Regulation of ferroptosis by non-coding RNAs in the development and treatment of cancer (Review)

YAJUN LUO[1,2*], QINGMEI HUANG[3*], BIN HE[4], YILEI LIU[2], SIQI HUANG[1] and JIANGWEI XIAO[2]

[1]Department of Gastrointestinal Surgery, The First Affiliated Hospital of Chongqing Medical University, Chongqing 400042; [2]Department of Gastrointestinal Surgery, The First Affiliated Hospital of Chengdu Medical College, Chengdu, Sichuan 610513; [3]Department of Oncology, The Affiliated Hospital of North Sichuan Medical College, Nanchong, Sichuan 637000; [4]Department of Orthopedics, The First Affiliated Hospital of Chongqing Medical University, Chongqing 400042, P.R. China

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Abstract. Ferroptosis, a relatively recently discovered type of cell death that is iron dependent and nonapoptotic, is involved in the accumulation of lipid reactive oxygen species (ROS), and has been shown to serve a vital role in various pathological processes, including those underlying neurodegeneration, ischemic reperfusion injury, acute organ injury, and in particular, tumor biology. Emerging evidence has highlighted the roles of ferroptosis in the development and resistance to chemoradiotherapy in cancer. Recently, an increasing number of studies have shown that non-coding RNAs modulate the process of ferroptotic cell death, and this has further highlighted the potential of regulation of ferroptosis as a means of cancer management. Although these studies have highlighted the critical role of ferroptosis in cancer therapeutics, the roles of ferroptosis induced by non-coding RNAs in cancer development remain unclear. Herein, the current body of knowledge of ferroptosis in cancer is summarized and an overview of the mechanisms of ferroptosis and the functions of non-coding RNAs in regulating ferroptotic cell death are discussed. The future status of ferroptosis in cancer management is deliberated and strategies for treatment of therapy-resistant cancers are discussed.

Correspondence to: Professor Jiangwei Xiao, The Department of Gastrointestinal Surgery, The key discipline of Sichuan Medical Science, The First Affiliated Hospital of Chengdu Medical College, 278 Baoguang Road, Xindu, Chengdu, Sichuan 610513, P.R. China
E-mail: xiaojiangwei@126.com

*Contributed equally

Abbreviations: RCD, regulated cell death; ROS, reactive oxygen species; PUFAs, polyunsaturated fatty acids; GSH, glutathione; GPX4, glutathione peroxidase 4; ncRNAs, non-coding RNAs; miRNA, microRNA; lncRNA, long non-coding RNA; circRNA, circular RNA; Fe^{2+}, ferrous iron; Fe^{3+}, ferric iron; TfR1, Transferrin receptor 1; TF, Transferrin; STEAP3, six transmembrane epithelial antigen of the prostate 3; IREs, iron-responsive elements; DMT1, divalent metal transporter 1; IRPs, iron-regulatory proteins; FPN-1, ferroportin 1; FTH1, ferritin heavy chain 1; TFRC, transferrin receptor; FTH, ferritin; FTL, ferritin light polypeptide; HSPB1, heat-shock 27-kDa protein 1; LOXs, lipoxygenases; ACSL4, acyl-CoA synthetase long-chain family member 4; LPCAT3, lysophosphatidylcholine acyltransferase 3; CS, citrate synthase; IREB2, iron response element binding protein 2; SCD1, stearoyl-CoA desaturase 1; AA, arachidonic acid; system xc-, cystine/glutamate transporter; Nrf2, nuclear factor erythroid 2-related factor 2; Keap1, kelch-like ECH-associated protein 1; GOT1, glutamic-oxaloacetic transaminase 1; CRR, clinically relevant radioresistant; ATF4, activation of transcription factor 4

Key words: ferroptosis, iron metabolism, lipid reactive oxygen species, non-coding RNAs, cancer therapeutics

Contents

1. Introduction

Ferroptosis, a novel form of regulated cell death (RCD), first proposed by Dixon *et al* (1) in 2012 and is characterized by the overwhelming iron-dependent accumulation of lethal lipid reactive oxygen species (ROS). The morphological hallmarks of ferroptotic death are a reduction or loss of mitochondrial cristae (1), condensation of the mitochondrial membrane (2) and rupture of the outer mitochondrial membrane (3). An initial characterization of ferroptotic biochemical demonstrated that cysteine depletion or inactivation of glutathione peroxidase 4 (GPX4) activity, which causes exhaustion of the intracellular pool of glutathione (GSH), iron accumulation and lipid peroxidation, specifically triggers this form of cell death (4). The genetic features of ferroptosis shows that it primarily dysregulates ferroptotic molecular on antioxidant

metabolism, iron and lipid metabolism, such as SLC7A11, GPX4, TfR1, ACSL4, which are involved in the initiation of ferroptosis (5-7). As shown in Table I, there are no forms of morphological, biochemical, or genetic crosstalk between ferroptosis and other types of RCD, including apoptosis, autosis, pyroptosis, autophagy, necroptosis and various other forms of RCD.

As a cellular process, ferroptosis can be triggered by various pathological conditions in humans and animals (4,8-10). Notably, emerging evidence has indicated that ferroptosis likely prevents tumorigenesis, such as gastric cancer (11), non-small-cell lung carcinoma (12), glioblastoma (13) and colorectal cancer (14). Ferroptosis is now accepted as an adaptive process in biological systems that acts as a tumor suppressive mechanism to eradicate the malignant cells, but the activation of oxidative stress pathways when metabolism is dysregulated leads to tumorigenesis (15). Interestingly, recent evidence has suggested that non-coding RNAs (ncRNAs), particularly micro RNAs (miRNAs/miRs), long non-coding RNAs (lncRNAs) and circular RNAs (circRNAs), serve vital roles in regulating ferroptosis (16). These ncRNAs are involved in iron metabolism, ROS metabolism and ferroptosis-related amino-acid metabolism, which regulates the process of ferroptosis initiation (17). Of particular interest, the accumulation of abundant lipid ROS in cells is the most critical factor for triggering ferroptosis (18). Conversely, ncRNAs can directly or indirectly regulating lipid ROS-related molecules to maintain redox dynamics during periods of high levels of ROS generation, and work to reduce ROS levels below toxic thresholds, which allows tumor cells to exhibit tolerances to relatively high levels of cellular ROS and avoids initiating ferroptosis (19). A moderate increase in cellular ROS levels promotes cell proliferation, survival and malignant transformation (19). These findings highlight the potential targets for anticancer treatments via genetic or pharmacological interference in ncRNA-regulated ferroptotic cell death. In the present review, the primary mechanism of ferroptosis initiation and the involvement of ncRNAs in ferroptosis in various types of cancer cells is summarized, with the aim of highlighting potentially novel strategies for personalized cancer treatment.

2. Mechanism of ferroptosis

Iron metabolism. Iron is an essential nutrient, as it is necessary for the maintenance of cellular metabolism and all several important physiological activities, such as oxygen transport, DNA synthesis and ATP production (20). As iron is ubiquitously present, cellular iron homeostasis is a complex and tightly regulated process though the acquisition, utilization, storage and recycling of iron (5). The cellular iron balance is maintained through the redox cycle and iron intake (Fig. 1). The cellular iron redox cycle is primarily dependent on the Fenton reaction (21). In the cellular Fenton reaction, ferrous iron (Fe^{2+}) is oxidized to ferric iron (Fe^{3+}) during the conversion of H_2O_2 into reactive hydroxyl radicals; conversely, Fe^{3+} is then reduced back to Fe^{2+} through superoxide radicals (22). In of iron intake, transferrin receptor 1 (TfR1) is expressed on the surface of the majority of cells, where it primarily takes up transferrin (TF)-bound iron into cells. The TfR1/TF-$(Fe^{3+})_2$ complex is endocytosed (23), and Fe^{3+} is released from TF (24), reduced to Fe^{2+} by ferric reductase six-transmembrane epithelial antigen of the prostate 3 (STEAP3), and then transported across the endosomal membrane by divalent metal transporter 1 (DMT1) (25).

