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

YAJUN LUO1,2*, QINGMEI HUANG3*, BIN HE4, YILEI LIU2, SIQI HUANG1 and JIANGWEI XIAO2

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

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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

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; Fe2+, ferrous iron; Fe3+, ferric iron; TR1, 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, lipoxigenases; 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
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, 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 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_{2}O_{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 (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 TFR, 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,
| 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-    | Increased lysosomal  | 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) |
|                   |                         | membrane lysosomes     | activity for the    |               |                             |
|                   |                         |                        | degradation and     |               |                             |
|                   |                         |                        | recycling of        |               |                             |
|                   |                         |                        | damaged proteins and |               |                             |
|                   |                         |                        | organelles          |               |                             |
| Kerr et al, 1972  | Apoptosis (1972)        | Cell shrinkage, plasma | Activation of        | Caspase, P53, Fas, Bcl-2, Bax | Endoplasmic reticulum       |
|                   |                         | membrane blebbing,     | caspases,           |               | pathway; Caspase-, Death   |
|                   |                         | reduced cellular and    | exteriorization of   |               | receptor-, P53-, and       |
|                   |                         | nuclear volume,         | phosphatidylserine, |               | Bcl-2-mediated signaling    |
|                   |                         | nuclear fragmentation,  | oligonucleosomal DNA|               | pathways                   |
|                   |                         | chromatin margination   | fragmentation       |               |                             |
| Cookson et al, 2001 | Pyroptosis (2001)      | Cell swelling and the   | Proinflammatory      | GSDMD, Caspase-1, IL-1β, IL-18 | Caspase-1 and               |
|                   |                         | formation of large      | cytokine releases,   |               | NLRP3-mediated signaling    |
|                   |                         | bubbles from the       | inflammatory         |               | pathways                   |
|                   |                         | plasma membrane,        | caspases            |               |                             |
|                   |                         | karyopyknosis           |                    |               |                             |
| Degterev et al, 2005 | Necroptosis (2005)     | Rapid swelling of cells | Proinflammatory      | TNFR1, RIPK1, TRADD, LEF1, RIP1, RIP3 | RIPC1/3-, MLKL-, TNFα-,     |
|                   |                         | and organelles, plasma  | Response; decreased  |               | TFR1-, TLR3-, TRAIL-,      |
|                   |                         | membrane rupture,       | ATP levels;         |               | - and PKC-MAPK-AP-1-       |
|                   |                         | moderate chromatin      | activation of RIP1,  |               | mediated signaling pathways|
|                   |                         | condensation            | RIP3, and MLKL      |               |                             |
| 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 cristal or loss of mitochondria cristal, 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.
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 physiological 8-O-β-glucopyranoside-induced ferroptosis by increasing intracellular Fe²⁺ 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 Fe²⁺, 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 sensitize 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).

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

IncRNA 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). IncRNA 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). IncRNA GABPB1-AS1 is an antisense IncRNA 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 as well (54). 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). IncRNA H19 is the
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\(^{3+}\) 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-CoA, which are lipid

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**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   | 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) |
| Zhang et al, 2017  |      |          |       |                    |        |
| Liu et al, 2019    |      |          | miR-935 |                    | (80)   |
| Andolfo et al, 2010 | DMT1 | Metal-iron transporter that is involved in iron absorption and use | miR-Let-7d | Suppresses the expression of DMT1 directly | (81) |
| Jiang et al, 2019  |      |          | miR-16, miR-195, miR-497, miR-15b | | (82) |

cRNA, 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.
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 | Promotes the expression of ACSL4 by completing miR-34a-5p and miR-204-5p | (93) |
| Jiang et al, 2020  |      |          | NEAT1 |                    | (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 |                    | (97) |
| Su et al, 2016     |      |          | miR-674-5p |                    | (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) |
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-7a-5p/miR-150-5p/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 IncRNA 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-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, serves 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 monounsaturated fatty acid (MUFA) synthesis that serves a central role in FA metabolism by converting the saturated fatty acids palmitate and stearate to the MUFA palmitoleate (PMA) and oleate. SCD1, as an inhibitor of ferroptosis, serves an important role in the negative regulation of ferroptosis through the products of MUFA (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, IncRNA 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 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-7a-5p/miR-150-5p/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 IncRNA NEAT1 promotes the transcription of ACSL4 by competing with miR-34a-5p and miR-204-5p, which may suppress ferroptosis (85).

