin overexpression, in turn, prevents miR-302a-3p-triggered ferroptosis and tumor suppression (116). Additionally, miR-302a-3p increases NSCLC cell sensitivity to DDP and paclitaxel. These results indicate that miR-302a-3p serves as a tumor suppressor by inducing ferroptosis through ferroportin targeting in NSCLC (116). miR-139 overexpression enhances the radiosensitivity of NSCLC cells *in vitro* and *in vivo* by targeting cJUN and Karyopherin-2 α (KPNA2), which inhibits Nrf2 signaling and promotes ionizing radiation-induced ferroptosis (117). Ionizing radiation induces miR-139 expression via early growth response 1, a transcription factor that binds to the promoter region to activate miR-139. These results suggest that miR-139 serves as a radiosensitizer by inhibiting Nrf2 expression in NSCLC (117).

*lncRNAs modulate ferroptosis in NSCLC*

*Targeting classical ferroptosis inhibitors*. Increased expression of lncRNA p53 upregulated regulator of P53 levels (PURPL) has been observed in lung cancer cells and patient samples (118) (Fig. 4; Table II). Overexpression of lncRNA PURPL promotes M2 macrophage polarization and suppresses ferroptosis by stabilizing SLC7A11 mRNA through regulation of RNA-binding motif 4 (118). Silencing SLC7A11 reverses the inhibitory effects of lncRNA PURPL on M2 macrophage polarization by inducing macrophage ferroptosis (118). Upregulation of lncRNA tyrosine protein kinase transmembrane receptor 1 antisense RNA 1 (ROR1-AS1), insulin-like growth factor 2 mRNA-binding protein 1 (IGF2BP1) and SLC7A11 is associated with poor prognosis in lung cancer. ROR1-AS1 stabilizes SLC7A11 mRNA through interaction with IGF2BP1 (119). Cancer-associated fibroblast (CAF)-derived exosomal ROR1-AS1 inhibits ferroptosis in lung cancer cells both *in vitro* and *in vivo* (119). Ferroptosis induced by overexpression of lncRNA ROR1-AS1 or IGF2BP1 is partially reversed by silencing IGF2BP1 or inhibiting SLC7A11 in lung cancer cells. These results suggest that CAF-secreted exosomal ROR1-AS1 inhibits ferroptosis by enhancing SLC7A11 expression or interacting with IGF2BP1 (119). Elevated levels of lncRNA-X-inactive specific transcript (XIST) mRNA and protein expression are also observed in clinical tissues