The imported cellular iron enters the transient cytosolic labile iron pool, a pool of chelatable and redox-active iron (26), which is utilized by cells for various metabolic processes or stored in ferritin (27). Excess cellular iron is exported out of the cell and transported into circulation by ferroportin 1 (FPN-1), after which it is oxidized by the ferroxidase-ceruloplasmin and binds to serum TF (28). Furthermore, cellular iron balance is also regulated by a network of iron-dependent proteins: The iron-responsive elements (IREs) and iron-regulatory proteins (IRPs). IRPs are cytosolic proteins that regulate the expression of genes involved in iron import (TfR1, DMT1), storage [ferritin (FTH), FTH1 and FTL] and export (FPN-1) by binding IREs (29).

Iron metabolism is an indispensable component of ferroptosis that distinguishes it from other types of RCD. Iron can gain and lose electrons, rendering it capable of contributing to free radical formation. When cellular iron is overloaded, the free radicals accumulate aberrantly, causing increased production of ROS. This effect leads to oxidative stress, which results in ferroptotic cell death (30). However, dysregulation of iron metabolism also serves an active role in carcinogenesis and promotes tumor growth (5,31).

TfR1 is a major regulator of intracellular iron uptake, and researchers found that abnormal accumulation of TfR1 on the cell surface is a specific marker of ferroptosis (32). In hepatocellular carcinoma, TfR1 and FTH1 are upregulated in erastin and sorafenib induced ferroptotic cell death (33), and TfR1 is also upregulated in erastin-induced cell death in myeloid leukemia cell lines (34). Furthermore, in Calu-1 lung cancer cells and HT-1080 fibrosarcoma cells, IRE-binding protein 2 (IREB2) is an essential gene for erastin-induced ferroptosis by regulating TFRC, FTH1 and FTL (1). Furthermore, several studies have suggested that inhibition of DMT1 may prevent iron translocation, leading to lysosomal iron overload, ROS production and ferroptotic cell death in cancer stem cells (35), and sulfasalazine induced ferroptosis is reduced by the inhibitory effect of estrogen receptor on TFRC and DMT1 in breast cancer cells (36). Artemisinin compounds sensitize cancer cells to ferroptosis by regulating IRP/IRE-controlled iron homeostasis (37). Therefore, targeting iron metabolic pathways may offer novel therapeutic options for cancer therapy.

Lipid metabolism. Fatty acid (FA) metabolism provides specific lipid precursors for energy storage, membrane biosynthesis, generation of signaling molecules and lipid oxidation that result in an accumulation of an abundance of lipid ROS (38). Although ferroptosis is induced by multiple stimuli, the accumulation of abundant lipid ROS in cells is the most critical factor causing ferroptotic cell death. In addition to iron-generated ROS production via the Fenton reaction, ROS from lipid oxidation appears to serve a role in ferroptosis (Fig. 1). Therefore, lipid peroxidation is crucial for induction of ferroptosis.

In the process of lipid metabolism, arachidonic acid (AA), a fatty acid substrate, is activated by acyl-CoA synthetase long-chain family member 4 (ACSL4) to produce AA-CoA,

Table I. Characteristics of the primary types of RCD.

First author, year	RCD (year of discovery)	Morphological features	Biochemical features	Genetic features	Regulatory pathways	(Refs.)
De Duve *et al,* 1966	Autophagy (1966)	Formation of double-membrane lysosomes	Increased lysosomal activity for the degradation and recycling of damaged proteins and organelles	ATG4/5/7/10/12, DRAM3, TFEB, Atg8, BECN1, LC3, BNIP3, ULK1/2, VPS34	MAPK-ERK1/2-mTOR, PI3K/AKT/mTOR and p53 signaling pathways	(205)
Kerr *et al*, 1972	Apoptosis (1972)	Cell shrinkage, plasma membrane blebbing, reduced cellular and nuclear volume, nuclear fragmentation, chromatin margination	Activation of caspases, exteriorization of phosphatidylserine, oligonucleosomal DNA fragmentation	Caspase, P53, Fas, Bcl-2, Bax	Endoplasmic reticulum pathway; Caspase-, Death receptor-, P53-, and Bcl-2-mediated signaling pathways	(206)
Cookson *et al*, 2001	Pyroptosis (2001)	Cell swelling and the formation of large bubbles from the plasma membrane, karyopyknosis	Proinflammatory cytokine releases, inflammatory caspases	GSDMD, Caspase-1, IL-1β, IL-18	Caspase-1 and NLRP3-mediated signaling pathways	(207)
Degterev *et al*, 2005	Necroptosis (2005)	Rapid swelling of cells and organelles, plasma membrane rupture, moderate chromatin condensation	Proinflammatory Response; decreased ATP levels; activation of RIP1, RIP3, and MLKL	TNFR1, RIPK1, TRADD, LEF1, RIP1, RIP3	RIPK1/3-, MLKL-, TNFα-, TNFR1-, TLR3-, TRAIL-, -and PKC-MAPK-AP-1-mediated signaling pathways	(208)
Overholtzer *et al*, 2007	Entosis (2007)	Formation of cell-in-cell structures, cell cannibalism, lack of ECM attachment	Internalization of one cell inside of another; adherens junction formation, lysosome-mediated degradation	Rho GTPase, ROCK, Par3/Par6/aPKC, Crumbs3/Pals1/Patj, Scribble/Lgl/Dlg	Rho–Rho-associated and ROCK-myosin pathways	(209)
Dixon *et al*, 2012	Ferroptosis (2012)	Condensed mitochondrial membrane, reduced mitochondria crista or loss of mitochondria crista, outer mitochondrial membrane rupture	Iron and ROS accumulation, inhibition of xCT, reduced GSH, inhibition of GPX4	xCT, GPX4, Nrf2, LSH, TFR1, ACSL4	xCT and GPX4, RAS-RAF-MEK signaling pathway, p62-Keap1-Nrf2 pathway, LSH signaling pathway, MVA, HSF1-HSPB1	(1)

RCD, regulated cell death.

