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Review

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Iron metabolism, ferroptosis, and lncRNA in cancer: knowns and unknowns

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Abstract: Cancer cells undergo substantial metabolic alterations to sustain increased energy supply and uncontrolled proliferation. As an essential trace element, iron is vital for many biological processes. Evidence has revealed that cancer cells deploy various mechanisms to elevate the cellular iron concentration to accelerate proliferation. Ferroptosis, a form of cell death caused by iron-catalyzed excessive peroxidation of polyunsaturated fatty acids (PUFAs), is a promising therapeutic target for therapy-resistant cancers. Previous studies have reported that long noncoding RNA (lncRNA) is a group of critical regulators involved in modulating cell metabolism, proliferation, apoptosis, and ferroptosis. In this review, we summarize the associations among iron metabolism, ferroptosis, and ferroptosis-related lncRNA in tumorigenesis. This information will help deepen understanding of the role of lncRNA in iron metabolism and raise the possibility of targeting lncRNA and ferroptosis in cancer combination therapy.

Key words: Iron metabolism; Ferroptosis; Long noncoding RNA (lncRNA); Tumorigenesis

1 Introduction

Iron is an integral fundamental trace element for various cellular processes. By being integrated into the heme and Fe-S cluster (Shimizu et al., 2019; Lill and Freibert, 2020), iron is necessary for many iron-containing enzymes involved in DNA synthesis and repair (Netz et al., 2011), cell respiration (Goldberg et al., 2008), oxygen transport (Goldberg et al., 2008), lipid oxidation (Kagan et al., 2017), and cell signaling (Cinelli et al., 2020). Therefore, iron is vital for cell replication, metabolism, and growth. However, the ease with which iron can gain or lose electrons gives it the ability to participate in harmful reactions generating reactive oxygen species (ROS), which can cause oxidative damage to proteins, lipids, and DNA, and lead to cell pathogenesis (Dixon and Stockwell, 2014). Therefore, iron is both beneficial and potentially toxic.

Abnormal iron metabolism in an organism is associated with many diseases. Iron deficiency usually causes iron deficiency anemia (Pasricha et al., 2021). In contrast, iron overload is a common cause of cancer (Torti and Torti, 2013). For example, iron may promote tumor initiation by inducing the generation of free radicals and subsequent cell damage (Barnes

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et al., 2018), as well as function as a nutrient that fosters tumor cell proliferation (Schonberg et al., 2015; Xue et al., 2016). Compared to normal cells, the expression of genes related to iron uptake, storage, and import is disturbed in cancer cells, and the net result is elevation of the cellular iron concentration (Torti and Torti, 2013; Wang et al., 2018). However, excess iron leads to the accumulation of lipid ROS and is one of the prerequisites for the execution of ferroptosis (Hassannia et al., 2019). Ferroptosis is a nonapoptotic form of cell death caused by multiple disrupted metabolic processes, including iron accumulation, lipid peroxidation, and glutathione (GSH) depletion (Stockwell et al., 2017; Jiang et al., 2021). Ferroptosis execution is triggered by iron-catalyzed peroxidation of phospholipids containing polyunsaturated fatty acids (PUFAs), and the subsequent deterioration of cell membranes (Dixon et al., 2012). Iron induces ferroptosis in various ways. On the one hand, by initiating the Fenton reaction, the ferrous iron (Fe^{2+}) is oxidized to ferric iron (Fe^{3+}) through reaction with H_2O_2, resulting in the production of highly reactive hydroxyl radicals to initiate the peroxidation of phospholipids and generation of free radicals of lipids (Conrad and Pratt, 2019; Hassannia et al., 2019). On the other hand, Fe^{2+} promotes the decomposition of phospholipid hydroperoxide to alkoxyl phospholipid radical, which by attacking another PUFA promotes further propagation of lipid peroxidation (Jiang et al., 2021). In addition, Fe^{3+} is necessary for maintaining the activation of lipoxygenases (LOXs), which catalyze the oxygenation of PUFAs and promote ferroptosis (Dufrusine et al., 2019). Therefore, targeting the induction of iron-dependent ferroptosis may be a promising new way to treat therapy-resistant cancers.

Long noncoding RNAs (lncRNAs) are defined as transcripts longer than 200 nucleotides (Schmitt and Chang, 2016). They play an emerging regulatory role in multiple processes, including modulating gene activation and silencing (Rinn and Chang, 2012), messenger RNA (mRNA)-alternative splicing (Guo et al., 2020) and stability (Xu et al., 2019), translation (Carrieri et al., 2012), post-translational protein modification (Shi et al., 2020), and signal transduction (Sun et al., 2016; Lin and Yang, 2018; Liu J et al., 2020; Tan et al., 2021). LncRNAs are important drivers of many cancer phenotypes, including cell proliferation, angiogenesis, invasion, and metabolic microenvironment remolding (Schmitt and Chang, 2016; Lin and Yang, 2018; Sun et al., 2018; Liu et al., 2021). Recent studies have reported that lncRNAs function as signaling mediators (Yuan et al., 2021), microRNA (miRNA) sponges (Wang et al., 2019), and epigenetic modulators (Wang ZL et al., 2021) to regulate iron metabolism and cancer ferroptosis. In this review, we first reveal the emerging evidence for abnormal iron metabolism in cancer progression. Further, based on the finding that cancer cells have a higher cellular iron content, we discuss the potential of iron-triggered ferroptosis as an antitumor treatment. We also summarize the functional role of lncRNAs in ferroptosis. This review contributes to a comprehensive understanding of the relationship between iron, ferroptosis and lncRNA in cancer progression and paves the way for targeting ferroptosis and lncRNA as a promising new approach to cancer treatment.

2 Aberrant iron metabolism and disrupted iron homeostasis in cancer progression

2.1 Iron metabolism and cellular regulation

In the human body, about 10% of iron (about 1–2 mg/d) is absorbed from the diet by enterocytes to compensate for the loss of iron, while the remaining 90% (about 20–25 mg/d) is derived from macrophage-red blood cell (RBC) recycling (Drakesmith et al., 2015; Korolnek and Hamza, 2015). Inorganic dietary-formed Fe^{3+} is first reduced to Fe^{2+} by duodenal cytochrome *b* (DcytB) on the surface of the duodenal enterocytes, and is then absorbed into cells via the divalent metal transporter 1 (DMT1) (Fig. 1a). Subsequently, Fe^{2+} is oxidized by hephaestin and then exported into the bloodstream by ferroportin (FPN), the only iron efflux pump in vertebrates (Hentze et al., 2010; Torti and Torti, 2013).