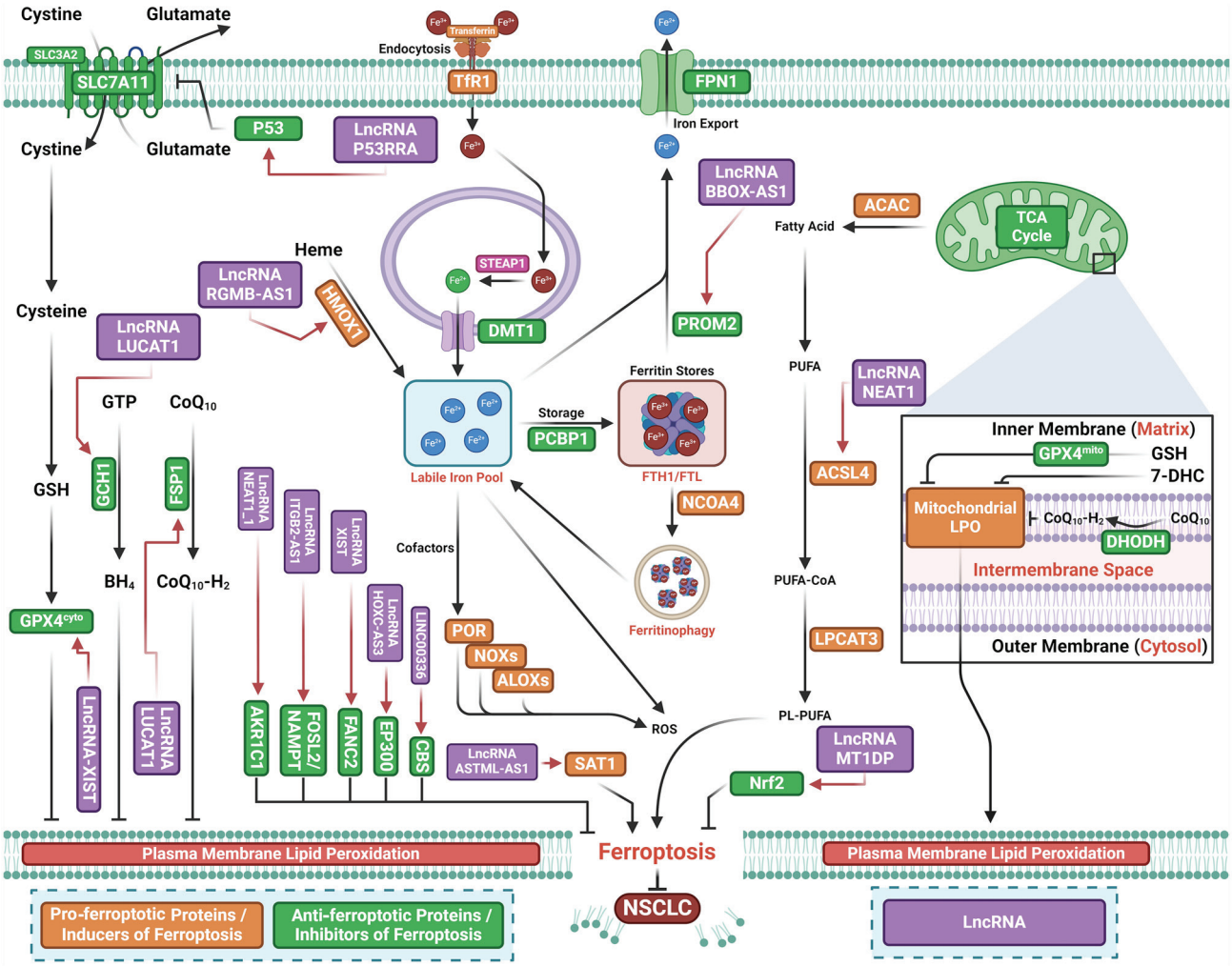


Figure 4. Regulatory lncRNA modulation of ferroptosis in non-small cell lung cancer. lncRNAs may modulate the pro/anti-ferroptotic balance, enhancing or suppressing the ability of ferroptotic induction. lncRNA-mediated silencing of pro-ferroptotic factors represses ferroptosis, while lncRNA-mediated silencing of anti-ferroptotic factors enhances ferroptosis. lncRNA, long noncoding RNAs.

and NSCLC cells (120). Silencing lncRNA-XIST reduces NSCLC cell viability by inducing ferroptosis, evidenced by increased ROS, MDA and $Fe^{2+}$ levels and decreased expression of SLC7A11 and FANCD2. Additionally. silencing XIST downregulates GPX4 in NSCLC cells (120). Overexpression of GPX4 reverses ferroptosis and decreases cell viability caused by lncRNA-XIST knockdown (120). Increased expression of lncRNA Uc.339 has been observed in patients with NSCLC (121). Uc.339 inhibits the maturation of miR-339 by competitively binding to pri-miR-339. As miR-339 targets and downregulates SLC7A11 expression, Uc.339 promotes cell proliferation, migration and invasion by inhibiting ferroptosis through upregulation of SLC7A11 via miR-339 downregulation (121). Silencing lncRNA nuclear paraspeckle assembly transcript 1 (NEAT1) inhibits proliferation and induces ferroptosis by upregulating ACSL4 and downregulating SLC7A11/GPX4 (122). Silencing lncRNA H19 promotes curcumenol-induced ferroptosis (123). Increased expression of lncRNA lung cancer associated transcript 1 (LUCAT1) is observed in LUAD and LUSC tissue (124). Elevated lncRNA LUCAT1 expression is found in RSL3-treated A549 cells; this increase is reversed by the ferroptosis inhibitor Fer-1. Overexpression of LUCAT1 enhances cell proliferation and suppresses RSL3- and erastin-induced ferroptosis while silencing LUCAT1 decreases cell proliferation and facilitates ferroptosis (124). Mechanistic study have shown that silencing LUCAT1 downregulates FSP1 and GCH1 and upregulates miR-34a-5p, thereby downregulating GCH1 (124). Together, these results suggest that inhibition of LUCAT1 promotes ferroptosis by downregulating GCH1 via upregulation of miR-34a-5p (124).