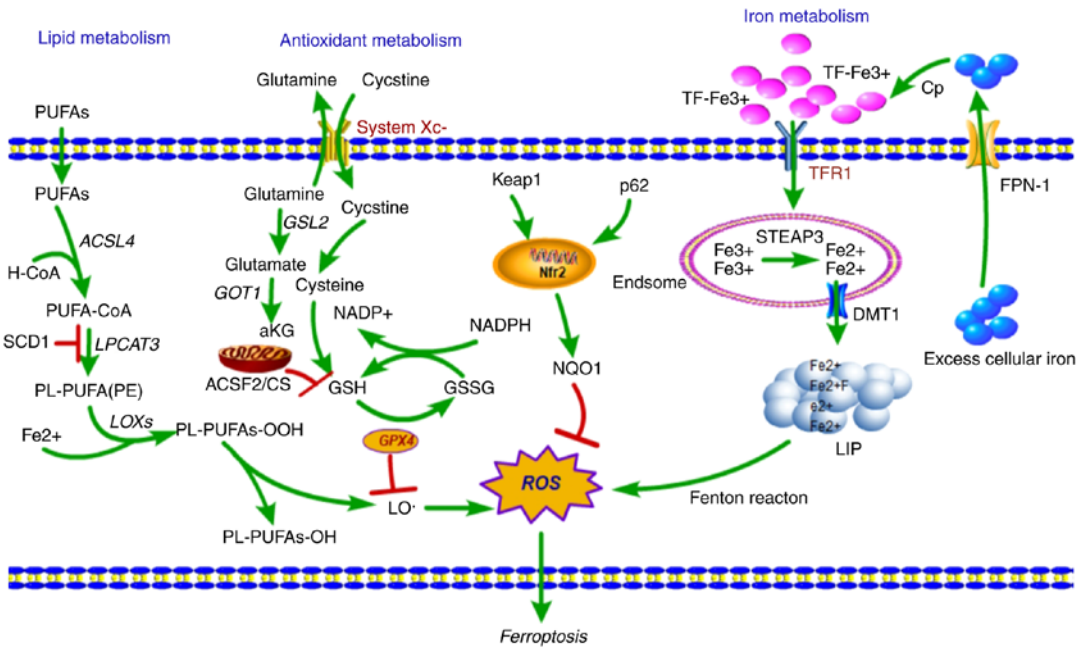

Figure 1. Overview of the mechanism of ferroptotic cell death. Fe^{3+} is loaded into the circulating apo-Tf, forming a TfR1-Tf-$(Fe^{3+})^2$ complex, which is endocytosed by TfR1, and iron is released from TF at same time. Fe^{3+} is reduced to Fe^{2+} by the ferric reductase STEAP3, and Fe^{2+} is then transported to the cytosol by DMT1, where it enters the cytosolic LIP for various metabolic needs. Excess iron is effluxed into circulation by FPN-1 and an associated ferroxidase, which causes the production of ROS, in-turn initiating ferroptosis. Lipid metabolism: Fatty acids are activated (ACSL4) and esterified (LPCAT3) into PL-PUFAs, then LOXs catalyze the dioxygenation of PL-PUFAs and generate PL-PUFAs-OOH. Lipid-OOHs are regulated by the balance of GPX4 activity. An excess of PUFAs enhances generation of ROS and toxic lipid peroxides and simultaneously decreases GPX4 activity, which initiates ferroptosis. Ferroptosis-related amino-acid metabolism: System Xc- imports cystine in exchange for glutamate, which is reduced to cysteine and used to synthesize GSH, a necessary cofactor of GPX4 for eliminating ROS. GSH is an antioxidant particularly important in protecting cells from ferroptosis. TfR1, Transferrin receptor 1; TF, Transferrin; LIP, labile iron pool; DMT1, divalent metal transporter 1; GPX4, glutathione peroxidase 4; STEAP3, six transmembrane epithelial antigen of the prostate 3; FPN-1, ferroportin 1; ROS, reactive oxygen species; PUFA, polyunsaturated fatty acids; LOXs, lipoxygenases; GSH, glutathione.

and then AA-CoA is esterified by lysophosphatidylcholine acyltransferase 3 (LPCAT3) to phosphatidyl-(PE)-AA (39). PE-AA is oxidized to cytotoxic PE-AA-OOH by lipoxygenases (LOXs) that are activated during catalysis of Fe^{2+} (40). Under physiological conditions, glutathione peroxidase 4 (GPX4) reduces cytotoxic PE-AA-OOH to non-cytotoxic PE-AA-OH, which protects cells from oxidative damage. When GPX4 is inactivated or depleted, PE-AA-OOH accumulates in the cell, and this induces ferroptosis (40). Thus, lipid peroxidation accounts for a large proportion of ferroptosis initiation.

ACSL4 is a key enzyme involved in the synthesis of long chain unsaturated fatty acids. ACSL4 was found to sensitize RSL3-induced ferroptosis through altering the cellular lipid composition (8). In hepatocellular carcinoma patients who had complete or partial responses to sorafenib-induced ferroptosis, and had higher ACSL4 expression in the pretreated tumor tissues than those who did not respond, ACSL4 was a predictive biomarker for sensitivity of sorafenib in hepatocellular carcinoma (41). Consistently, ACSL4 suppresses the proliferation of tumor cells through activation of ferroptosis in glioma cells (42). Furthermore, a CRISPR-based genetic screen identified ACSL4 and LPCAT3 as promoting of RSL3- and DPI7-induced ferroptosis, but they did not affect erastin-induced ferroptosis (39). Several studies have supported the conclusion that PUFAs can be oxidized, producing the lipid peroxides that promote the induction of ferroptosis (43). Therefore, targeting the lipid metabolism pathway may also be a novel means of tumor therapy.

Antioxidant metabolism. GSH, a thiol-containing tripeptide, is a potent antioxidant whose synthesis is limited by the constant import of cysteine and the availability of cystine/cysteine. The system Xc^- antiporter is a cystine/glutamate transporter that takes up extracellular cystine in exchange for intracellular glutamate (44). SLC7A11, expressed at the cell surface, is a regulatory light chain component of the system Xc^- transporter and is essential for cystine cellular uptake and serves a role in intracellular GSH synthesis (19). Once imported into cells, intracellular cystine is reduced to cysteine, a precursor of GSH used in GSH biosynthesis. GPX4, a central mediator of ferroptosis, which has phospholipid peroxidase activity, catalyzes the reduction of lipid peroxides to lipid alcohols using GSH as an essential co-factor, thus preventing cells from undergoing too much lipid peroxidation (45). Blockade of a member of the system Xc^- antiporter, SLC7A11, and inhibition of GPX4 were shown to induce ferroptosis (1). Both interventions impaired cellular antioxidant defenses, thereby facilitating toxic ROS accumulation, suggesting antioxidant pathways as potential regulators of ferroptosis.

Erastin, a RAS-selective lethal compound, triggers ferroptosis by directly inhibiting system Xc^- activity to reduce GSH levels in cancer cells (1,2). Similarly, sulfasalazine, a drug used to treat chronic inflammation, also triggers ferroptosis through directly inhibiting SLC7A11 activity (46). Similar to the above two compounds, p53, a well-characterized tumor suppressor, was also shown to sensitize cells to ferroptosis through the repression of SLC7A11 (47,48). Furthermore, the tumor suppressor BRCA1-associated protein 1 suppresses

SLC7A11 transcription by decreasing H2Aub, leading to elevated lipid peroxidation and thus, increased ferroptosis (49). kelch-like ECH-associated protein 1 (Keap1) can also suppress the expression of SLC7A11 through degrading the transcription factor nuclear factor erythroid 2-related factor 2 (Nrf2), which is a master transcription factor of the antioxidant response (50). Another molecular mechanism of ferroptosis is the direct suppression of GPX4 by promoting its degradation or the loss of its activity. GPX4 was identified as a target protein of the classical ferroptosis inducer RSL3 (51), which directly binds to GPX4 to inactivate the peroxidase activity of GPX4 and induce ferroptosis (52). Several ferroptosis inducers directly inhibit GPX4 function including DPI7, DPI10, DPI12, DPI13, DPI17, DPI18, DPI19 and ML162 (52,53), and several ferroptosis inducers have an indirect effect on GPX4 function, including SRS13-45 (46), SRS13-60 (46), buthionine (54), sulfoximine (52), DPI2 (52), lanperisone (55), sorafenib (56) and erastin derivatives (52). Taken together, these studies show that the SLC7A11-GSH-GPX4 axis primarily mediates the initiation of ferroptosis, and that GPX4 serves a central role in regulating ferroptosis.

3. Role of ncRNAs in ferroptosis and cancer development

Well-established regulatory mechanisms that regulate changes in iron and ROS metabolism in cancer have recently been identified. ncRNAs are being increasingly recognized as vital regulatory mediators of ferroptosis.

miRNAs in ferroptosis. A set of miRNAs that post-transcriptionally regulate gene expression by RNA silencing have been demonstrated to be involved in the regulation of iron and ROS metabolism. The levels of these miRNAs are directly or indirectly correlated with ferroptosis.