In the bloodstream, one transferrin (TF) can combine with two circulating Fe^{3+}, and this complex subsequently binds to transferrin receptor 1 (TfR1) located on the cell surface to deliver iron into cells for subsequent utilization (Torti and Torti, 2013). Next, the TF-$[Fe^{3+}]_2$-TfR1 complex is incorporated and endocytosed into an endosome. In the acidic microenvironment of the endosome, Fe^{3+} is dissociated from TF-TfR1 and reduced to Fe^{2+} by reductase six-transmembrane epithelial antigen of prostate 3 (STEAP3), and finally

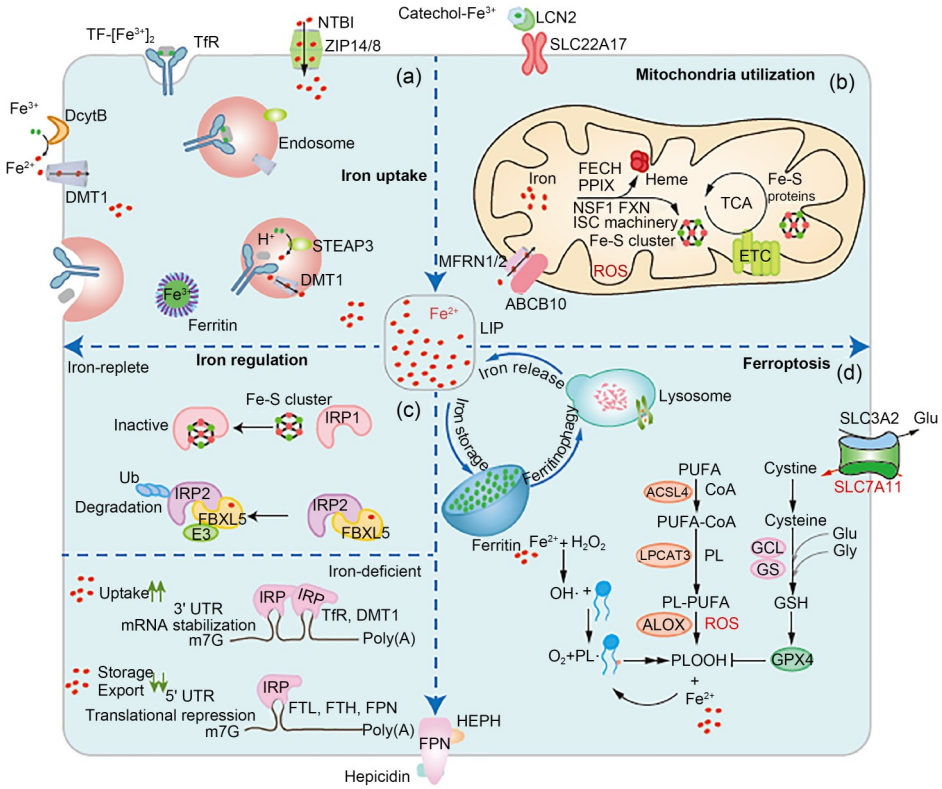

Fig. 1 Metabolism, utilization, and regulation of cellular iron. (a) The process of iron uptake. Cells acquire iron from plasma mainly by TfR-mediated endocytosis of the TF-$[Fe^{3+}]_2$-TfR complex. Subsequently, in the acid environment of the endosome, iron is released and reduced by STEAP3, and then crosses DMT1 to the LIP, while TF and TfR are recycled to the plasma membrane for further use. In addition, NTBI can be transported into cells by ZIP14/8. LCN2 also mediates iron uptake by binding with iron carrier catechol, and then binds to LCN2 receptor SLC22A17. (b) The utilization of iron in mitochondria. Iron can be imported into mitochondria by MFRN1/2 together with ABCB10 to further heme and Fe-S cluster synthesis. In mitochondria, iron FECH facilitates the insertion of iron into PPIX to produce heme. Iron is also used for Fe-S cluster synthesis. The core components of the ISC NSF1 and FXN are mainly involved in this process. Fe-S clusters are incorporated in mitochondrial proteins for TCA cycle and ETC. (c) Iron homeostasis regulation by the IRE/IRP system. Under iron-replete conditions (upper), the IRP1 conformational switch is induced by binding to the Fe-S cluster which then precludes the IRE-binding activity of IRP1; IRP2 is regulated by the iron sensor FBXL5. After binding to IRP2, FBXL5 recruits E3 ligase to promote IRP2 ubiquitination and degradation. Under iron-deficient conditions (lower), IRP1/2 *cis*-regulatory hairpin structures and IREs are present in the UTRs of mRNAs involved in iron metabolism proteins. The binding of IRPs to the 5' UTRs of target mRNAs (mainly FTL, FTH, and FPN) inhibits their translation, whereas IRP interaction with multiple 3' UTR of TfR and DMT1 mRNA increases its stability. Thus, the net result is increasing cellular iron. (d) Iron involved in ferroptosis. Excessive iron is stored in ferritin, which can be targeted into lysosome to ferritinophagy by NCOA4 and causes subsequent iron release. Ferritinophagy can promote ferroptosis. System Xc^- is composed of disulfide-linked heterodimers SLC7A11 (also known as xCT) and SLC3A2 to import cystine and export glutamate, respectively. Further, a reduced form of cysteine together with Glu and Gly can synthesize GSH via glutamate-cysteine ligase (GCL) and glutathione synthase (GS). GPX4 uses the GSH to protect the cell membrane from peroxidation. PUFA is catalyzed by ACSL4 and LPCAT3 to produce polyunsaturated phospholipid, which can be oxidated to lipid ROS-driving ferroptosis. Lipids can be degraded by ALOXs. Iron in LIP involved in Fenton reaction generates ROS, which cause lipid peroxidation, and O_2 accelerates this process. In addition, Fe^{2+} can cascade lipid peroxidation by promoting phospholipid hydroperoxide (PLOOH) to alkoxyl phospholipid radical (PLO·). TfR: transferrin receptor; TF: transferrin; STEAP3: six-transmembrane epithelial antigen of prostate 3; DcytB: duodenal cytochrome *b*; DMT1: divalent metal transporter 1; LIP: labile iron pool; NTBI: non-transferr in-bound iron; ZIP14/8: ZRT/IRT-like protein 14/8; LCN2: lipocalin 2; SLC22A17: solute carrier family 22 member 17; MFRN1/2: mitoferrin 1/2; ABCB10: ATP-binding cassette subfamily B member 10; FECH: ferrochelatase; PPIX: protoporphyrin IX; ISC: iron-sulfur cluster; NSF1: nitrogen fixation 1; FXN: frataxin; TCA: tricarboxylic acid; ETC: electron transport chain; IRE: iron response element; IRP: iron regulatory protein; FBXL5: F-box and leucine-rich repeat protein 5; UTR: untranslated region; mRNA: messenger RNA; FTL: ferritin light chain; FTH: ferritin heavy chain; FPN: ferroportin; NCOA4: nuclear receptor coactivator 4; Glu: glutamate; Gly: glycine; GSH: glutathione; GPX4: glutathione peroxidase 4; PUFA: polyunsaturated fatty acid; CoA: coenzyme A; ACSL4: acyl-CoA synthetase long-chain family member 4; LPCAT3: lysophosphatidylcholine acyltransferase 3; ROS: reactive oxygen species; ALOX: arachidonate lipoxygenase; Ub: ubiquitination; m7G: N^7-methylguanosine; PL: phospholipid; HEPH: hephaestin.