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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 getting 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) |
| Khadrzy 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-IncRNA|         |                       |                                                             | (163)   |
| Liu et al, 2019    | AK094457 |          |                       |                                                             | (164)   |
| Porsch et al, 2019 | Linc01213|          |                       |                                                             | (165)   |
| Xiao X et al, 2019 | IncRNA 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; Hu | MEG3 |          |       | Activates the expression of Nrf2 by miR-136 or    | (127, 128, 181) |
|                     |      |          |       | miR-34a                                          |        |
| 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)  |
| Rezewan 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-757 (114), miR-181 (115), miR-302b-3p (116), miR-141 (117), 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, 136), miR-153 (137), miR-28 (138), 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 direct 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-146b-5p (154), and miR-98-5p (155) 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 IncRNAs Blnc1 (157), MALAT1 (158-162), Nrf2-ncRNA (163), AK094457 (164), Linc01213 (165), IncRNA74.1 (166), ODRUL (167), SNHG14 (168), UCA1 (169), LUCAT1 (169), TUG1 (170-172), LOC344887 (173), H19 (174), Mhrt (175), MIAT (176), MRAK052686 (177), ATB (178), HOTAIR (179), NRAL (180), Sox2OT (181), LINC00016 (182), H19 (183), Mhrt (184), MT1DP (185), MEG3 (186), and KRAL (187) may be involved in the regulation of ferroptosis. 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, IncRNAs 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). IncRNA 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
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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Competing interests
The authors declare that they have no competing interests.

References
1. Dixon SJ, Lemberg KM, Lamprecht MR, Skouta R, Zaitsev EM, Gleason CE, Patel DN, Bauer AJ, Cantley AM, Yang WS, et al: Ferroptosis: An iron-dependent form of nonapoptotic cell death. Cell 149: 1060-1072, 2012.
2. Yagoda N, von Rechenberg M, Zaganjor E, Bauer AJ, Yang WS, Patzke G, Zaitsev EM, Skouta R, Lemberg KM, Lamprecht MR, et al: Identification of a ferrireductase required for ferroptosis in the family of regulated cell death. Cell Death Differ 26: 150-157, 2017.
3. Badgley MA, Kremer DM, Maurer HC, DelGiorne KE, Lee HJ, Purohit V, Sagalovskiy IR, Ma A, Kapilian J, Firl CEM, et al: Cysteine depletion induces pancreatic tumor ferroptosis in mice. Science 368: 85-89, 2020.
4. Trachootham D, Alexandre J and Huang P: Targeting cancer cells by ROS-mediated mechanisms: A radical therapeutic approach? Nat Rev Drug Discov 8: 579-591, 2009.
5. Altamura S, Marques O, Colucci S, Mertens C, Alihankan Y and Muckenthaler MU: Regulation of iron homeostasis: Lessons from mouse models. Mol Aspects Med 75: 100872, 2020.
6. Koppenol WH and Hider RC: Iron and redox cycling. Do's and don'ts. Free Radic Biol Med 133: 3-10, 2019.
7. Kajarabille N and Latunde-Dada GO: Programmed cell-death by ferroptosis: Antioxidants as mitigators. Int J Mol Sci 20: 4968, 2019.
8. Frazer DM and Anderson GJ: The regulation of iron transport. Biofactors 40: 206-214, 2014.
9. El Hage Chahine JM, Hemadi M and Ha-Duong NT: Uptake and release of metal ions by transferrin and interaction with receptor 1. Biochim Biophys Acta 1820: 334-347, 2012.
10. Wang N, Zeng GZ, Yin JL and Bian ZX: Artesunate activates the ATF4-CHOP-CHAC1 pathway and affects ferroptosis in Burkitt's Lymphoma. Biochem Biophys Res Commun 519: 533-539, 2019.
11. Wang C, Shi M, Ji J, Cai Q, Zhao Q, Jiang J, Liu J, Zhang H, ZHU Z and Zhang J: Stearoyl-CoA desaturase 1 (SCD1) facilitates the growth and anti-ferroptosis of gastric cancer cells and predicts poor prognosis of gastric cancer. Aging (Albany NY) 12: 15374-15391, 2020.
12. Liu P, Wu D, Duan J, Xiao H, Zhou Y, Zhao L and Feng Y: NRF2 regulates the sensitivity of human NSCLC cells to cysteine deprivation-induced ferroptosis via FOCD-AK signaling pathway. Redox Biol 37: 101702, 2020.
13. Zhang Y, Fu X, Jia J, Wikerholm T, Xi K, Kong Y, Wang J, Chen H, Ma Y, Li Z, et al: Glioblastoma therapy using co-delivery of cisplatin and glutathione peroxidase targeting siRNA from iron oxide nanoparticles. ACS Appl Mater Interfaces 12: 43408-43421, 2020.
14. Sharma P, Shimura T, Banwait JK and Goel A: Andrographis-mediated chemosensitization through activation of ferroptosis and suppression of β-catenin/Wnt-signaling pathways in colorectal cancer. Carcinogenesis 41: 1385-1394, 2020.
15. Fanzani A and Poli M: Iron: Oxidative damage and ferroptosis in rhabdomyosarcoma. Int J Mol Sci 18: 1718, 2017.
16. Mou Y, Wang J, Wu J, He D, Zhang C, Duan C and Li B: Ferroptosis, a new form of cell death: Opportunities and challenges in cancer. J Hematol Oncol 12: 34, 2019.
17. Fearnhead HO, Vandenabeele P and Vanden Berghe T: How do we fit ferroptosis in the family of regulated cell death? Cell Death Differ 24: 1991-1998, 2017.
18. Harris ZL, Durley AP, Man TK and Gitlin JD: Characterization, measurement, and participation in cellular functions of iron regulatory proteins in iron homeostasis -an update. Int J Mol Sci 16: 1180-1191, 2014.
19. Andrographis -mediated chemosensitization through activation of ferroptosis and suppression of β-catenin/Wnt-signaling pathways in colorectal cancer. Cell Rep 30: 3411-3423.e7, 2020.
20. Wang N, Zeng GZ, Yin JL and Bian ZX: Artesunate activates the ATF4-CHOP-CHAC1 pathway and affects ferroptosis in Burkitt's Lymphoma. Biochem Biophys Res Commun 519: 533-539, 2019.
21. Wang C, Shi M, Ji J, Cai Q, Zhao Q, Jiang J, Liu J, Zhang H, ZHU Z and Zhang J: Stearoyl-CoA desaturase 1 (SCD1) facilitates the growth and anti-ferroptosis of gastric cancer cells and predicts poor prognosis of gastric cancer. Aging (Albany NY) 12: 15374-15391, 2020.
22. Liu P, Wu D, Duan J, Xiao H, Zhou Y, Zhao L and Feng Y: NRF2 regulates the sensitivity of human NSCLC cells to cysteine deprivation-induced ferroptosis via FOCD-AK signaling pathway. Redox Biol 37: 101702, 2020.
23. Zhang Y, Fu X, Jia J, Wikerholm T, Xi K, Kong Y, Wang J, Chen H, Ma Y, Li Z, et al: Glioblastoma therapy using co-delivery of cisplatin and glutathione peroxidase targeting siRNA from iron oxide nanoparticles. ACS Appl Mater Interfaces 12: 43408-43421, 2020.
34. Ye F, Chai W, Xie M, Yang M, Yu Y, Cao L and Yang L: HMGBl regulates erastin-induced ferroptosis via RAS-JNK/p38 signaling in HL-60/NSA4031 cells. Am J Cancer Res 7: 730-739, 2019.