*Targeting iron regulators*. lncRNA γ-butyrobetaine hydroxylase 1-antisense 1 (BBOX1-AS1) promotes cell proliferation, migration and invasion by inhibiting ferroptosis through post-transcriptional upregulation of prominin 2 (PROM2) expression by miR-326 sponging (125). lncRNA repulsive guidance molecule b-antisense 1 (RGMB-AS1) enhances ferroptosis by interacting with HO-1, preventing its ubiquitination by E3 ligase TRC8, which leads to increased HO-1 stability. Additionally, RGMB-AS1 binds to and promotes acetyltransferase activity of N-alpha-acetyltransferase 10, further contributing to ferroptosis (126).

*Targeting transcription factors*. The upregulated lncRNA ITGB2-AS1 is found in DDP-resistant NSCLC cells and cancer

Table II. Regulatory role of lncRNAs in modulation of ferroptosis in non-small cell lung cancer.

| lncRNA | Expression status | Function | Targets of ferroptosis | Effects | (Refs.) |
|---|---|---|---|---|---|
| PURPL | Increased | Oncogene | SLC7A11 | PURPL promotes M2 macrophage polarization and suppresses ferroptosis by maintaining the mRNA stability of xCT via regulating RBM4 | (118) |
| ROR1-AS1 | - | Oncogene | IGF2BP1/ SLC7A11 | CAF-secreted exosomal ROR1-AS1 inhibits ferroptosis by enhancing expression of SLC7A11 by interacting with IGF2BP1 | (119) |
| XIST | Increased | Oncogene | SLC7A11, GPX4 and FANCD2 | Silencing XIST inhibits the viability of NSCLC cells by inducing ferroptosis, evidenced by increased ROS, MDA and $Fe^{2+}$ and decreased expression of SLC7A11 and FANCD2. Silencing XIST downregulates GPX4 | (120) |
| T-UCR Uc.339 | Increased | Oncogene | miR-339/ SLC7A11 | Uc.339 knockdown inhibits proliferation, migration and invasion *in vitro* and *in vivo* through promoting ferroptosis | (121) |
| NEAT1 | ND | Oncogene | ACSL4; SLC7A11/GPX4 | Silencing NEAT1 inhibits proliferation, inducing ferroptosis by upregulating ACSL4 and downregulating SLC7A11/GPX4 | (122) |
| H19 | Increased | Oncogene | SLC40A1/GPX4; FTH1 | H19 silencing enhances curcumenol-induced. ferroptosis | (123) |
| LUCAT1 | Increased | Oncogene | GCH1; FSP1 | LUCAT1 overexpression promotes cell proliferation by decreasing ferroptosis, while inhibition of LUCAT1 decreases proliferation by promoting ferroptosis. Silencing LUCAT1 downregulates GCH1 and FSP1 and upregulates miR-34a-5p. Inhibition of LUCAT1 expression promotes ferroptosis by downregulating GCH1 via upregulating miR-34a-5p | (124) |
| BBOX1-AS1 | ? | Oncogene | Prominin 2 | BBOX1-AS1 promotes cell proliferation, migration and invasion via inhibiting ferroptosis by post-transcriptionally upregulating PROM2 expression via sponging miR-326 | (125) |
| RGMB-AS1 | Decreased | Tumor suppressor | HO-1;NAA10 | RGMB-AS1 enhances ferroptosis through interacting with HO-1 to prevent HO-1 ubiquitination by the E3 ligase TRC8, leading to increased HO-1 stability. RGMB-AS1 binds to and promotes acetyltransferase activity of NAA10, further contributing to ferroptosis | (126) |
| P53RRA | Decreased | Tumor suppressor | p53 | Promotes ferroptosis to suppress cancer progression | (127) |
| MT1DP | Decreased | Tumor suppressor | Nrf2 | MT1DP increases sensitivity of NSCLC cells to erastin-induced ferroptosis by downregulating Nrf2 | (128) |
| NEAT1_1 | ? | Oncogene | AKR1C1 | Promotes gefitinib resistance through increasing AKR1C1-mediated ferroptosis evasion | (129) |
| ITGB2-AS1 | Increased | Oncogene | FOSL2/NAMPT | Promotes resistance to cisplatin by inhibiting ferroptosis via activating the FOSL2/NAMPT axis | (130) |
| HOXC-AS3 | Increased | Oncogene | EP300 | Increased HOXC-AS3 expression by methylation promotes binding of HOXC-AS3 to EP300, thereby suppressing ferroptosis | (131) |
| ASMTL-AS1 | Decreased | Tumor suppressor | SAT1 (promote ferroptosis) | ASMTL-AS1 upregulation resulted in inhibits LUAD cell proliferation and xenograft tumor growth through stabilizing SAT1 to stimulate ferroptosis | (132) |