moves into the cytosolic labile iron pool (LIP) through DMT1, while the TF-TfR1 complex recycles to the cell surface (Ohgami et al., 2005; Rouault, 2013). Multiple divalent metal transporters, including ZRT/IRT-like protein 14 (ZIP14) or ZIP8, also mediate the import of non-transferrin bound iron (NTBI) into the cytosol LIP (Zhang and Zhang, 2015). Moreover, lipocalin 2 (LCN2) (also named neutrophil gelatinase-associated lipocalin (NGAL)) is involved in iron uptake. In the bloodstream, LCN2 has a high affinity with siderophores/catechol, a small Fe^{3+} chelator, and binds to its receptors low-density lipoprotein receptor-related protein 2 (LRP2) and solute carrier family 22 member 17 (SLC22A17) on the cell membrane to elevate cellular iron levels (Xiao et al., 2017). Iron can also be transported into the mitochondria by mitoferrin 1/2 (MFRN1/2) with ATP-binding cassette subfamily B member 10 (ABCB10) to synthesize heme and Fe-S clusters (Fig. 1b) (Shaw et al., 2006; Chen et al., 2009). With the help of ferrochelatase (FECH), iron is inserted into protoporphyrin IX (PPIX) to produce heme (Wu et al., 2001; Keel et al., 2008), which can be further used to synthesize hemoglobin, myoglobin, and cytochrome *c* to participate in O_2 transport and storage, and cell respiration (Gozzelino et al., 2010). Simultaneously, iron is also used for the de novo synthesis of the Fe-S cluster, which is initiated by the core iron-sulfur cluster (ISC) component cysteine desulfurase nitrogen fixation 1 (NFS1), leucine-tyrosine-arginine motif (LYRM) protein (ISD11), and acyl carrier protein (ACP), and actively regulated by frataxin (FXN) and glutaredoxin-related protein 5 (GLRX5) (Patra and Barondeau, 2019). The Fe-S cluster is a cofactor of various proteins and enzymes involved in the synthesis and repair of DNA (Gari et al., 2012; Stehling et al., 2012), cell respiration (Saxena et al., 2016), and generation of ROS (Chu et al., 2019). The dysregulated synthesis of heme, Fe-S clusters, or relevant enzymes causes various diseases. A genetic defect of the 5-aminolevulinate synthase 2 (ALAS2) enzyme blocks the synthesis of the heme precursor PPIX and causes porphyrias and X-linked sideroblastic anemia (To-Figueras et al., 2011; Sankaran et al., 2015). Deficiency of FXN causes the neurodegenerative disorder Friedreich's ataxia (Torti and Torti, 2013).

Apart from the iron in the LIP, excess intracellular iron is stored by ferritin, which contains 24 subunits composed of a ferritin heavy chain (FTH) and a ferritin light chain (FTL) and has a high affinity to store nearly 4500 iron atoms in its center (Torti and Torti, 2013). Iron efflux is mediated by the FPN, which is regulated by the hormone peptide hepcidin (Hentze et al., 2010). Hepcidin binds to FPN to cause its internalization and subsequent degradation by lysosomes in iron-deficient cells, which prevents iron efflux to the extracellular matrix (Billesbølle et al., 2020). Iron homeostasis is maintained in two main ways: by the FPN/hepcidin system and the iron regulatory protein (IRP)/iron response element (IRE) system. The FPN/hepcidin axis is responsible for systemic iron homeostasis (Hentze et al., 2010), while intracellular iron homeostasis is predominantly controlled by IRPs (IRP1 and IRP2) (Fig. 1c). IRPs interact with the IREs of mRNA, encoding iron metabolism-related proteins in the post-transcriptional process (Hentze et al., 2010; Muckenthaler et al., 2017). The regulatory effects of IRE-IRP depend on which types of IRE (5' untranslated region (UTR) or 3' UTR of the targeting mRNA) the IRP binds (Hentze et al., 2010; Bogdan et al., 2016; Muckenthaler et al., 2017). When cellular iron is deficient, IRP1/2 binds 5' UTR IREs, such as ferritin and FPN, to repress their translation. Meanwhile, IRP interacts with the 3' UTRs of TfR1 and DMT1 to improve mRNA stability (Hentze et al., 2010; Bogdan et al., 2016; Muckenthaler et al., 2017). Otherwise, under an iron-replete condition, the F-box and leucine-rich repeat protein 5 (FBXL5), an iron sensor, can directly bind iron to recruit the E3 ligase complex to promote IRP1/2 ubiquitination and proteasome degradation (Salahudeen et al., 2009). IRP1 is ligated with the Fe-S cluster by family with sequence similarity 96 member A (FAM96A) and loses its enzymatic activity (Stehling et al., 2013). In addition, Fe^{2+} can bind directly to the IRE stem-loop and alter its conformation to decrease its affinity for IRPs (Khan et al., 2009; Ma et al., 2012).

2.2 Disrupted iron homeostasis in cancers

Dysregulated iron metabolism is related to human diseases, including cancers. Over recent decades, significant efforts have been made to clarify the relationship between iron metabolism and cancer development. Also, many critical signal pathways and molecules have been discovered and their roles in modulating iron metabolism elucidated (Torti and Torti,

2013). Previous epidemiological evidence had reported a relationship between high dietary iron and increased colorectal cancer risk (Osborne et al., 2010). Consistent with this finding, high-iron diets promote tumor progression in mouse models with higher expression of TfR1 and DMT1 than controls (Radulescu et al., 2012). Low iron levels inactivate prolyl hydroxylases (PHDs), enabling hypoxia-inducible factor α (HIFα) to stabilize (Linehan and Rouault, 2013). In another mouse model, upregulated expression of DMT1 mediated by the HIF-2α signaling pathway also promotes the development of colorectal cancer (Xue et al., 2016).