35. Turcu AL, Versini A, Khene N, Gaillet C, Cañéque T, Müller S and Rojo de la Vega M: miR-137 regulates ferroptosis induced by sorafenib in human hepatocellular carcinoma cells. Cancer Lett 536: 971-981, 2021.

36. Zhang K, Wang L, Zhang P, Luo M, Du J, Gao T, O'Connell D, Wang G, Wang H and Yang Y: miR-9 regulates ferroptosis by targeting glutamic-oxaloacetic transaminase GOT1 in mela-noma. Mol Cancer 57: 1566-1576, 2018.

37. Wang M, Mao C, Ouyang L, Liu Y, Liu L, Liu N, Shi Y, Chen L, Xiao D, Yu F, et al: Long noncoding RNA LINCO0336 inhibits ferroptosis in lung cancer by functioning as a competing endog-uous RNA. Cell Death Differ 26: 2329-2343, 2019.

38. Luo M, Wu L, Zhang K, Wang H, Zhang T, Gutierrez L, O'Connell D, Zhang P, Li Y, Gao T, et al: miR-137 regulates ferroptosis by targeting glutamine transporter SLC1A5 in mela-noma. Cell Death Differ 25: 1457-1472, 2018.

39. Gomaa A, Peng D, Chen Z, Sotto M, Abebelez K, Corvalan A and El-Rifai W: Epigenetic regulation of AURKA by miR-4715-3p in upper gastrointestinal cancers. Sci Rep 9: 16970, 2019.

40. Niu Y, Zhang J, Tong Y, Li J and Liu B: Physcion 8-O-β-glucopyranoside induced ferroptosis via regulating miR-103a-3p/GLS2 axis in gastric cancer. Life Sci 237: 116893, 2019.

41. Yu K, Fukumoto M, Itoh K, Kuwahara Y, Igarashi K, Nagasawa T, Suzuki M, Kurimasa A and Sato T: miR-7-5p is a key factor that controls radioresistance via intracellular Fe²⁺ content in clinically relevant radiosensitive. Biochem Biophys Res Comm 515: 712-719, 2019.

42. Qin Z, Freitas E, Sullivan R, Mohan S, Bacceli e R, Brand D, Romano M, Keary F, Oates J, Plaisance K, et al: Upregulation of xCT by KSHV-encoded microRNAs facilitates KSHV dissemination and persistence in an environment of oxidative stress. PLoS Pathog 6: e1000742, 2010.