As shown in Table II, miRNAs can participate in the ferroptotic process. In A375 and G-361 melanoma cell lines, miR-9 directly suppresses glutamic-oxaloacetic transaminase 1 (GOT1) by binding to its 3'-UTR, which subsequently inhibited erastin- and RSL3-induced ferroptosis (57). In A549 and SPC-A-1 lung cancer cell lines, miR-6852 regulates the expression of cystathionine-β-synthase (CBS), a surrogate marker of ferroptosis, by competing for LINC00336, which increases the intracellular concentrations of iron, lipid ROS and mitochondrial superoxide and decreases the mitochondrial membrane potential (58). Another study showed that miR-137 suppressed erastin- and RSL3-induced ferroptosis through directly targeting the glutamine transporter SLC1A5 in melanoma (58). In the STKM2, MKN45 and OE33 gastric cancer cell lines, miR-4715-3p inhibited AURKA expression by directly targeting its 3'-UTR, leading to downregulation of expression of GPX4. Therefore, depletion of miR-4715-3p promoted ferroptotic cell death by inhibiting GPX4 (60). In MGC-803, MKN-45 and other gastric cancer cell lines, miR-103a-3p directly suppressed glutaminase 2 expression, promoting physcion 8-O-β-glucopyranoside-induced ferroptosis by increasing intracellular Fe^{2+} and ROS levels (61). miR-7-5p expression was shown to be upregulated in clinically relevant radioresistant (CRR) cells, and increased miR-7-5p levels could decrease mitoferrin levels and thus reduce Fe^{2+}, causing CRR cells to suppress ferroptosis (62). miR-K12-11 was found to suppress BACH-1 to induce SLC7A11 expression, leading to Kaposi's sarcoma-associated herpesvirus dissemination and persistence in an environment of oxidative stress via inhibition of ferroptosis (63). In endothelial cells, miR-17-92 directly suppressed the expression of ACSL4 by directly targeting A20, protecting endothelial cells from erastin-induced ferroptosis (64). In HepG2 and Hep3B cells, erastin enhanced the activation of transcription factor 4 (ATF4), whereas overexpression of miR-214-3p could sensitized cells to erastin-induced ferroptosis by directly suppressing the expression of ATF4 (65). miR-761 expression is downregulated in glioma, whereas overexpression of miR-761 confers resistance to erastin-induced ferroptosis by directly repressing integrin subunit β8 expression in LN229 and U251 cells (66).

lncRNAs and circRNAs in ferroptosis. lncRNAs are a class of non-coding RNAs >200 nucleotides in length that function to regulate gene expression by epigenetic, transcriptional and translational modulation. lncRNAs have been implicated in various biological processes. Recent studies have shown dysregulation of several lncRNAs is also involved in the ferroptotic process (Table II).

lncRNA P53RRA is downregulated in lung cancer and acts as a tumor suppressor. In the cytoplasm, P53RRA interacts with G3BP1 to activate the p53 signaling pathway, which in-turn promotes erastin-induced ferroptosis by increasing lipid ROS and altering the iron concentration (67). lncRNA LINC00336 is upregulated in lung cancer and functions as an oncogene. LINC00336 competes with miR-6852 for CBS, inhibiting ferroptosis by decreasing iron concentrations, ROS and mitochondrial superoxide levels, as well as the mitochondrial membrane potential (58). lncRNA GABPB1-AS1 is an antisense lncRNA of GABPB1 that downregulates GABPB1 levels by blocking GABPB1 translation, leading to peroxiredoxin-5 peroxidase suppression and increased lipid ROS concentrations, ultimately promoting erastin-induced ferroptosis (68).

CircRNAs are class of non-coding RNA characterized by a covalently closed loop structure leaving no free ends and have been demonstrated to be involved in tumorigenesis. CircTTBK2 is upregulated in glioma and functions as a master regulator of CPEB4 by sponging miR-217. Knockdown of circTTBK2 promoted erastin-induced ferroptosis accompanied with an increase in the intracellular concentrations of ROS, iron and ferrous iron by competing with miR-217 for CBS in glioma cells (66).

NcRNA related modulators of ferroptosis. Iron metabolism (Table III), lipid metabolism (Table IV) and antioxidant metabolism (Table V) are basic functions in the ferroptotic process, and they serve a vital role in ferroptosis. The primary modulators of iron, lipid and antioxidant metabolism-related genes are also involved in regulating the process of ferroptosis and act as ferroptotic markers. Therefore, these metabolism-related ncRNAs may also be involved in regulating the process of ferroptosis.

Iron metabolism. Previous studies have demonstrated that cellular iron overload causes ferroptosis. TfR1 is a critical transporter involved in iron uptake and a specific ferroptosis

Table II. Summary of non-coding RNAs involved in ferroptosis.

A, MicroRNA

First author, year	Modulatory effect	Cell lines	(Refs.)
Zhang *et al*, 2018	Decreases lipid peroxidation and inhibits erastin- and RSL3-induced ferroptosis	A375, G-361	(57)
Wang *et al*, 2019	Promotes ferroptosis by regulate CBS expression	ADC, A549, SPC-A-1, PC9	(58)
Luo *et al*, 2018	Suppresses erastin- and RSL3-induced ferroptosis by repression of SLC1A5 expression	A375, G-361	(59)
Gomaa *et al*, 2019	Overexpression confers resistance to ferroptosis by promoting of GPX4	STKM2, MKN45, OE33	(60)
Niu *et al*, 2019	Promotes PG-induced ferroptosis by suppressing GLS2 expression	MGC-803, MKN-45	(61)
Tomita *et al*, 2019	Decreases mitoferrin and overexpression sensitizes to ferroptosis induced by radiation	HeLa, SAS	(62)
Qin *et al*, 2010	Induces SLC7A11 expression and inhibits ferroptosis induced by oxidative stress	RAW	(63)
Xiao *et al*, 2019	Suppresses erastin-induced ferroptosis by repression of ACSL4 expression	HUVECs	(64)
Bai *et al*, 2020	Overexpression sensitizes to erastin-induced ferroptosis by directly target ATF4	HepG2, Hep3B	(65)
Zhang *et al*, 2020	Overexpression sensitizes to erastin-induced ferroptosis by directly target ITGB8	LN229, U251	(66)

B, Long non-coding RNA

First author, year	Modulatory effect	Cell lines	(Refs.)
Mao *et al*, 2018	Knockdown suppresses erastin-induced ferroptosis	SPCA1, H522, A549	(67)
Wang *et al*, 2019	Overexpression suppresses erastin- and RSL3-induced ferroptosis by repression of CBS expression	ADC, A549, SPC-A-1, PC9	(58)
Qi *et al*, 2019	Knockdown sensitizes to erastin-induced ferroptosis by downregulating of GABPB1	HepG2, Huh7, Hep3B	(68)

C, Circular RNA

First author, year	Modulatory effect	Cell lines	(Refs.)
Zhang *et al*, 2020	Knockdown sensitizes to erastin-induced ferroptosis by directly target ITGB8	LN229, U251	(66)

marker, which imports Tf-iron from the extracellular environment into cells, contributing to the cellular iron pool required for ferroptosis (32). miR-320 (69), miR-107 (70), miR-148a (71), miR-7-5p/miR-141-3p (72), miR-152 (73) and miR-210 (74) are all involved in suppression of TfR1 by directly targeting TfR1. Therefore, it has been reasonably shown that these miRNAs can suppress ferroptosis by targeting TfR1.

FTH1, a major intracellular iron storage protein, is an iron regulators involved in iron storage. Expression levels of FTH1 are regulated by oncogenic RAS signaling, which controls the cellular iron pool and ferroptosis sensitivity in tumor cells (51). FTH1 is regulated by NRF2 in ferroptosis, knockdown of FTH1 enhances erastin or sorafenib-induced ferroptosis sensitivity in hepatocellular carcinoma, suggesting that reduced iron storage may contribute to cellular iron overload causing ferroptosis and that FTH1 may serve as a specific marker of ferroptosis marker as well (54). miR-200b is involved in the repression of FTH1 by directly targeting FTH1, which transforms H_2O_2 and O_2 into the reactive •OH radical, thus inducing tumor cell death (75). Oncogenic miR-638 and miR-362 have been identified as targets of FTH1 transcript or multiple FTH1 pseudogenes by an unbiased screen in prostate cancer (76). lncRNA H19 is the

Table III. Summary of primary modulators of iron metabolism-related ncRNAs involved in ferroptosis.