2.2.1 Enhanced iron uptake in cancers

Iron plays critical roles in cell metabolism and growth. Cancer cells acquire more iron and promote cell proliferation and cancer progression by regulating various iron metabolism-related genes and signaling pathways (Pinnix et al., 2010; Torti and Torti, 2013; Schonberg et al., 2015; Xue et al., 2016, 2017; Gomez-Chou et al., 2017). Studies have revealed that TfR1 is highly expressed in many cancers, including breast, lung, and colorectal cancers (Daniels et al., 2012; Torti and Torti, 2013). In glioblastoma, increased expression of TF, TfR1, and ferritin promotes iron uptake and activates the signal transducer and activator of transcription 3 (STAT3)/forkhead box protein M1 (FOXM1) pathway to promote the cell cycle progression and stemness of cancer cells (Schonberg et al., 2015). Moreover, upregulated redistribution of TfR1 on the surface of cancer cells mediated by epidermal growth factor receptor (EGFR) enhances iron uptake. This promotes tumor progression in non-small-cell lung carcinoma (NSCLC) cells (Wang et al., 2016). Advanced cancer therapies can be developed by targeting TfR1 expression. Therapies targeting the interaction between TF and TfR1, including TfR1 antibodies, effectively inhibit the proliferation of cancer cells (Jones et al., 2006; Callens et al., 2008) and improve the tumor microenvironment (Tarín et al., 2016). TfR1 conjugated with a drug molecule has also been used in a tumor-selective delivery system for cancer treatment (Daniels et al., 2012; Johnsen et al., 2019). The expression of TfR1 is also modulated by cellular-myelocytomatosis viral oncogene (c-Myc), a transcription factor regulated by circadian clock molecules. Its circadian rhythm suggests that by optimizing the time to deliver TF-conjugated liposomes encapsulating a drug, it could be a promising target for cancer therapy (Okazaki et al., 2010).

The upregulated expression of LCN2 is also related to various signaling pathways in cancers (Shi et al., 2008; Leng et al., 2009; Wang JF et al., 2021). In clear cell renal cell carcinoma (ccRCC), protein arginine methyltransferase 1 (PRMT1) epigenetically upregulates the expression of LCN2. LCN2 further activates the protein kinase B (Akt)/retinoblastoma protein (Rb) signal pathway induced by the NGAL receptor (NGALR) (receptor of LCN2) and promotes cancer growth and drug resistance (Wang JF et al., 2021). In breast cancer, overexpression of LCN2 causes increased phosphatase and tensin homolog (PTEN) activation, which promotes the migration and invasion abilities of 4T1 cells in vitro, and inhibition of Akt signaling, thus promoting lung metastasis in vivo (Shi et al., 2008). Deficiency of LCN2 also significantly inhibits mammary tumor formation in a mouse model (Leng et al., 2009; Berger et al., 2010). Besides the Akt signal pathway, LCN2 is also upregulated by the inflammatory cytokine interleukin-6 (IL-6)-associated pathway to promote epithelial-mesenchymal transition (EMT) (Cheng et al., 2014) and leptomeningeal metastases (Chi et al., 2020).

Some metalloreductases of the STEAP family, such as STEAP3, a ferrireductase reducing endosomal Fe^{3+} to Fe^{2+}, are also abnormal in cancers (Challita-Eid et al., 2007; Kobayashi et al., 2007; Xue et al., 2017; Wu et al., 2018). Monoclonal antibodies targeting the STEAP protein activate helper T lymphocytes (HTLs), thereby enhancing antitumor immunity and inhibiting cancer growth (Challita-Eid et al., 2007; Kobayashi et al., 2007). Abnormal overexpression of DMT1 has also been implicated in cancer (Brookes et al., 2006; Xue et al., 2012, 2016). The activated Wnt signaling pathway promotes the transcription of DMT1 and TfR1 through the Wnt downstream target c-Myc in the adenomatous polyposis coli (APC)-deficient mouse model of intestinal cancer (Radulescu et al., 2012). Inhibition and disruption of DMT1 expression attenuate cancer growth (Xue et al., 2012, 2016).

2.2.2 Regulation of iron storage and efflux in cancers

Ferritin protects cells from ROS oxidative damage by decreasing the LIP iron concentration and

is dysregulated in many cancers. By activating Akt/glycogen synthase kinase 3β (GSK3β)/β-catenin signaling, HIF-1α promotes FTL expression, leading to EMT and chemoresistance of glioma in vitro and in vivo (Liu JH et al., 2020). In addition, ferritin secreted by macrophages is enriched in the breast cancer microenvironment and serum, which causes an inflammatory status and stimulates tumorigenesis (Alkhateeb et al., 2013). An elevated FTL level in the MCF-7 breast cancer cell line also enhances the chemotherapeutic resistance of doxorubicin and cisplatin, which indicates its potential as a diagnostic and prognostic marker for breast cancer (Chekhun et al., 2013). Therefore, drug approaches such as cationic liposomes containing knockdown FTH-targeting ferritin could be significant for cancer therapy.

Cancer cells also increase the cellular iron concentration by decreasing FPN expression. In multiple cancer cells, hepcidin upregulated by the bone morphogenetic protein (BMP) signal pathway and inflammatory stimuli promotes the degradation of FPN and blocks the iron efflux (Vela and Vela-Gaxha, 2018). The Wnt signaling pathway also upregulates hepcidin to cause the degradation of FPN, which promotes prostate cancer cell proliferation. Compared to primary prostate cancer, metastatic tissue has more iron and presents an inferior prognosis (Tesfay et al., 2015). In multiple myeloma, FPN reduction significantly increases the LIP and the growth of myeloma cells by activating STAT3/myeloid cell leukemia-1 (Mcl-1) signaling, which also induces osteoclast differentiation (Gu et al., 2015).