43. Xiao FJ, Zhang D, Wu Y, Jia QH, Zhang L, Yang YF, Wang H, Wu CT and Wang LS: miRNA-17-92 protects endothel-i al cells from erastin-induced ferroptosis through targeting the A20-ACSL4 axis. Biochem Biophys Res Comm 515: 448-454, 2019.

44. Bai T, Liang R, Zhu R, Wang W, Zhou L and Sun Y: MicroRNA-214-3p enhances erastin-induced ferroptosis by targeting ATP4 in hepatoma cells. J Cell Physiol 235: 5657-5648, 2020.

45. Zhang HY, Zhang BW, Zhang ZB and Deng QJ: Circular RNA TTBK2 regulates cell proliferation, invasion and ferroptosis via miR-701-1TBG8 axis in glioma. Eur Rev Med Pharmacol Sci 24: 2585-2600, 2020.

46. Mao C, Wang X, Liu Y, Wang M, Yan B, Jiang Y, Shi Y, Shen Y, Liu X, Lai W, et al: A G3BP1-interacting IncRNA promotes ferroptosis and apoptosis in cancer via nuclear sequestration of p53. Cancer Res 78: 3484-3496, 2018.

47. Mao G, Qu F, Angeli JP, Doll S, Croix CS, Dar HH, Wu L, Zhang K, Wang H, Zhang T, Gutiérrez L, O’Connell D, Zhang P, Li Y, Gao T, et al: miR-137 regulates ferroptosis by targeting glutamine transporter SLC1A5 in melanoma. Cell Death Differ 25: 1457-1472, 2018.

48. Schaar DG, O’Connell D, Zhang P, Li Y, Gao T, et al: miR-761/ITGB8 axis in glioma. Eur Rev Med Pharmacol Sci 24: 5679-5680, 2020.

49. Xiao FJ, Zhang D, Wu Y, Jia QH, Zhang L, Yang YF, Wang H, Wu CT and Wang LS: miRNA-17-92 protects endothelial cells from erastin-induced ferroptosis through targeting the A20-ACSL4 axis. Biochem Biophys Res Comm 515: 448-454, 2019.

50. Bai T, Liang R, Zhu R, Wang W, Zhou L and Sun Y: MicroRNA-214-3p enhances erastin-induced ferroptosis by targeting ATP4 in hepatoma cells. J Cell Physiol 235: 5657-5648, 2020.

51. Schaar DG, Medina DJ, Moore DF, Strair RK and Ting Y: miR-320 targets transferrin receptor 1 (CD71) and inhibits cell proliferation. Exp Hematol 37: 245-255, 2009.

52. Schaar DG, O’Connell D, Zhang P, Li Y, Gao T, et al: miR-761/ITGB8 axis in glioma. Eur Rev Med Pharmacol Sci 24: 5679-5680, 2020.

53. Xiao FJ, Zhang D, Wu Y, Jia QH, Zhang L, Yang YF, Wang H, Wu CT and Wang LS: miRNA-17-92 protects endothelial cells from erastin-induced ferroptosis through targeting the A20-ACSL4 axis. Biochem Biophys Res Comm 515: 448-454, 2019.

54. Bai T, Liang R, Zhu R, Wang W, Zhou L and Sun Y: MicroRNA-214-3p enhances erastin-induced ferroptosis by targeting ATP4 in hepatoma cells. J Cell Physiol 235: 5657-5648, 2020.

55. Luo F and Liu S: Sulfasalazine-induced ferroptosis in breast cancer cells is reduced by the inhibitory effect of estrogen receptor on the transferrin receptor. Oncol Rep 42: 826-839, 2019.

56. Wu L, Zhang K, Wang H, Zhang T, Gutierrez L, O’Connell D, Zhang P, Li Y, Gao T, et al: miR-137 regulates ferroptosis by targeting glutamine transporter SLC1A5 in melanoma. Cell Death Differ 25: 1457-1472, 2018.

57. Groisman E, Gabsider G, Doz F, de la Rose-Farfan H, Shibata Y, Schreiber SL and Munoz B: Development of small-molecule inhibitors of the kinase CSNK1D. Nature 500: 535-539, 2013.

58. Deng Z, Zhou H, Liu Z, Wei X, Zhu W and Zhang L: LncRNA GABPB1-AS1 and GABPB1 regulate oxidative stress during cancer cell death. J Cell Biochem 169: 173-184, 2016.

59. Yoshio Y, Kosaka N, Ochiya T and Kato T: Micromanaging iron homeostasis: Hypoxia-inducible microRNA-210 suppresses iron homeostasis-related proteins. J Biol Chem 287: 34110-34119, 2012.

60. Xue D, Liu D, Wang B, Chen C, Chen Z, Li D, Yang Y, Chen H and Kong MG: In Situ OH Generation from O₂⁻ and H₂O₂ plays a critical role in plasma-induced cell death. PLoS One 10: e0128205, 2015.
76. Chan JJ, Kwok ZH, Chew XH, Zhang B, Liu C, Soong TW, Yang H and Tay YH: A FTH1 gene-pseudogene: microRNA network regulates tumorigenesis in prostate cancer. Nucleic Acids Res 47: 1-13, 2019.