Table II. Continued.

| lncRNA | Expression status | Function | Targets of ferroptosis | Effects | (Refs.) |
|---|---|---|---|---|---|
| LINC00336 | Increased | Oncogene | miR6852/CBS | LINC00336 promotes cell proliferation and colony and tumor formation by inhibiting ferroptosis via absorbing miR6852, which serves as a ceRNA and increases the mRNA levels of CBS | (133) |
| SDCBP2-AS1 | Increased | Oncogene | CRIM1 | SDCBP2-AS1 promotes cancer by inhibiting ferroptosis via sponging miR-656-3p, which directly targets CRIM1 | (134) |
| OGFRP1 | Increased | Oncogene | SLC38A1 | OGFRP1 promotes cell proliferation through inhibiting ferroptosis by inhibiting miR-299-3p to upregulate SLC38A1 | (135) |
| H19 | Decreased | Tumor suppressor | - | β-elemene increases sensitivity to erlotinib by inducing ferroptosis via increasing lncRNA H19 | (136) |

ACSL4, acyl-CoA synthetase long-chain family member 4; AKR1C1, aldo-keto reductase family 1 member C1; CBS, cystathionine-β-synthase; CRIM1, cysteine-rich transmembrane BMP regulator 1; FANCD2, Fanconi anemia complementation group D2; FOSL2, FOS-like antigen 2; FSP1, ferroptosis suppressor protein 1; FTH1, ferritin heavy chain 1; GCH1,GTP cyclohydrolase 1; HO-1, heme oxygenase-1; IGF2BP1, insulin-like growth factor 2 mRNA-binding protein 1; SAT1, spermidine/spermine N1-acetyltransferase 1; SLC38A1, Solute Carrier Family 38 Member 1; NAA10, Nα-acetyltransferase 10; NAMPT, nicotinamide phosphoribosyltransferase.