First author, year	Gene	Function	ncRNA	Modulatory effect	(Refs.)
Schaar *et al*, 2009	TfR1	Cellular transferrin-iron uptake	miR-320	Suppresses the expression of TfR1 directly	(69)
Fu *et al*, 2019			miR-107		(70)
Babu *et al*, 2019			miR-148a		(71)
Miyazawa *et al*, 2018			miR-7-5p, miR-141-3p		(72)
Kindrat *et al*, 2016			miR-152		(73)
Yoshioka *et al*, 2012			miR-210		(74)
Xu *et al*, 2015	FTH1	Subunit of major intracellular iron storage protein	miR-200b	Suppresses the expression of FTH1 directly	(75)
Chan *et al*, 2018			miR-638, miR-362		(76)
Di Sanzo *et al*, 2018			miR-675		(77)
Di Sanzo *et al*, 2018			H19	The pre-miRNA template for the miR-675 and suppresses the expression of FTH1 by miR-675	(77)
Ripa *et al*, 2017 Zhang *et al*, 2017	IREB2	Regulates iron levels in the cells by regulating the translation and stability of mRNAs that affect iron homeostasis	miR-29	Suppresses the expression of IREB2 directly	(78,79)
Liu *et al*, 2019			miR-935		(80)
Andolfo *et al*, 2010	DMT1	Metal-iron transporter that is involved in iron	miR-Let-7d	Suppresses the expression of DMT1 directly	(81)
Jiang *et al*, 2019		Absorption and use	miR-16, miR-195, miR-497, miR-15b		(82)

ncRNA, non-coding RNA; miR, microRNA; TfR1, transferrin receptor 1; FTH1, ferritin heavy chain 1; IREB2, iron response element binding protein 2; DMT1, divalent metal transporter 1.

pre-miRNA template of miR-675, and knockdown of FTH1 upregulates H19 expression and thus its cognate miR-675, and H19/miR-675 activation primarily contributes to altered iron metabolism induced by FTH1 silencing (77). Therefore, it has been reasonably confirmed that these miRNAs may suppress ferroptosis by targeting TfR1. Together, these studies have shown that these ncRNAs may be involved in regulating the process of ferroptosis through iron storage.

IREB2 is an intra-cellular iron metabolism RNA-binding protein which regulates the translation and the stability of iron homeostasis related genes. Knock down of IREB2 suppresses erastin-induced ferroptosis by amino acid/cystine deprivation (1). miR-29 regulates IREB2 directly, thus affecting both energy production and redox status of the cell (78). Furthermore, miR-29a-related genetic variants alter the expression of IREB2 and may modify the risk of lung cancer together with dietary iron intake (79). Oncogenic miR-935 is elevated in renal cell carcinoma, and miR-935 directly suppresses the transcription of IREB2 by binding to the 3'-UTRs of IREB2 (80). Therefore, these miRNAs may suppress ferroptosis by targeting IREB2.

DMT1 is a widely expressed key iron transporter located within the plasma membrane and membranes of lysosomes and endosomes, which enables the uptake of Fe^{2+} to the cytosol following iron endocytosis. DMT1 inhibitors were selected as a target in cancer stem cells by blocking lysosomal iron translocation, which leads to lysosomal iron accumulation, and thus production of ROS and induction of ferroptotic cell death (35). DMT1 is also involved in sulfasalazine-induced ferroptosis via activation of iron metabolism in breast cancer cells (36). miR-Let-7d binds to the 3'-UTR of DMT1-IRE decreasing its expression at both the mRNA and protein levels in K562 and HEL cells (81). miR-16 family members miR-16, miR-195, miR-497 and miR-15b have been shown to suppress intestinal DMT1 expression by targeting DMT1 3'-UTR in HCT116 cells (82). These miRNAs may be involved in ferroptosis by targeting DMT1.

Lipid metabolism. ACSL is expressed on the mitochondrial outer membrane and endoplasmic reticulum, where they catalyze fatty acids to form acyl-CoAs, which are lipid

Table IV. Summary of primary modulators of iron metabolism-related ncRNAs involved in ferroptosis.

First author, year	Gene	Function	ncRNA	Modulatory Effect	(Refs.)
Jiang *et al*, 2020	ACSL4	Converts free fatty acids into fatty acyl-CoAs	miR-34a-5p/miR-204-5p	Suppresses the expression of ACSL4 directly	(85)
Park *et al*, 2018			miR-141		(86)
Wu *et al*, 2018			miR-3595		(87)
Bai *et al*, 2017; Ooi J *et al*, 2017			miR-34a/c		(88,89)
Zhou *et al*, 2017			miR-548p		(90)
Cui *et al*, 2014			miR-205		(91)
Peng *et al*, 2013			miR-224-5p		(92)
Park *et al*, 2018			miR-19b-3p/miR-17-5p/miR-130a-3p/ miR-150-5p/miR-7a-5p/miR-144-3p/miR-16-5p		(93)
Jiang *et al*, 2020			NEAT1	Promotes the expression of ACSL4 by completing miR-34a-5p and miR-204-5p	(85)
Li *et al*, 2019	LOXs	Catalyzes the dioxygenation of polyunsaturated fatty acids in lipids	miR-18a/miR-203	Suppresses the expression of 15-LOX1 directly	(96)
Li *et al*, 2019			miR-17/miR-20a/miR-20b/miR-106a/ miR-106b/miR-93/miR-590-3p	Suppresses the expression of 15-LOX2 directly	(96)
Fredman *et al*, 2012			miR-219-2	Suppresses the expression of 15-LOX directly	(97)
Su *et al*, 2016			miR-674-5p	Suppresses the expression of 5-LOX directly	(98)
Wang *et al*, 2018			miR-216a-3p		(99)
Busch S *et al*, 2015			miR-19a-3p/miR-125b-5p		(100)
Xue *et al*, 2018; Min *et al*, 2018	GPX4	Lipid repair enzyme	miR-181a-5p	Decreases protein expression of GPX4 by targeting SBP2 or SECISBP2	(101,102)
Zhang *et al*, 2017	SCD1	Converts the saturated fatty acids palmitate and stearate to the monounsaturated fatty acids palmitoleate PMA and oleate	miR-27a	Suppresses the expression of SCD1 directly	(104)
Guo *et al*, 2017			miR-212-5p		(105)
Zhang *et al*, 2020			miR-103		(106)
Mysore *et al*, 2016			miR-192*		(107)
Zhang *et al*, 2016			miR-378		(108)
Guo *et al*, 2018			miR-4668		(109)

Table IV. Continued.

First author, year	Gene	Function	ncRNA	Modulatory Effect	(Refs.)
El *et al*, 2017			miR-600		(110)
Zhou *et al*, 2019			miR-Let-7c		(111)
Guo *et al*, 2018			uc.372	Promotes the expression of SCD1 by completing miR-4668	(109)
Zeng *et al*, 2016; Pinto *et al*, 2017	CS	Regulates the metabolism of mitochondrial fatty acid	miR-122/ miR-19	Suppresses the expression of SCD1 directly	(112,113)

ncRNA, non-coding RNA; miR, microRNA; ACSL4, acyl-CoA synthetase long-chain family member 4; GPX4, glutathione peroxidase 4; SCD1, stearoyl-CoA desaturase 1; CS, citrate synthase.

metabolic intermediates that facilitate fatty acid metabolism and membrane modifications (83). According to genome-wide recessive genetic screening, ACSL4 has been identified as an essential pro-ferroptotic gene and as a critical determinant of ferroptosis sensitivity by shaping cellular lipid composition (8). Another study also showed that ACSL4 is a biomarker and contributor of ferroptosis via ACSL4-mediated production of 5-hydroxyeicosatetraenoic acid (5-HETE) (84). miR-34a-5p/miR-204-5p (85), miR-141 (86), miR-3595 (87), miR-34a/c (88,89), miR-548p (90), miR-205 (91), miR-224-5p (92) and miR-19b-3p/miR-17-5p/miR-130a-3p/miR-150-5p/miR-7a-5p/miR-144-3p/miR-16-5p (93) can suppress the transcription of ACSL4. These miRNAs may inhibit ferroptosis by targeting ACSL4. In addition, a recent study reported that lncRNA NEAT1 promotes the transcription of ACSL4 by competing with miR-34a-5p and miR-204-5p, which may suppress ferroptosis (85).