77. Di Bazzano M, Chirollo R, Aversa I, Biamonte F, Santamaria G, Giovannone ED, Faniello MC, Cuda G and Costanzo F: shRNA targeting of ferritin heavy chain activates H19/miR-675 axis in K562 cells. shRNA 65: 97-99, 2018.

78. Ripa K, Doli L, Terrigno M, Pandolfini L, Savino A, Arducci V, Groth M, Toncelli Fozzini E, Baumgart M and Cellerino A: MicroRNA miR-29 controls a compensatory response to limit neuronal iron accumulation during adult life and ageing. BMC Biol 15: 9, 2017.

79. Zhang L, Ye Y, Tu H, Hildebrandt MA, Zhao L, Heymach J, Roth JA et al: MicroRNA-17 regulated genetic variants in iron regulatory genes, dietary iron intake, microRNAs and lung cancer risk. Ann Oncol 28: 1124-1129, 2017.

80. Liu F, Chen Y, Chen B, Liu X and Ding J: miR-935 promotes clear cell renal cell carcinoma migration and invasion by targeting IREB2. Cancer Manag Res 11: 10891-10900, 2019.

81. Andolfo I, De Falco L, Asci R, Russo R, Colucci S, Greorese M, Zollo M and Iolascon A: Regulation of divalent metal transporter 1 (DMT1) non-IRE isoform by the microRNA Let-7d in erythroid cells. Haematologica 95: 1244-1252, 2010.

82. Jiang S, Guo S, Li H, Ni Y, Ma W and Zhao R: Identification and functional characterization of a family of microRNA-16 family targeting intestinal divalent metal transporter 1 (DMT1) in vitro and in vivo. Front Physiol 10: 819, 2019.

83. Soupene E and Kuypers FA: Mammalian long-chain acyl-CoA synthetases. Exp Biol Med (Maywood) 233: 507-521, 2008.

84. Yuan H, Wang X, Wang G, Sun Z and Zhang J: Identification of ACSL4 as a biomarker and contributor of ferroptosis. Biochem Biophys Res Commun 478: 1338-1343, 2018.

85. Jiang X, Guo S, Zhang Y, Zhao Y, Li X, Jia Y, Xu Y and Ma B: IncRNA NEAT1 promotes docetaxel resistance in prostate cancer by regulating ACSS4 via sponging miR-34a-5p and miR-204-5p. Cell Signal 65: 109422, 2020.

86. Park S, Oh J, Kim YI, Choe SK, Chun CH and Jin EJ: Suppression of ABCD2 dysregulates lipid metabolism via dysregulation of miR-141:ACSL4 in human osteoarthritis. Cell Biochem Funct 36: 366-376, 2018.

87. Wu X, Zhi F, Lun W, Deng Q and Zhang W: Baicalin inhibits 15-lipoxygenases to promote lung carcinogenesis. J Exp Clin Cancer Res 38: 359, 2019.

88. Frendedt G, Li Y, Dalil J, Chiang N and Serhan CN: Self-limited versus delayed resolution of acute inflammation: Temporal regulation of pro-resolving mediators and microRNA. Sci Rep 2: 4602, 2012.

89. Su K, Wang Q, Qi L, Hua D, Tao J, Mangan CJ, Lou Y and Li M: MicroRNA-674-5p/5-LO axis involved in autoimmune reaction of Concanavalin A-induced acute liver injury. Toxicol Lett 258: 101-107, 2016.

90. Wang D, Li Y, Zhang C, Li X and Yu J: miR-216a-3p inhibits colorectal cancer cell proliferation through direct targeting COX-2 and ALOX5. J Cell Biochem 119: 1755-1766, 2018.

91. Busch S, Auth E, Scholl F, Huneke C, Koehl U, Suess B and Steinhilber D: S-5-LOxxygenase is a direct target of miR-19a-3p and miR-125b-5p. J Immunol 194: 1646-1653, 2015.

92. Xue J, Min Z, Xu T, Sheng G, Lan B, Zhang F, Han Y, Wang K and Sun J: The hsa-miR-181a-5p reduces oxygen resistance by controlling SECSIBP2 in osteoarthritics. BMC Musculoskelet Disord 19: 355, 2018.

93. Min Z, Guo Y, Sun M, Hussain S, Zhao Y, Guo D, Huang H, Meng L, Zhang F, Ning Q, et al: Selenium-sensitive microRNA-181a-5p targets SBP2 regulates selenoproteins expression in cartilage. J Cell Mol Med 22: 5888-5898, 2018.