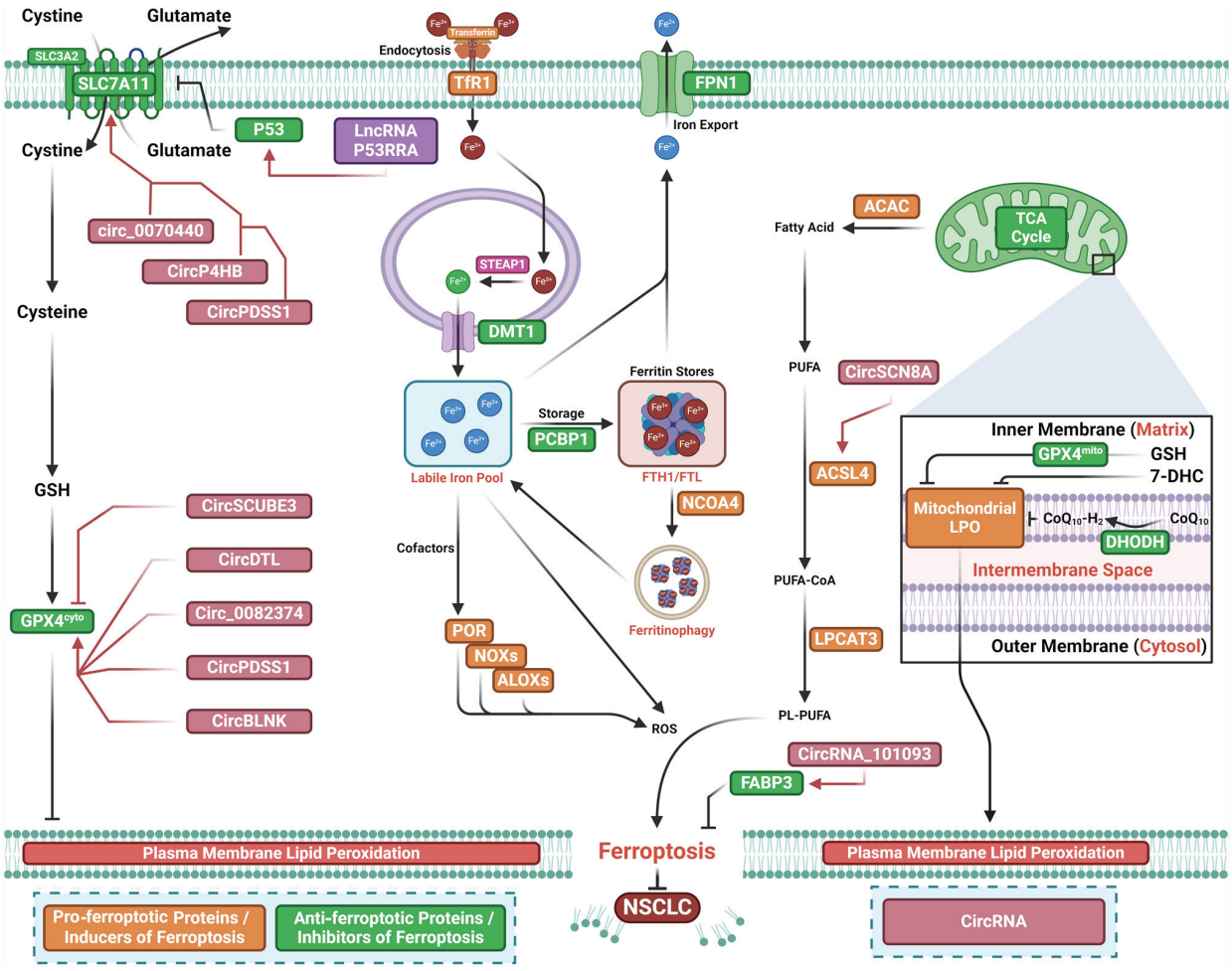


Figure 5. Regulatory circRNA modulation of ferroptosis in non-small cell lung cancer. circRNAs may modulate the pro-/anti-ferroptotic balance, enhancing or suppressing ferroptotic induction. circRNA-mediated silencing of pro-ferroptotic factors suppresses ferroptosis, while circRNA-mediated silencing of anti-ferroptotic factors enhances ferroptosis. circRNA, circular RNAs.

Table III. Regulatory role of circRNAs in modulation of ferroptosis in NSCLC.