Moreover, crosstalk among multiple signaling pathways is also involved in this process. For example, in prostate cancer, by inhibiting the BMP antagonist sclerostin domain-containing 1 protein (SOSTDC1), the Wnt signal pathway can activate BMP4/7 and increase the level of hepcidin. The IL-6-mediated pathway can also promote the autocrine loop of hepcidin through STAT3 (Tesfay et al., 2015). The expression level of FPN is closely associated with the survival of cancer patients. Breast cancer patients with both a pro-export phenotype (high FPN and low hepcidin expression) and an anti-import phenotype (low TfR1 and high hemochromatosis protein (HFE) expression) have a favorable prognosis, while both anti-export and pro-import phenotypes significantly increase the probability of cancer metastasis (Pinnix et al., 2010; Miller et al., 2011). Multiple strategies targeting hepcidin, such as hepcidin antibodies and small interfering RNAs (siRNAs), can block the iron overload and improve disease symptoms (Poli et al., 2014; Crielaard et al., 2017). In addition, a marked reduction of FPN induces a more aggressive and invasive breast cancer phenotype, which indicates that FPN may be a good marker for breast cancer prognosis prediction (Pinnix et al., 2010). All this evidence suggests that the FPN/hepcidin axis is vital for cancer progression and provides a potential therapeutic target.

2.2.3 Iron regulatory proteins and iron response elements in cancers

The IRP/IRE system is a master regulator in maintaining intercellular iron homeostasis that blocks the increase of iron concentration when a cell is in a high-iron condition but increases cellular iron uptake when a cell is in a low-iron condition (Muckenthaler et al., 2008). Iron homeostasis dysregulation raises the occurrence of diseases, including neurodegeneration (Meyron-Holtz et al., 2004), type 2 diabetes (T2D) (dos Santos et al., 2020), and cancers (Wang et al., 2014). The iron metabolism and multiple signaling pathways influence each other to regulate iron homeostasis. Transcription factor c-Myc, a vital target of the Wnt signal pathway, can repress the expression of the subunit of ferritin and stimulate IRP2 expression at the transcriptional level (Wu et al., 1999). In colorectal cancer, upregulation of IRP2 is closely correlated with TfR1 expression. Furthermore, further bioinformatic analyses found that the increase of IRP2 is correlated with B-type Raf kinase (BRAF) and mitogen-activated protein kinase kinase (MEK) activation (Horniblow et al., 2017). In renal cell cancer, inactivation of the tricarboxylic acid (TCA) cycle enzyme fumarate hydratase (FH) attenuates the activities of adenosine monophosphate-activated protein kinase (AMPK) and p53. This decreases the expression of DMT1, further promoting the expression of IRP1/2 (Tong et al., 2011). In the FBXL5-defective mouse model, the overload of iron caused by FBXL5 deficiency leads to oxidative damage of DNA and promotes hepatocellular carcinoma (HCC) (Muto et al., 2019).

Compared to normal cells, cancer cells increase their iron concentration to support rapid proliferation. Gaining insights into cellular iron homeostasis regulation and how the interaction between iron metabolism

and signaling pathways affects tumor development may provide a theoretical basis for cancer treatment. Iron chelators, such as deferoxamine (DFO), could be used to reduce the cellular iron level. However, because they are non-specific, the use of iron chelators carries serious side effects for cancer treatment (Wu et al., 2020). Methods that use antibodies of iron metabolic proteins, such as TF (Jones et al., 2006; Callens et al., 2008) or TfR1 (Daniels et al., 2012; Johnsen et al., 2019), have been shown to be effective in antagonizing the growth of cancers. Moreover, a higher iron concentration makes cancer cells more vulnerable to ferroptosis, an iron-catalyzed programmed cell death, which is a promising approach to cancer treatment.

3 Ferroptosis in cancer progression

3.1 Execution of ferroptosis

Ferroptosis is a nonapoptotic form of cell death triggered by iron-catalyzed peroxidation of PUFAs, and was first discovered by Stockwell and his colleagues (Dixon et al., 2012). They found that in rat sarcoma oncogene (RAS)-mutated cells, erastin-induced cell death is different from apoptosis, but has a typical necrotic morphology, including destroyed small mitochondria with decreased crista, a condensed membrane, and a ruptured outer membrane. During this process, cells are characterized by an elevated intracellular iron concentration and lipid ROS. Evidence has shown that ferroptosis is regulated by various processes (Fig. 1d), including the metabolic balance of iron, lipids, and amino acids, redox homeostasis, and normal functioning of mitochondria (Stockwell et al., 2020; Jiang et al., 2021). Sufficient iron is necessary to initiate the Fenton reaction to produce ROS and then promote the peroxidation of PUFA in the cell membranes (Dixon and Stockwell, 2014). The main enzymes controlling the synthesis and peroxidation of PUFA include acyl-CoA synthetase long-chain family member 4 (ACSL4) (Doll et al., 2017), lysophosphatidylcholine acyltransferase 3 (LPCAT3) (Dixon et al., 2015), and the LOX family (Kagan et al., 2017). Aberrant expression of these enzymes disturbs ferroptosis. ACSL4 can convert the free acids into fatty acyl-CoAs (Doll et al., 2017), which can be inserted into phospholipids by LPCAT3 (Wang and Tontonoz, 2019). Activated ACSL4 and LPCAT3 increase the risk of ferroptosis. LOXs are non-heme iron-containing enzymes. These enzymes, especially LOX12/15, catalyze the deoxygenation of PUFAs to produce peroxided PUFAs that promote ferroptosis (Li et al., 2018; Chu et al., 2019). Moreover, abnormalities of mitochondria-related processes, including the mitochondrial TCA cycle, electron transport chain (ETC) (Gao et al., 2019; Wei et al., 2020), and Fe-S cluster synthesis (Alvarez et al., 2017; Du et al., 2020), are also relevant to ferroptosis. Glutaminolysis, producing glutamate (the intermediate for the TCA cycle), is necessary for cysteine deprivation-induced ferroptosis, which is not relevant to glutathione peroxidase (GPX) (Gao et al., 2015). Further study suggested that under cysteine deprivation, the anaplerotic role of glutaminolysis in the TCA cycle causes hyperpolarization of the mitochondrial membrane potential and lipid ROS accumulation, and promotes ferroptosis (Gao et al., 2019).