94. Ooi J, Bernardo BC, Singla S, Patterson NL, Lin RCY and Tordjman J: miR-600 acts as a hepatic hypoxia biomarker. Am J Physiol Lung Cell Mol Physiol 313: E335-E343, 2017.

95. Yang WS, Groth M, Terzibasi Tozzini E, Baumgart M and Cellerino A: Regulation of divalent metal transporter 1 (DMT1) non-IRE isoform by the microRNA Let-7d in erythroid cells. Haematologica 95: 1244-1252, 2010.

96. Yi M, Luan W, Xia Z, Cheng B, Lan B, Zhang F, Han Y, Wang K and Sun J: The hsa-miR-181a-5p reduces oxygen resistance by controlling SECSIBP2 in osteoarthritics. BMC Musculoskelet Disord 19: 355, 2018.

97. Myint Z, Guo Y, Sun M, Hussain S, Zhao Y, Guo D, Huang H, Meng L, Zhang F, Ning Q, et al: Selenium-sensitive microRNA-181a-5p targets SBP2 regulates selenoproteins expression in cartilage. J Cell Mol Med 22: 5888-5898, 2018.

98. Konstorum A, Tesfay L, Paul BT, Torti FM, Laubenbacher RC and Torti SV: Systems biology of ferroptosis: A modeling approach. J Theor Biol 493: 112222, 2020.

99. Zhang M, Sun W, Zhang J and Tang Y: MicroRNA-27 regulates hepatic lipid metabolism and alleviates NAFLD via repressing FAS and SCD1. Cell Rep 7: 14493, 2017.

100. Guo Y, Yu J, Wang C, Li K, Liu B, Du Y, Xiao F, Chen S and Guo F: miR-212-5p suppresses lipid accumulation by targeting FAS and SCD1. J Cell Mol Med 19: 905-217, 2015.

101. Zhang M, Tang Y, Tang E and Lu W: MicroRNA-103 suppresses hepatic de novo lipogenesis and alleviates NAFLD via targeting FASN and SCD1. Biochem Biophys Res Commun 524: 716-722, 2020.

102. Myint Z, Zhou Y, Sadevita S, Savolainen-Peltanon H, Nidhina Haridas PA, Soronen J, Leivonen M, Sarin AP, Fischer-Posovszky P, Wabitsch M, et al: MicroRNA-192* impairs adipocyte triglyceride storage. Biochim Biophys Acta 1861: 345-351, 2016.

103. Zhang Y, Li C, Li H, Song Y, Zhao Z, Li Z, Wang H, Zhong R, Tang H and Zhu D: miR-378 activates the pyruvate-PEP futile cycle and enhances lipolysis to ameliorate obesity in mice. Ebiomedicine 5: 93-104, 2016.

104. Guo J, Fang W, Sun L, Yu D, Lou Y, Huang X, Tang W, Yu L and Li J: Ultraconserved element uc.372 drives hepatic lipid accumulation by suppressing miR-195/miR4668 maturation. Nat Commun 9: 45, 2018.

105. El Helou R, Pinna G, Cabaud O, Wicinski J, Bhajun R, Guyon L, Rioulain C, Finetti P, Gros A, Mari B, et al: miR-600 acts as a bimodal switch that regulates breast cancer stem cell fate through the miR-20a cluster. Cell Rep 18: 2226-2236, 2017.

106. Zhou Z, Lu Y, Wang Y, Du L, Zhang Y and Tao J: Let-7c regulates proliferation and osteodifferentiation of human adipose-derived mesenchymal stem cells under oxidative stress by targeting SOD1. Am J Physiol Cell Physiol 316: C57-C69, 2019.

107. Zeng Y, Ly Y, Tao L, Ma J, Zhang H, Xu H, Xiao B, Shi Q, Ma K and Chen L: G6PC3, ALDOA and CS induction participates miR-122 down-regulation in the mechanical asphyxia and can serve as hypoxia biomarkers. Oncotarget 8: 74526-74536, 2016.

108. Pinto SK, Lamon S, Stephenson EJ, Kalanon M, Mikovic J, Koch LG, Britton SL, Hawley JA and Camera DM: Expression of microRNAs in slow skeletal muscle of rats selectedly bred for high and low running capacity. Am J Physiol Regul Integr Comp Physiol 318: R226-R236, 2017.