LOXs are a family of iron-containing enzymes, including six LOX genes in humans; LOX5, LOX12, LOX12B, LOX15, LOX15B and LOXE3 (94). These genes can catalyze dioxygenation of PUFAs to produce fatty acid hydroperoxides in a stereospecific manner (94). Oxidation of PUFAs by LOXs had been implicated in erastin-induced ferroptosis (94). LOX15-driven enzymatic generation of lipid peroxidation is a hallmark of ferroptotic signals (95). In the miR-17 family, miR-18a and miR-203 bind to four sites of the 3'-UTR in 15-LOX1, and miR-17, miR-20a, miR-20b, miR-106a, miR-106b, miR-93 and miR-590-3p bind to four sites of the 3'-UTR of 15-LOX2 (96). Oncogenic miR-219-2 (97) directly targets the 3'-UTR of 15-LOX, whereas miR-674-5p (98), miR-216a-3p (99) and miR-19a-3p/miR-125b-5p (100) regulate 5-LOX through directly targeting the 3'-UTR of 5-LOX.

GPX4, unlike other members of the GPX family, serve a unique role in physiology; they catalyze the reduction of lipid peroxides in a complex cellular membrane environment. Overexpression or knockdown of GPX4 modulates the lethality of ferroptosis inducers, indicating that GPX4 is an essential regulator of ferroptotic cell death (52). miR-181a-5p decreases the expression of GPX4 by targeting SBP2 or SECISBP2 and reduces the ability to counter oxidation, which may promote ferroptosis (101,102).

Stearoyl-CoA desaturase 1 (SCD1) is a rate-limiting step catalytic enzyme in mono-unsaturated fatty acid (MUFA) synthesis that serves a central role in FA metabolism by converting the saturated fatty acids palmitate and stearate to the MUFAs palmitoleate (PMA) and oleate. SCD1, as an inhibitor of ferroptosis, serves an important role in the negative regulation of ferroptosis through the products of MUFAs (103). miR-27a (104), miR-212-5p (105), miR-103 (106), miR-192* (107), miR-378 (108), miR-4668 (109), miR-600 (110) and let-7c (111) significantly suppress the relative expression of SCD1 by directly binding to its 3'-UTR. Moreover, lncRNA uc.372 promotes the transcription of SCD1 by competing with miR-4668 (109).

Citrate synthases (CSs) are implicated in the regulation of mitochondrial fatty acid metabolism, which supply a specific lipid precursor necessary for ferroptotic cell death (1). Silencing CS suppresses erastin-induced ferroptosis (1). miR-122 suppresses the expression of mRNAs and proteins related to CS (112), whereas miR-19 only regulates the expression of

Table V. Summary of primary modulators of antioxidant metabolism-related ncRNAs involved in ferroptosis.

First author, year	Gene	Function	ncRNA	Modulatory Effect	(Refs.)
Luo *et al*, 2019; Zhao *et al*, 2019	Nrf2	Key regulator of anti-oxidant related genes expression	miR-675/miR-181	Suppresses Nrf2 signaling	(114,115)
Zhang *et al*, 2019			miR-302b-3p	Suppresses Nrf2 signaling by directly geting FGF15	(116)
Wu *et al*, 2018; Zhou *et al*, 2019			miR-141	Suppresses Nrf2 signaling by directly targeting Keap1	(117,118)
Reziwan *et al*, 2019			miR-1225		(119)
Duan *et al*, 2019			miR-25	Suppresses Nrf2 signaling by directly targeting KLF2	(120)
Zhao *et al*, 2019			miR-128-3p	Suppresses Nrf2 pathway by targeting Sirt1	(121)
Liu *et al*, 2019			miR-19b	Suppresses Nrf2 pathway by targeting SIRT1	(122)
Chen *et al*, 2019			miR-125b	Suppresses Nrf2 pathway by targeting PRXL2A	(123)
Ling *et al*, 2018			miR-494	Suppresses Nrf2 pathway by targeting NQO1	(134)
Gao *et al*, 2018			miR-365	Suppresses the expression of Nrf2 directly	(135)
Geng *et al*, 2018			miR-495	Activates Nrf2 signaling by directly targeting PSD-93	(126)
Wang *et al*, 2018			miR-136		(127)
Huang *et al*, 2018			miR-34a		(128)
Wu *et al*, 2019			miR-340-5p		(129)
Zhang *et al*, 2020			miR-125b		(130)
Qin *et al*, 2019; Dong *et al*, 2019			miR-101-3p		(131,132)
Chen *et al*, 2019			miR-155		(133)
Cai *et al*, 2019			miR-380-3p		(134)
Srinoun *et al*, 2019; Yin *et al*, 2018; Li *et al*, 2019			miR-144		(135-137)
Zhu *et al*, 2019			miR-153		(138)
Khadrawy *et al*, 2019			miR-28/ miR-708		(139)
Sun *et al*, 2019			miR-129-3p		(140)
Huang *et al*, 2019			miR-27b		(141)
Liu *et al*, 2019			miR-140-5p		(142)
Singh *et al*, 2013			miR-93		(143)
Chorley *et al*, 2012			miR-365-1/ miR-193b/ miR-29-b1		(144)
Zhang *et al*, 2019			miR-152-3p	Activates Nrf2 signaling by directly targeting PSD-93	(145)

Table V. Continued.

First author, year	Gene	Function	ncRNA	Modulatory Effect	(Refs.)
Kim *et al*, 2014			miR-101	Activates Nrf2 signaling by directly targeting Cul3	(146)
Xu *et al*, 2017			miR-455		(147)
Chen *et al*, 2019			miR-601		(148)
Kabaria *et al*, 2015			miR-7	Activates Nrf2 signaling by targeting Keap1	(149)
Eades *et al*, 2011			miR-200a		(150)
Wang *et al*, 2019			miR-873-5p		(151)
Xiao *et al*, 2018			miR-24-3p		(152)
Huang *et al*, 2019			miR-34b		(153)
Ding *et al*, 2019			miR-223		(154)
Li *et al*, 2019			miR-146b-5p	Activates Nrf2 signaling by targeting Brd4	(155)
Sun *et al*, 2018			miR-98-5p	Activates Nrf2 signaling by targeting Bach1	(156)
Feng *et al*, 2019			Blnc1	Activates Nrf2 signaling	(157)
Li *et al*, 2019; Fan *et al*, 2018; Chen *et al*, 2018; Amodio *et al*, 2018; Zeng *et al*, 2018			MALAT1		(158-162)
Joo *et al*, 2019			Nrf2-lncRNA		(163)
Liu *et al*, 2019			AK094457		(164)
Porsch *et al*, 2019			Linc01213		(165)
Xiao X *et al*, 2019			lncRNA 74.1		(166)
Gao *et al*, 2017			ODRUL		(167)
Dong *et al*, 2018			SNHG14	Activates Nrf2 signaling by directly targeting PABPC1	(168)
Geng *et al*, 2018			UCA1	Increases the expression of Nrf2 by miR-495	(126)
Luzon-Toro *et al*, 2019			LUCAT1	Increases the expression of Nrf2	(169)
Sun *et al*, 2019; Zhang *et al*, 2019; Gong *et al*, 2019			TUG1		(170-172)
Wu *et al*, 2017			Loc344887		(173)
Zheng *et al*, 2016			H19		(174)
Li *et al*, 2016			Mhrt		(175)
Zhou *et al*, 2015			MIAT		(176)
Yuan *et al*, 2015			MRAK052686		(177)
Zhao *et al*, 2015			AATBC		(178)
Zhang *et al*, 2015			HOTAIR		(179)

Table V. Continued.