Generally, system Xc^- and GPX4 pathways are two main master regulators protecting cells from ferroptosis by removing cellular lipid hydroperoxides (Yang et al., 2014; Wang LY et al., 2020; Jiang et al., 2021). System Xc^-, also known as cystine/glutamate antiporter, is an important intracellular antioxidant. It is composed of the light chain solute carrier family 7 member 11 (SLC7A11, also known as xCT) and the heavy chain SLC3A2 (Parker et al., 2021). These two components work together to import cystine and export glutamate, respectively (Liu JY et al., 2020). Their normal function is important for GSH synthesis (Xie et al., 2016; Stockwell et al., 2017). GPX4, one of the selenium-dependent GPXs, can protect membrane lipids from peroxidation damage when there is sufficient tripeptide antioxidant GSH (Brigelius-Flohé and Maiorino, 2013). Ferroptosis suppressor protein 1 (FSP1) is another mediator, independent of GPX4, which protects cells against ferroptosis. Mechanically, FSP1 catalyzes the regeneration of coenzyme Q10 (CoQ10; its reduced form is ubiquinol) using NAD(P)H, trapping lipid peroxyl radicals to clear excessive cellular lipid peroxidation and attenuate ferroptosis (Viswanathan et al., 2017). Therefore, deficiency of system Xc^-, GPX4, and FSP1 will accelerate ferroptosis (Yang et al., 2014; Yang and Stockwell, 2016; Viswanathan et al., 2017). Since iron is overloaded in cancer cells, deeply exploring the exact mechanism of iron-induced ferroptosis and the relationship between

ferroptosis and cancer progression should provide promising methods for cancer treatment.

3.2 Roles of iron in cancer cell ferroptosis

As iron is a core factor triggering ferroptosis, processes involved in iron metabolism, including iron uptake, storage, usage, and efflux, are vital to modulate ferroptosis. Previous research has reported that iron overload can promote ferroptosis by initiating lipid peroxidation through the Fenton reaction (Dixon and Stockwell, 2014). Moreover, many iron-related proteins are involved in this process (Gao et al., 2015; Feng et al., 2020). Cell density-dependent ferroptosis is mediated by E-cadherin cooperating with neurofibromin 2 (NF2)/Yes-associated protein (YAP) to promote the expression of TfR1 and ACSL4, ultimately causing ferroptosis (Wu et al., 2019). In neuroblastoma cells, by targeting the Kelch-like ECH-associated protein 1 (KEAP1), the ferroptosis-inducing agent withaferin A (WA) can activate the nuclear factor erythroid 2-related factor 2 (NRF2) pathway. This promotes the expression of heme oxygenase 1 (HMOX1) and elevates cellular iron to induce ferroptosis and improve prognosis (Hassannia et al., 2018). In breast cancer, downregulation of ataxia telangiectasia-mutated protein (ATM, the DNA damage response serine/threonine kinase) results in the transcriptional activation of FPN, FTH, and FTL by the transcription factor metal-regulatory transcription factor 1 (MTF1). This protects cancer cells from cystine-deprived ferroptosis (Chen et al., 2020). In lung cancer, ubiquitin-specific protease 35 (USP35) directly interacts with FPN to protect FPN from degradation. Moreover, USP35 knockdown significantly increases the iron level and confers cancer cell sensitivity to ferroptosis under the stimulation of erastin (Tang et al., 2021). Modulating ferritinophagy, the degradation of ferritin in lysosomes, alters cellular iron levels and is closely associated with ferroptosis. Ferritinophagy can lead to the release of iron (Zhou et al., 2020) and is mediated by nuclear receptor coactivator 4 (NCOA4), a selective cargo receptor for the autophagic degradation of ferritin (Mancias et al., 2014). Knockdown of autophagy-related gene 5 (*atg5*) and *atg7* (the main components forming autophagosomes) or genetic inhibition of NCOA4 inhibits ferritin degradation and decreases cellular iron and ferroptosis (Gao et al., 2016; Hou et al., 2016; Chen X et al., 2021).

3.3 Dysregulated brakes in cancer cell ferroptosis

Lipid peroxidation of the cell membrane, the major event in ferroptosis, can be triggered by the inhibition of system Xc^- or GPX4 (Li and Li, 2020). Cancer cells deploy various mechanisms to modulate the expression and/or activity of system Xc^- (especially SLC7A11) and GPX4 to regulate ferroptosis. The oncoprotein NRF2 is a vital regulator of the antioxidant response. Many downstream targets of NRF2, including GPX4 and system Xc^-, are required to keep the cellular redox balance and protect cells from ferroptosis (Roh et al., 2017; Dodson et al., 2019). The tumor suppressor alternative reading frame (ARF) can trigger cell death by attenuating tumor progress (Hayes and Dinkova-Kostova, 2017). Recent studies have shown that the ARF interacts with NRF2 to inhibit the transcription of SLC7A11 and promote ferroptosis, and furthermore, the ARF/NRF2 regulatory axis in ferroptosis is independent of the p53 pathway (Chen et al., 2017; Koppula et al., 2018). p53 plays a central role in the regulation of cellular metabolism (Kastenhuber and Lowe, 2017). Evidence has revealed that p53 also mediates ferroptosis in cancer by modulating its downstream metabolic targets cystine/glutamate antiporter SLC7A11 (Jiang et al., 2015) and arachidonate 12-lipoxygenase (ALOX12) (Chu et al., 2019). Zhang et al. (2018) found that tumor suppressor BRCA1-associated protein 1 (BAP1) represses the expression of SLC7A11 through epigenetic regulation of HA2 ubiquitination on the SLC7A11 promoter, which leads to elevated ferroptosis and tumor suppression.

The oxidative stress generated by mitochondria also causes ferroptosis. Mitochondrial ROS have been reported to activate the AMPK/Unc-51-like kinase (ULK) signal pathway and promote ferritinophagy and other causes of cell ferroptosis (Qin et al., 2021). Disruption of the synthesis of the Fe-S cluster is correlated with a high accumulation of iron and ROS. Recent evidence has revealed that suppressed expression of FXN modulates erastin-induced ferroptosis and inhibits tumor growth induced by accumulated free iron and lipid peroxidation, which also resulted in damaged mitochondria (Du et al., 2020). NFS1 is also reported to be highly expressed and amplified in metastatic primary lung cancer. Suppression of its expression, along with inhibition of cysteine transport, causes ferroptosis and slows down tumor growth in vivo, indicating that NFS1 could protect cells from ferroptosis and

promote lung tumor growth (Alvarez et al., 2017). All this evidence indicates the vital role of mitochondria in ferroptosis.

Targeting the vital molecules that trigger ferroptosis, including the iron chelator DFO and lipophilic radical traps such as vitamin E and ferrostatin-1 (Fer1), is a promising therapeutic strategy to kill therapy-resistant cancer cells (Hassannia et al., 2019). GPX4 and FSP1 are two parallel mechanisms preventing membrane lipid peroxidation (Stockwell et al., 2017), and targeted inhibition of GPX4 and FSP1 makes cancer cells more prone to ferroptosis (Dixon et al., 2012; Yang et al., 2014; Hangauer et al., 2017). Ferroptosis is closely related to the development of cancer, and targeting the triggers of ferroptosis is a promising cancer therapeutic strategy.