109. Zhou Z, Lu Y, Wang Y, Du L, Zhang Y and Tao J: Let-7c regulates proliferation and osteodifferentiation of human adipose-derived mesenchymal stem cells under oxidative stress by targeting SOD1. Am J Physiol Cell Physiol 316: C57-C69, 2019.
Cai Z, Zheng F, Ding Y, Zhan Y, Gong R, Li J, Aschner M, Dong XQ, Zhang YH, Shang XQ and Zeng YJ: Effects of Huang X, Gao Y, Qin J and Lu S: The mechanism of long Wu LL, Gao M, Li C, Xu M, Liu Y, Cong M and Liu S: lncRNA MT1DP Duan Q and Si E: MicroRNA -25 aggravates A 515-529, 2019. Liu X, Zhao H, Luo C, Du D, Huang J, Ming Q, Jin F, Wang D and Huang W: Acetaminophen responsive miR-19b modulates toxicity in mouse neuroblastoma N2a cells. Toxicol Sci 171: 101140, 2019. Zhang Q, Wu S and Li H: Nrf2-regulated miR-380-3p blocks the silencing reduces sciatic nerve injury in diabetic peripheral }
156. Sun X, Li M, Ma S, Guo Y and Li Y: MicroRNA-98-5p ameliorates oxygen-glucose deprivation/reoxygenation (OGD/R)-induced neuronal injury by inhibiting Bach1 and promoting miR2ARE Agying. Biochim Biophys Acta 1855: 154-174, 2016.

157. Feng X, Zhao J, Ding J, Shen X, Zhou J and Xu Z: IncRNA Binc1 expression and its effect on renal fibrosis in diabetic nephropathy. Am J Transl Res 11: 5664-5672, 2019.

158. Li H, Zhu X, Hu L, Li Q, Ma J and Yan J: Loss of exosomal MALAT1 from ox-LDL-treated vascular endothelial cells induces apoptosis of dendritic cells in atherosclerosis development. Cell Cycle 18: 2255-2267, 2019.

159. Fan JB, Zhang Y, Liu W, Zhu XH, Xu DW, Zhao JN and Cui ZM: Long non-coding RNA MALAT1 regulates generation of reactive oxygen species and the insulin responses in male mice. Biochem Pharmacol 152: 94-103, 2018.

160. Amadio N, Stamato MA, Juli G, Morelli E, Fulciniti M, Manzon M, Taiana E, Agnelli L, Cantafio MEG, Romeo E, et al: Drugging the IncRNA MALAT1 via LNA gapmer ASO inhibits gene expression of proteasome subunits and triggers anti-multiple myeloma activity. Leukemia 32: 1946-1959, 2018.

161. Zuo R, Zhang X, Li N, Li Y, Lu Z, Liu C and Ye W: The long non-coding RNA MALAT1 activates Nrf2 signaling to protect human umbilical venous endothelial cells from hydrogen peroxide. Biochem Biophys Res Commun 495: 2532-2538, 2020.

162. Joo MS, Shin SB, Kim EJ, Koo JH, Yim H and Kim SG: Nrf2-miR-223 cell fate cell by modulating p53-dependent Nrf2 mediated activation as an miRNA sponge for PIK3 and p2195. FASEB J 33: 7953-7969, 2019.

163. Liu M, Song Y and Han Z: Study on the effect of IncRNA AK094457 on OX-LDL induced vascular smooth muscle cells. Am J Transl Res 11: 5623-5633, 2019.

164. Porsch M, Özdemir E, Wisniewski M, Graf S, Bull F, Xiao X, Yuan Q, Chen Y, Huang Z, Fang X, Zhang H, Peng L, Zheng ZG, Xu H, Suo SS, Xu XL, Ni MW, Gu LH, Chen W, Gao M, Zhao B, Chen M, Liu Y, Xu M, Wang Z, Liu S and Zhang Z: lncRNA TUG1 through IncRNA-TUG1/Nrf2. Cell Cycle 18: 1549-1559, 2019.

165. Chen J, Ke S, Zheng L, Wu J, Tseng A, Morpurgo B, Golovko A, Wang G, Cai JJ, Ma X, et al: Long noncoding RNA MALAT1 expression and its effect on renal fibrosis in diabetic nephropathy. Am J Transl Res 11: 5664-5672, 2019.

166. Dong H, Wang W, Mo S, Liu Q, Chen X, Chen R, Zhang Y, Sun Z, Huang G and Cheng H: Transcription factor Nrf2 induces maturation of dendritic cells in atherosclerosis development. Cell Cycle 18: 2255-2267, 2019.

167. Zeng R, Zhang R, Song X, Ni L, Lai Z, Liu C and Ye W: The long non-coding RNA MALAT1 regulates renal fibrosis in diabetic nephropathy. Biochem Biophys Res Commun 507: 114-121, 2018.

168. Luo Y, Wang C, Yong P, Liu Z, Fu Z, Lu F, Xiang W, Tan W and Cui ZM: Long non-coding RNA MALAT1 protects human umbilical vein endothelial cells from hydrogen peroxide. Biochem Biophys Res Commun 495: 2532-2538, 2020.

169. Joo MS, Shin SB, Kim EJ, Koo JH, Yim H and Kim SG: Nrf2-miR-223 cell fate cell by modulating p53-dependent Nrf2 mediated activation as an miRNA sponge for PIK3 and p2195. FASEB J 33: 7953-7969, 2019.