| circRNA | Expression status | Function | Targets of ferroptosis | Effect | (Refs.) |
|---|---|---|---|---|---|
| circ_0070440 | Decreased | Tumor suppressor | SLC7A11 | Promotes malignant progression by suppressing ferroptosis via sponging miR-485-5p and upregulating SLC7A11 expression | (139) |
| CircP4HB | Increased | Oncogene | SLC7A11 | Inhibits ferroptosis by upregulating SLC7A11 by sponging and inhibiting miR-1184 | (140) |
| CircPDSS1 | Increased | Oncogene | SLC7A11/ GPX4/GCLC | Silencing CircPDSS1 inhibits viability of NSCLC cells by inducing ferroptosis by downregulating SLC7A11, GPX4 and GCLC via sponging miR-137 | (141) |
| Circ_0082374 | Increased | Oncogene | GPX4 | Enhances tumorigenesis by suppressing ferroptosis through upregulating GPX4 via sponging miR-491-5p | (142) |
| CircSCUBE3 | Decreased | Tumor suppressor | GPX4 | Inhibits LUAD development by inducing ferroptosis via the CREB/GPX4/GSH axis | (143) |
| CircDTL | Increased | Oncogene | GPX4 | Silencing circDTL increases sensitivity of NSCLC cells to chemotherapy and inhibits growth of tumors *in vivo* | (144) |
| CircSCN8A | Decreased | Tumor suppressor | ACSL4 | Suppresses malignant progression through inducing ferroptosis via sponging miR-1290 to upregulate ACSL4 | (145) |
| circRNA_101093 | Increased | Oncogene | FABP3 | Inhibits ferroptosis through upregulating the downstream factor FABP3 | (146) |

ACSL4, acyl-CoA synthetase long-chain family member 4; FABP3, fatty acid-binding protein 3; GPX4, glutathione peroxidase 4.

tissue from patients with NSCLC. Silencing ITGB2-AS1 inhibits cell proliferation and enhances apoptosis and ferroptosis in DDP-resistant NSCLC cells (137). ITGB2-AS1 promotes nicotinamide phosphoribosyltransferase (NAMPT) expression by binding to FOS-like antigen 2 (FOSL2), thereby suppressing p53 expression. FOSL2, a member of the activator protein 1 transcription factor family, enhances NSCLC malignancy (137). p53 increases cell sensitivity to ferroptosis by transcriptionally suppressing SLC7A11 expression (138). The cytosolic lncRNA P53RRA functions as a tumor suppressor by inducing ferroptosis via p53 activation (127). Downregulation of P53RRA inhibits cancer progression by acting as a tumor suppressor. Chromatin remodeling proteins CxxC finger protein 1 (Cfp1) and lymphoid-specific helicase (LSH) regulate P53RRA expression. P53RRA binds to Ras GTPase-activating protein-binding protein 1 (G3BP1) to form a P53RRA-G3BP1 cytosolic complex, displacing p53 from a G3BP1 complex and promoting p53 retention in the nucleus, which leads to cell cycle arrest, apoptosis and ferroptosis (127). The lncRNA metallothionein 1D pseudogene (MT1DP) increases sensitivity of NSCLC cells to erastin-induced ferroptosis by downregulating Nrf2 via stabilization of miR-365a-3p (128).

*Targeting other factors*. Increased expression of the ferroptosis suppressor aldo-keto reductase family 1 member C1 (AKR1C1) is found in gefitinib-resistant LUAD cells and associated with poor prognosis in patients with LUAD receiving first-generation epidermal growth factor receptor-tyrosine kinase inhibitor therapy (129). Silencing AKR1C1 increases the sensitivity of LUAD cells to gefitinib-induced ferroptosis (129). Reduced miR-338-3p expression leads to upregulation of AKR1C1 in gefitinib-resistant LUAD cells (129). lncRNA NEAT1_1 activates AKR1C1 by sponging miR-338-3p, thereby reducing miR-338-3p-mediated inhibition of AKR1C1. These results suggest that lncRNA NEAT1_1 promotes gefitinib resistance by suppressing ferroptosis via the upregulation of AKR1C1 via miR-338-3p sponging (129). Silencing lncRNA ITGB2-AS1 overcomes NSCLC resistance to DDP *in vivo* by inhibiting p53-mediated ferroptosis through activation of the FOSL2-NAMPT axis (130). Increased lncRNA HOXC-AS3 expression due to methylation promotes its binding to EP300, thereby suppressing ferroptosis in NSCLC cells (131). Upregulation of lncRNA ASMTL-AS1 inhibits tumor growth *in vitro* and *in vivo* by stabilizing spermidine/spermine N1-acetyltransferase 1, thereby stimulating ferroptosis (132). LINC00336 promotes malignancy by inhibiting ferroptosis via the absorption of miR6852, acting as a competing endogenous RNA (ceRNA) to increase the mRNA levels of cystathionine-β-synthase (133). The lncRNA syndecan-binding protein 2-antisense RNA 1 (SDCBP2-AS1) promotes cancer by inhibiting ferroptosis via sponging miR-656-3p, directly targeting cysteine-rich transmembrane BMP regulator 1 (CRIM1). SDCBP2-AS1 inhibits ferroptosis via miR-656-3p, while CRIM1 overexpression counteracts the effects of miR-656-3p on ferroptosis (134). lncRNA opioid