4 LncRNAs in ferroptosis and iron metabolism

LncRNAs are widely accepted as master regulators in various cellular programs and as indicators of specific cellular states (Wang and Chang, 2011). Aberrant expression of lncRNAs closely matches cytopathology such as cancers (Schmitt and Chang, 2016). It has been reported that lncRNAs modulate tumorigenesis (Xu et al., 2020; Zhao et al., 2020) and progression in several ways, including cell proliferation (Hung et al., 2014), cell death (Mao et al., 2018), invasion (Liu et al., 2021), and metabolism remodeling (Liu XR et al., 2018; Sang et al., 2018; Liu J et al., 2020) by interacting with chromosomes (Wu et al., 2020), mRNAs (Guo et al., 2020), and proteins (Sang et al., 2018, 2021) (Fig. 2). By acting as an adapter molecule, lncRNA highly upregulated in liver cancer (*HULC*) enhances the interactions between fibroblast growth factor receptor 1 (FGFR1) and two glycolytic enzymes lactate dehydrogenase A (LDHA) and pyruvate kinase M2 (PKM2), promoting their enzymatic activity and glycolysis and cancer progression (Wang CQ et al., 2020). In HCC, Liu et al. (2018) found that lncRNA nuclear enriched abundant transcript 1 (*NEAT1*) helps upregulate the expression of adipose triglyceride lipase (ATGL) by acting as an

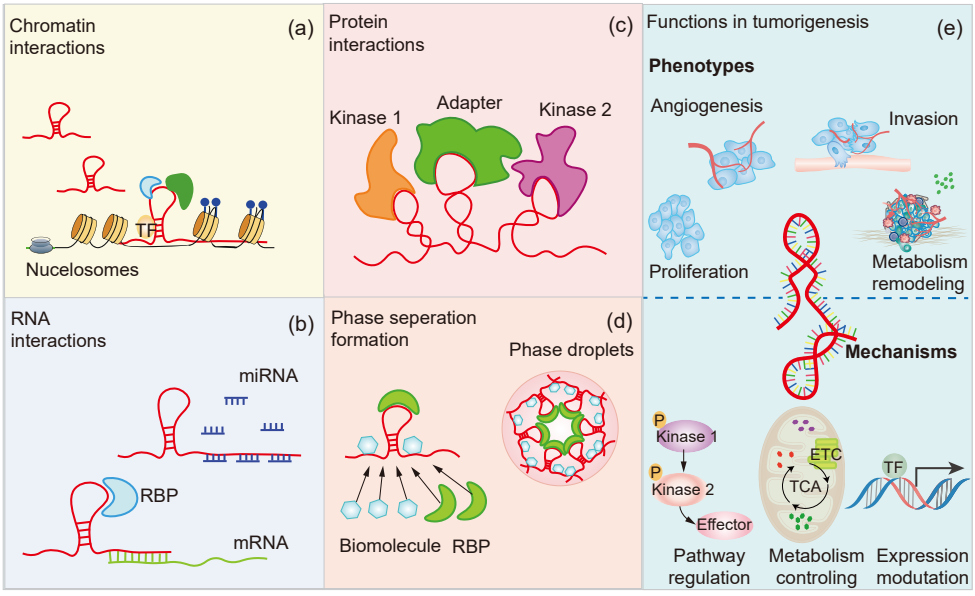

Fig. 2 Mechanisms of action of lncRNA in the cell and its functions in tumorigenesis. (a–d) The mechanisms of lncRNA modulate cell activities by interacting with multiple biomolecules: (a) LncRNA interacts with chromatin to epigenetically modulate gene expression; (b) LncRNA interacts with miRNA away from target mRNA (upper), and also binds to mRNA to affect its splicing, stability, and translation (lower); (c) LncRNA functions as a scaffold to modulate the interaction of function proteins (including signal pathway kinase and metabolic enzymes); (d) LncRNA sequesters biomolecules to form phase separation droplets to regulate cellular activities. (e) Functions of lncRNA in tumorigenesis: lncRNA promotes tumor progression through proliferation, angiogenesis, invasion, and metabolism remodeling by modulating signal pathways, cell metabolism, and gene expression. LncRNA: long noncoding RNA; miRNA: microRNA; mRNA: messenger RNA; TF: transferrin; RBP: RNA-binding protein; P: phosphorylation; TCA: tricarboxylic acid; ETC: electron transport chain.

RNA sponge of miR-124-3p downregulating the expression of ATGL, thereby promoting lipid metabolism. Moreover, lncRNAs can also cooperate with multiple signal pathways, such as the mechanistic target of rapamycin (mTOR) (Malakar et al., 2019), phosphatidylinositol 3,4,5-trisphosphate (PIP3)/Akt (Lin et al., 2017), HIF-1α (Lin et al., 2016), Hippo (Zheng et al., 2017), and nuclear factor-κB (NF-κB) (Sang et al., 2018), to modulate cancer cell glycolysis and Ca^{2+} metabolism, causing microenvironment remodeling and tumor progression. Interestingly, emerging evidence suggests that lncRNA may have the potential to regulate gene expression and signal transduction by modulating liquid-liquid phase separation, thereby further promoting cancer development (Fox et al., 2018; Yamazaki et al., 2018; Li RH et al., 2021). This indicates the significance of lncRNAs in modulating cancer metabolism and cancer progression, and suggests that lncRNAs have the potential to provide prognostic value and even new strategies for clinical therapies (Schmitt and Chang, 2016; Li YJ et al., 2021).