170. Liu M, Song Y and Han Z: Study on the effect of IncRNA AK094457 on OX-LDL induced vascular smooth muscle cells. Am J Transl Res 11: 5623-5633, 2019.

171. Porsch M, Özdemir E, Wisniewski M, Graf S, Bull F, Xiao X, Yuan Q, Chen Y, Huang Z, Fang X, Zhang H, Peng L, Zheng ZG, Xu H, Suo SS, Xu XL, Ni MW, Gu LH, Chen W, Gao M, Zhao B, Chen M, Liu Y, Xu M, Wang Z, Liu S and Zhang Z: lncRNA TUG1 through IncRNA-TUG1/Nrf2. Cell Cycle 18: 1549-1559, 2019.

172. Zeng R, Zhang R, Song X, Ni L, Lai Z, Liu C and Ye W: The long non-coding RNA MALAT1 activates Nrf2 signaling to protect human umbilical venous endothelial cells from hydrogen peroxide. Biochem Biophys Res Commun 495: 2532-2538, 2020.

173. Joo MS, Shin SB, Kim EJ, Koo JH, Yim H and Kim SG: Nrf2-miR-223 cell fate cell by modulating p53-dependent Nrf2 mediated activation as an miRNA sponge for PIK3 and p2195. FASEB J 33: 7953-7969, 2019.

174. Liu M, Song Y and Han Z: Study on the effect of IncRNA AK094457 on OX-LDL induced vascular smooth muscle cells. Am J Transl Res 11: 5623-5633, 2019.
195. Xu XZ, Tang Y, Cheng LB, Yao J, Jiang Q, Li KR and Zhen YF: Targeting Keap1 by miR-626 protects retinal pigment epithelium cells from oxidative injury by activating Nrf2 signaling. Free Radic Biol Med 143: 387-396, 2019.

196. Akdemir B, Nakajima Y, Inazawa J and Inoue J: miR-432 induces NRF2 stabilization by directly targeting KEAP1. Mol Cancer Res 15: 1570-1578, 2017.

197. Gao M, Monian P, Quadri N, Ramasamy R and Jiang X: Glutaminolysis and transferrin regulate ferroptosis. Mol Cell 59: 298-308, 2015.

198. Wang J, Wang B, Ren H and Chen W: miR-9-5p inhibits pancreatic cancer cell proliferation, invasion and glutamine metabolism by targeting GOT1. Biochem Biophys Res Commun 509: 241-248, 2019.

199. Moskalev EA, Schubert M and Hoheisel JD: RNA-directed epigenomic reprogramming: An emerging principle of a more targeted cancer therapy? Genes Chromosomes Cancer 51: 105-110, 2012.

200. Li Y, Duo Y, Zhai P, He L, Zhong K, Zhang Y, Huang K, Luo J, Zhang H and Yu X: Dual targeting delivery of miR-328 by functionalized mesoporous silica nanoparticles for colorectal cancer therapy. Nanomedicine (Lond) 13: 1753-1772, 2018.

201. Li F, Wang F, Zhu C, Wei Q, Zhang T and Zhou YL: miR-221 suppression through nanoparticle-based miRNA delivery system for hepatocellular carcinoma therapy and its diagnosis as a potential biomarker. Int J Nanomedicine 13: 2295-2307, 2018.

202. Bader AG: miR-34-a microRNA replacement therapy is headed to the clinic. Front Genet 3: 120, 2012.

203. Gong N, Teng X, Li J and Liang XJ: Antisense oligonucleotide-conjugated nanostructure-targeting IncRNA MALAT1 inhibits cancer metastasis. ACS Appl Mater Interfaces 11: 37-42, 2019.

204. Wang WT, Han C, Sun YM, Chen TQ and Chen YQ: Noncoding RNAs in cancer therapy resistance and targeted drug development. J Hematol Oncol 12: 55, 2019.

205. De Duve C and Wattiaux R: Functions of lysosomes. Annu Rev Physiol 28: 435-492, 1966.

206. Kerr JF, Wylie AH and Currie AR: Apoptosis: A basic biological phenomenon with wide-ranging implications in tissue kinetics. Br J Cancer 26: 239-257, 1972.

207. Cookson BT and Brennan MA: Pro-inflammatory programmed cell death. Trends Microbiol 9: 113-114, 2001.

208. Degterev A, Huang Z, Boyce M, Li Y, Jagtap P, Mizushima N, Cuny GD, Mitchison TJ, Moskowitz MA and Yuan J: Chemical inhibitor of nonapoptotic cell death with therapeutic potential for ischemic brain injury. Nat Chem Biol 1: 112-119, 2005.

209. Overholtzer M, Mailleux AA, Mouneimne G, Normand G, Schnitt SJ, King RW, Cibas ES and Brugge JS: A nonapoptotic cell death process, entosis, that occurs by cell-in-cell invasion. Cell 131: 966-979, 2007.