growth factor receptor pseudogene 1 promotes NSCLC cell proliferation by inhibiting ferroptosis and suppressing miR-299-3p, leading to upregulation of SLC38A1 expression (135). β-elemene, a primary bioactive compound derived from *Curcuma wenyujin*, enhances sensitivity of cancer cells to erlotinib by inducing ferroptosis via upregulation of lncRNA H19 (136).

*circRNAs modulate ferroptosis in NSCLC*

*Targeting SLC7A11*. Increased circ_0070440 expression is observed in LUAD cells. Silencing circ_0070440 inhibits cell proliferation and enhances apoptosis and ferroptosis in LUAD cells (139). circ_0070440 promotes malignant progression by suppressing ferroptosis through upregulation of SLC7A11 expression via miR-485-5p sponging (139) (Fig. 5; Table III). Increased expression of circP4HB is observed in LUAD. circP4HB inhibits erastin-induced ferroptosis by promoting GSH synthesis (140). Mechanistic study indicates that circP4HB upregulates SLC7A11 by serving as a competing endogenous RNA and modulating miR-1184 expression (140). circPDSS1 expression is elevated in NSCLC cells (141). Silencing circPDSS1 inhibits NSCLC cell viability and induces ferroptosis (141). Mechanistic study suggest that circPDSS1 functions as a competing endogenous RNA 'sponge' to negatively regulate miR-137 expression (141). Silencing circPDSS1 also downregulates GPX4 and the glutamate-cysteine ligase catalytic subunit (141).

*Targeting GPX4*. circ_0082374 promotes tumorigenesis in NSCLC by suppressing ferroptosis via upregulation of GPX4 via miR-491-5p sponging (142). Increased circ_0082374 levels are observed in NSCLC tissue and cells. Silencing circ_0082374 inhibits cell proliferation and tumor metastasis while facilitating ferroptosis by decreasing iron and LPO levels in NSCLC (142). Mechanistic study show that circ_0082374 enhances GPX4 expression by sequestering miR-491-5p (142). In LUAD samples and cell lines, decreased circRNA signal peptide-CUB-EGF domain-containing protein 3 (circSCUBE3) expression is noted (143). Overexpression of circSCUBE3 decreases GSH levels and GSH/GSSG ratio in LUAD cells, while loss of circSCUBE3 reverses erastin-induced ferroptosis (143). circSCUBE3 downregulates GPX4 expression in LUAD cells, and silencing GPX4 counteracts the ferroptosis induced by circSCUBE3 deficiency (143). circSCUBE3 downregulates GPX4 expression by competitively interacting with CREB, which activates GPX4 transcription. These results suggest that circSCUBE3 inhibits LUAD development by promoting ferroptosis via the CREB/GPX4/GSH axis (143). Increased circDTL expression has been detected in NSCLC cells (144). Silencing circDTL promotes apoptosis and ferroptosis in NSCLC cells (144) and enhances their sensitivity to chemotherapy, thus inhibiting tumor growth *in vivo*. CircDTL acts as an oncogene by suppressing ferroptosis and increasing GPX4 expression via miR-1287-5p sponging (144).