First author, year	Gene	Function	ncRNA	Modulatory Effect	(Refs.)
Wu *et al*, 2019			NRAL	Activates the expression of Nrf2 by miR-340-5p	(129)
Luo *et al*, 2019			H19	Suppresses Nrf2 signaling	(114)
Li *et al*, 2017			Sox2OT		(180)
Gao *et al*, 2018			MT1DP	Activates the expression of Nrf2 by miR-365	(125)
Wang *et al*, 2018; Huang *et al*, 2018; Wang *et al*, 2017			MEG3	Activates the expression of Nrf2 by miR-136 or miR-34a	(127, 128, 181)
Wu *et al*, 2018			KRAL	Activates Nrf2 signaling by directly targeting Keap1	(117)
Li *et al*, 2020			circ4099	Activates Nrf2 signaling	(182)
Drayton *et al*, 2014	SLC7A11	Subunit of system Xc^- to import cystine	miR-27a	Suppresses the expression of SLC7A11 directly	(183)
Wu *et al*, 2017			miR-375		(184)
Liu *et al*, 2011			miR-26b		(185)
Luo *et al*, 2017			SLC7A11-AS1	Suppresses the expression of SLC7A11	(186)
Yuan *et al*, 2017			AS-SLC7A11		(187)
Xian *et al*, 2020	Keap1	Binds to and regulates Nrf2 by keeping its levels	miR-26b	Suppresses the expression of Keap1 directly	(190)
Li *et al*, 2020			miR-941		(191)
Jiang *et al*, 2020; Wang *et al*, 2020			miR-200a		(192,193)
Duan *et al*, 2019			miR-421		(194)
Xu *et al*, 2019			miR-626		(195)
Reziwan *et al*, 2019			miR-1225		(119)
Zhou *et al*, 2019			miR-141		(118)
Akdemir *et al*, 2017			miR-432		(196)
Amodio *et al*, 2018			MALAT1	Epigenetically regulates Keap1	(161)
Wu *et al*, 2018			KRAL	Activates Nrf2 signaling by completing with miR-141	(127)
Zhang *et al*, 2018; Wang *et al*, 2019	GOT1	Synthesis of a-ketoglutarate from glutamate	miR-9	Suppresses the expression of Keap1 directly	(57,198)

ncRNA, non-coding RNA; miR, microRNA; nuclear factor erythroid 2-related factor 2; Keap1, kelch-like ECH-associated protein 1.

proteins related to CS (113). Therefore, these ncRNAs have been implicated in promoting ferroptosis by targeting lipid metabolism-related genes.

Antioxidant metabolism. Nrf2 is a pivotal inhibitor of ferroptosis due to its ability to inhibit cellular iron uptake, limit ROS production, and upregulate SLC7A11 expression by regulating the Nrf2-targeted genes FTH1, HO-1 and NQO1. Certain miRNAs can directly or indirectly suppress the transcription of Nrf2 or Nrf2 signaling to promote ferroptosis. For example, miR-675 (114), miR-181 (115), miR-302b-3p (116), miR-141 (117,118), miR-1225 (119), miR-25 (120), miR-128-3p (121), miR-19b (122), miR-125b (123) and miR-494 (124) restrain Nrf2 signaling by targeting Nrf2-related genes. In contrast, miR-365 (125), miR-495 (126), miR-136 (127), miR-34a (128), miR-340-5p (129), miR-125b (130), miR-101-3p (131,132), miR-155 (133), miR-380-3p (134), miR-144 (135-137), miR-153 (138), miR-28/miR-708 (139), miR-129-3p (140), miR-27b (141), miR-140-5p (142), miR-93 (143) and miR-365-1/miR-193b/miR-29-b1 (144) have been shown to decrease Nrf2 levels through directly binding to the 3'-UTR of Nrf2. Additionally, certain miRNAs activate Nrf2 signaling via a variety of mechanisms, ultimately resulting in inhibition of ferroptosis. For example, miR-152-3p (145), miR-101 (146), miR-455 (147), miR-601 (148), miR-7 (149), miR-200a (150), miR-873-5p (151), miR-24-3p (152), miR-34b (153), miR-223 (154), miR-146b-5p (155) and miR-98-5p (156) activate Nrf2 signaling by targeting Nrf2-related genes. It is thus hypothesized that these miRNAs can regulate ferroptosis by targeting Nrf2, but this has not yet been demonstrated.

Emerging evidence has indicated that lncRNAs Blnc1 (157), MALAT1 (158-162), Nrf2-lncRNA (163), AK094457 (164), Linc01213 (165), lncRNA74.1 (166), ODRUL (167), SNHG14 (168), UCA1 (126), LUCAT1 (169), TUG1 (170-172), Loc344887 (173), H19 (174), Mhrt (175), MIAT (176), MRAK052686 (177), AATBC (178), HOTAIR (179), NRAL (129), H19 (114), Sox2OT (180), MT1DP (125), MEG3 (127,128,181) and KRAL (117) may activate Nrf2 signaling by targeting Nrf2-related genes. Furthermore, circRNA-4099 may activate Nrf2 signaling by targeting miR-706, which augments H_2O_2-induced cell damage in the $L0_2$ cells (182). Notably, these ncRNAs are involved in regulating ferroptosis and may be a potential target for cancer therapy.

SLC7A11, the subunit of cystine-glutamate antiporter, is a crucial mediator in the process of ferroptosis. Studies have shown that miR-27a (183), miR-375 (184) and miR-26b (185) directly suppress the transcription of SLC7A11 by binding to its 3'-UTR. Therefore, these miRNAs have been implicated in promoting ferroptosis by directly targeting SLC7A11. Furthermore, lncRNAs SLC7A11-AS1 (186) and AS-SLC7A11 (187), the antisense lncRNAs of SLC7A11, suppress the transcription of SLC7A11. Therefore, these two SLC7A11-antisense lncRNAs have been hypothesized to suppress ferroptosis by downregulating SLC7A11 levels.

Keap1 is a member of the BTB-kelch protein family, which are primarily located in the perinuclear region of the cytoplasm (188). Keap1 represses Nrf2 transcriptional activity, a transcriptional target of Keap1. Overexpression of Keap1 enhanced erastin- and RSL3-induced ferroptosis, while knockdown conferred resistance to ferroptosis (189). Studies have shown that overexpression of miR-7 (149), miR-873-5p (151), miR-24-3p (152), miR-34b (153), miR-223 (154), miR-26b (190), miR-941 (191), miR-200a (192,193), miRNA-421 (194), miR-626 (195), miR-1225 (119), miR-141 (118) and miR-432 (196) suppressed Keap1 3'-UTR expression and downregulated its mRNA and protein expression. Notably, lncRNA MALAT1 could epigenetically downregulate Keap1 expression (161). lncRNA KRAL functions as a ceRNA by effectively binding to miR-141 and then restoring Keap1 expression (117). These studies suggest that Keap1 related-ncRNAs are involved in the process of ferroptosis.

GOT1 is essential for cell sustaining proliferation and maintenance of redox homeostasis. Reduced GOT1 suppresses erastin-induced ferroptosis by amino acid/cystine deprivation (197). According to previous studies, both in pancreatic cancer and melanoma, miR-9-5p inhibited the expression of GOT1 by directly binding to its 3'-UTR, ultimately resulting in decreased proliferation, glutamine metabolism and redox homeostasis, which suppresses the process of ferroptosis (57,198).

Collectively, the modulators of ferroptotic markers are their related ncRNAs, which serve critical roles in the regulation of ferroptosis. As discussed above, ncRNAs possess tumor suppressor or oncogenic roles in the process of ferroptosis during the course of tumorigenesis and progression. Thus, targeting ncRNAs may be a viable strategy in the development of novel cancer treatments.