*Targeting ACSL4*. Downregulated circSCN8A expression has been observed in NSCLC tissue and cells. Decreased circSCN8A expression is positively associated with aggressive clinicopathological characteristics and predicts poor prognosis in patients with NSCLC (145). circSCN8A suppresses tumor growth *in vivo* and inhibits cell proliferation, migration, invasion and epithelial-mesenchymal transition *in vitro*. circSCN8A enhances ferroptosis in NSCLC cells. Mechanistic studies revealed that circSCN8A functions as a ceRNA by sponging miR-1290 to upregulate ACSL4 (145). Silencing ACSL4 or overexpressing miR-1290 reverses circSCN8A-induced ferroptosis and inhibits cell proliferation and tumor metastasis (145). These results indicate that circSCN8A suppresses malignant progression by inducing ferroptosis through miR-1290 sponging to enhance ACSL4 expression (145).

*Targeting other factors*. Plasma exosomes from patients with LUAD show decreased LPO and reduced sensitivity of LUAD cells to ferroptosis (146). Exosomal circRNA_101093 maintains elevated intracellular circRNA_101093 levels in LUAD cells to modulate AA (146). circRNA_101093 binds to and upregulates fatty acid-binding protein 3 (FABP3), which transports AA and enhances its reaction with taurine (146). These results indicate that circRNA_101093 inhibits ferroptosis by upregulating FABP3 and suggest that blocking exosomes may be a novel therapeutic approach for LUAD (146).

## 4. Conclusion

The present review summarizes the role of ncRNA-mediated epigenetic modulation of ferroptosis in NSCLC and the roles of miRNAs, lncRNA and circRNA in regulating ferroptosis in NSCLC cells. However, studies on ncRNA-induced epigenetic modifications that modulate ferroptosis in NSCLC are in their early stages and the present study has limitations. First, other ncRNAs that modulate ferroptosis require further exploration. Second, while ncRNA-mediated epigenetic modifications of ferroptosis in NSCLC have been identified, it remains unclear whether small-molecule compounds effectively target these ncRNA-mediated mechanisms. Third, ncRNAs modulate the crosstalk between ferroptosis and regulated cell death mechanisms in cancer (147). However, the role of ncRNAs in the interplay between ferroptosis and novel RCD mechanisms, such as cuproptosis, in NSCLC remains largely unknown (148). The aforementioned studies primarily focused on classical pathways of ferroptosis, such as the ACSL4-dependent LPO or SLC7A11-GPX4 system. However, the effects of other ferroptosis inhibitors, including DHODH-$CoQH_2$, MBOAT1/2-MUFA, GCH1-$BH_4$ and SC5D-7-DHC, are still poorly understood. Fifth, many ncRNAs directly modulate ferroptosis by regulating ferroptosis-associated genes involved in antioxidant defense and iron and lipid metabolism or indirectly target ferroptosis modulators, such as activated transcription factor 4 in NSCLC (149). However, whether ncRNAs modulate other transcription factors, including Nrf2, remain poorly understood.

The clinical application of RNA-based therapeutics has made progress, primarily using antisense oligonucleotides and small interfering RNA (150). However, no lncRNA-based therapeutics or circRNA-targeted treatments have entered clinical practice, although miRNA mimics and anti-miRNA therapeutics are under clinical development (150-152). Emerging evidence suggests that small molecule compounds can target ncRNAs for cancer treatment (153). Small molecules targeting miRNA (154,155) and lncRNA (136,156) that regulate ferroptosis may offer new opportunities for NSCLC therapy. However, no small molecules targeting miRNAs and lncRNAs involved in regulating ferroptosis have yet been introduced for clinical use in NSCLC treatment.

Collectively, ncRNAs modulate the tumor burden in NSCLC by regulating ferroptosis through proteins or genes associated with pro- and anti-ferroptotic factors. The present review summarizes advances in understanding the ncRNA-mediated mechanisms affecting ferroptosis in NSCLC, highlighting a novel therapeutic avenue for NSCLC through the ncRNA-ferroptosis axis.

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**Authors' contributions**

YW, JC, and MD designed and conceived the review. ZZ, HW and JSF edited the manuscript. YW, YL and YC wrote the manuscript. YW and JSF generated the figures. Data authentication is not applicable. All authors have read and approved the final manuscript.

**Ethics approval and consent to participate**

Not applicable.

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**Competing interests**

The authors declare that they have no competing interests.

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