4. Therapeutic approaches for ncRNAs targeting ferroptosis in cancer

Ferroptosis likely inhibits tumor development and/or progression, thus inducing ferroptosis is a promising strategy for anticancer therapy. ncRNA expression patterns show specificity for specific tumor and tissue types, highlighting ncRNAs as potential therapeutic targets in cancer. With advances in biotechnologies, such as genome editing, high-throughput sequencing and nanotechnology, ncRNAs can be theoretically used as molecular targets for cancer therapy. Therefore, ncRNAs are considered as an emerging and viable candidates for precision medicine depending on its property of tissue-specific expression.

Thus far, among the annotated ncRNAs, miRNAs, lncRNAs and circRNAs are the most extensively investigated. They function as either oncogenes or tumor suppressors, which induce or inhibit ferroptosis by targeting their mRNAs, respectively. Previously, several preclinical studies have investigated RNA-guided precision medicine for cancer treatment (161,199-201). For example, miR-34a mimic-mediated tumor suppression was the first miRNA-based therapy to be used in the clinic (202). lncRNA MALAT1 with antisense oligonucleotide-conjugated nanostructure inhibited metastasis of lung cancer cells (203). In total, three strategies have been proposed for ncRNA-based therapy: i) ncRNA-guided nanoparticles, ii) ncRNA modification and iii) an oncolytic adenovirus strategy (204).

The methods described above are currently the most promising ncRNA-based treatment strategies for cancer. These

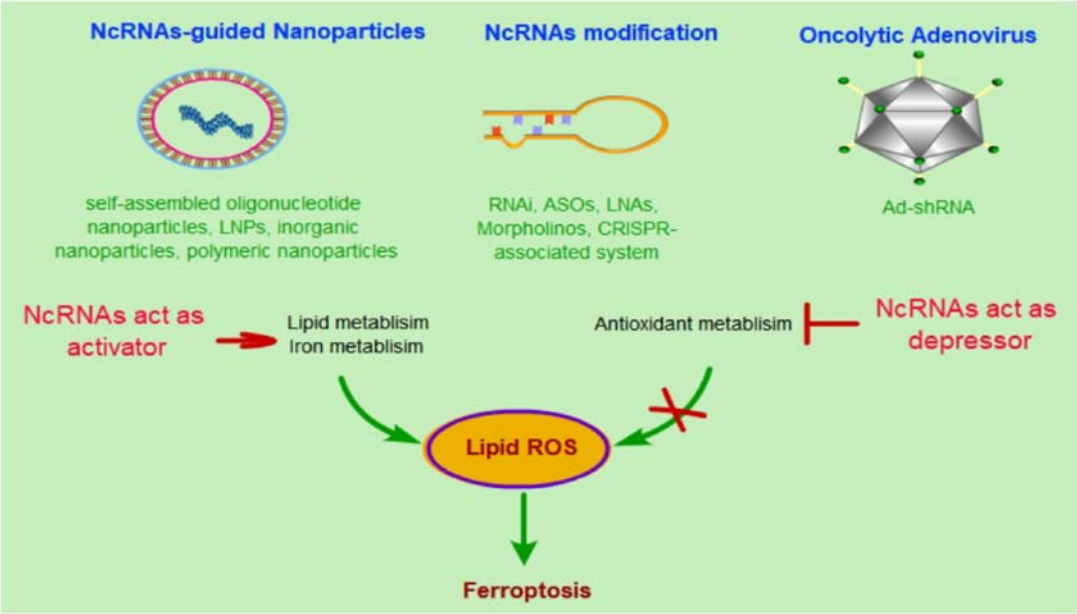

Figure 2. Therapeutic approaches for use of ncRNAs for targeting ferroptosis in cancer. In anticancer approaches, induction of the occurrence of ferroptosis by lipid ROS is the primary approach of ferroptosis based cancer therapy. Targeting ncRNA-related ferroptosis via activation of lipid and iron metabolism or suppression of antioxidant metabolism by ncRNA-guided nanoparticles, ncRNA modification or oncolytic adenovirus strategy. NcRNA-guided nanoparticles strategies primarily include self-assembled oligonucleotide nanoparticles, LNPs, inorganic nanoparticles, and polymeric nanoparticles; ncRNA modification strategies primarily include RNAi, ASOs, LNAs, Morpholinos and CRISPR-associated system; and oncolytic adenovirus strategies primarily includes the use of Ad-shRNA. LNPs, lipid-based nanoparticles; RNAi, double stranded RNA-mediated interference; ASOs, single stranded antisense oligonucleotides; LNAs, locked nucleic acids; Ad-shRNA, adenovirus-shRNA. ncRNA, non-coding RNA; ROS, reactive oxygen species.

therapeutic approaches can also be used in ncRNAs targeting ferroptosis for cancer treatment. Most of the ncRNAs regulate lipid ROS-related molecules and antioxidant metabolism-related molecules, which leads to increased tumor cell tolerance for relatively higher ROS levels and thus reduced possibility of initiating ferroptosis. At same time, high levels of cellular ROS promote tumor cell growth. To initiate ferroptotic cell death, stimulating ncRNAs need to activate lipid and iron metabolism or otherwise activate antioxidant metabolism, which in turn leads to an accumulation of cellular ROS and eventually cell death (Fig. 2). Thus, ncRNAs have been considered not only as therapeutic targets for cancer therapy, but also as potentially promising therapeutic tools for precision medicine. However, the majority of studies regarding the use of ncRNAs therapeutically are still in their early stages. Several problems need to be overcome before they can be used clinically, such as the off-target effects, short half-life, severe toxicity and low transfection efficiency in ncRNA guided strategies (204). A large number of further studies are still required.

5. Conclusions and future perspectives

Ferroptosis is a novel type of cell death with distinct functions intricately involved in numerous physiological processes and various diseases. Substantial progress in exploring the mechanisms of ferroptosis and understanding on how oncogenic states drive sensitivity to ferroptosis has been made. Collectively, these studies have demonstrated ferroptosis as a tumor suppressive mechanism that inhibits tumor growth and contributes to chemotherapy sensitivity, and that induction of ferroptosis is a viable anticancer therapeutic strategy, particularly for drug-resistant tumors.

However, cellular sensitivity to ferroptosis likely depends on the cell type and physiological conditions. What types of physiological processes are associated with ferroptosis? Under what context do cells benefit from ferroptotic cell death? Studies exploring the association between cancer and ferroptosis are still limited. Although several candidate primary markers of ferroptosis have been identified, and the pathways they target are known, several candidates fail to acquire their special cellular conditions and exhibit poor pharmacokinetics. A large number of recent studies have demonstrated that miRNAs, lncRNAs and circRNAs serve an important role in the process of ferroptosis, and that these ncRNAs may affect the regulation of ferroptosis in a cell type-dependent or tissue type-dependent manner. Due to the heterogeneity of gene expression on a per individual basis, ncRNA-based treatment strategies can be used for personalized cancer treatment and may eventually exhibit more specificity than ferroptosis-inducing drugs such as erastin, sulfasalazine and RSL3. Thus, targeting ncRNAs may at present be considered a prototypic intervention which has the potential to be superior in terms of precision compared with established anti-tumor drugs. Moreover, with the development of gene related technologies, ncRNAs constitute promising potential targets for gene therapy. However, a deeper understanding of the mechanisms by which ncRNAs regulate ferroptosis is still required, and tissue specific expression of ncRNAs and the variety of off-target effects are major challenges.

In summary, ncRNAs may serve as anticancer targets by regulating ferroptosis, which is a novel and promising means of treating drug-resistant cancer. Targeting key ncRNA-related ferroptotic molecules may create novel opportunities for gene therapy for the treatment of cancer.

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Authors' contributions

YL and QH wrote the manuscript. YL, QH, BH, YL and SH created the figures and tables. YL and JX conceived the topic of this review. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

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Competing interests

The authors declare that they have no competing interests.

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