Recent studies also reported that lncRNAs function as adapters (Mao et al., 2018), RNA sponges (Luo et al., 2021; Zhang YY et al., 2021), and epigenetic modulators (Wang ZL et al., 2021), regulating cancer cell ferroptosis by modulating several ferroptosis-related processes, including iron metabolism, GSH metabolism, and system Xc^- (especially the expression of SLC7A11) (Fig. 3 and Table 1). Notably, during ferroptosis regulation, lncRNAs tightly cooperate with the well-known signaling pathways regulating cell survival, including p53 and NRF2. As a typical tumor suppressor regulator, p53 is necessary to elicit cell-cycle arrest, apoptosis, and/or senescence in response to cellular stress (Junttila and Evan, 2009; Berkers et al., 2013). SLC7A11, the key component of the cystine/glutamate antiporter (Lo et al., 2008), was identified as a novel target of p53, and its mRNA expression can be repressed by p53 (Jiang et al., 2015). In breast and lung cancers, p53-related lncRNA *P53RRA*, as a tumor suppressor, is significantly downregulated. Mechanistically, *P53RRA* can displace p53 to form the cytosolic *P53RRA*-GTPase-activating protein (SH3 domain)-binding protein 1 (G3BP1) complex, leading to more extensive retention of p53 in the nucleus and decreased expression of SLC7A11. This is followed by increases in the cellular iron concentration and lipid ROS, which finally promotes cell-cycle arrest and ferroptosis (Mao et al., 2018). As a critical regulator of epigenetic regulation of genes, the nuclear-localized lncRNA long intergenic non-protein coding RNA 618 (*LINC00618*) inhibits the expression of SLC11A7 and accelerates ferroptosis by directly interacting with lymphoid-specific helicase (LSH), a member of the sucrose nonfermenting 2 (SNF2) family of chromatin-remodeling ATPases. It reduces its expression in acute myeloid leukemia (AML), which further increases the levels of lipid ROS and iron (Wang ZL et al., 2021). Interestingly, *LINC00618*-mediated ferroptosis is dependent on apoptosis, which indicates that *LINC00618* acts as a chemotherapeutic marker for AML (Wang ZL et al., 2021).

Moreover, lncRNAs and miRNAs can coordinately regulate ferroptosis. In prostate cancer, lncRNA Opa-interacting protein 5-antisense RNA 1 (*OIP5-AS1*), a miRNA sponge, inhibits ferroptosis by regulating the miR-128-3p/SLC7A11 axis (Zhang YY et al., 2021). In lung cancer, *LINC00336* acts as a miRNA sponge for cystathionine-β-synthase (CBS), a marker of the trans-sulphuration pathway and responsible for the biosynthesis of GSH (Hayano et al., 2016), and plays a functional role in ferroptosis. High expression of *LINC00336* inhibits ferroptosis by reducing intracellular iron and lipid ROS levels and promoting cancer cell proliferation (Wang et al., 2019). In bladder cancer, lncRNA *RP11-89* promotes the expression of prominin 2 (PROM2) by acting as an RNA sponge to silence the expression of miR-129-5p, which enhances the PROM2-mediated formation of ferritin-containing multivesicular bodies (MVBs) and the release of iron, and finally promotes ferroptosis resistance (Luo et al., 2021).

LncRNAs can also regulate ferroptosis by modulating other oxidative stress responders. NRF2 is a transcription activator responsible for the transcription of genes coding for mitochondrial respiratory and antioxidant molecules (Ma, 2013). As an activator of NRF2, GA-binding protein transcription factor subunit β1 (GABPB1) is necessary for the transcriptional activation of antioxidant-related genes (Bell et al., 2015). The NRF2/GABPB1 pathway plays a vital role in responding to oxidative stress (Ma, 2013). In NSCLC, lncRNA metallothionein 1D pseudogene (*MT1DP*) downregulates the expression of NRF2 by stabilizing the expression of miR-365a-3p, which can promote the erastin-induced ferroptosis of cancer

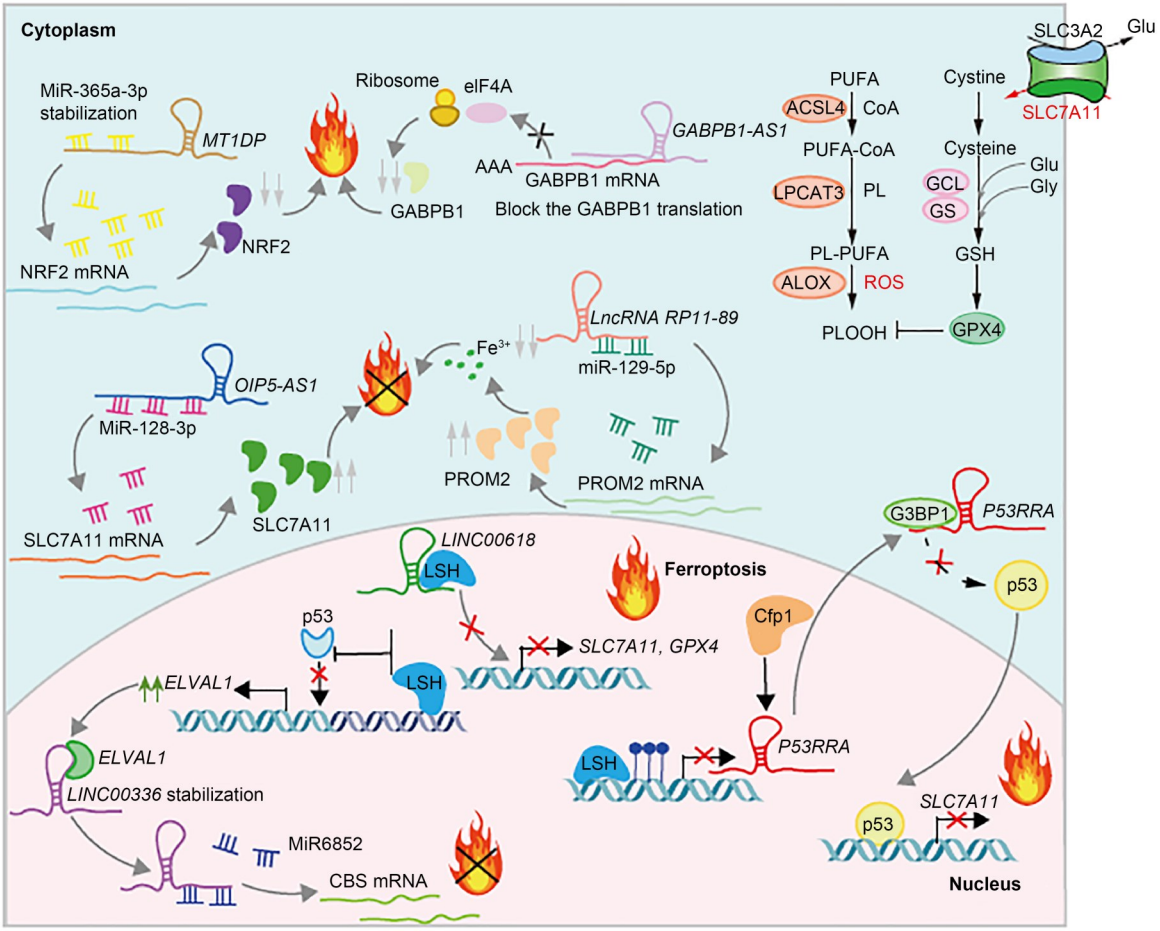

Fig. 3 Involvement of lncRNA in ferroptosis. LncRNA *OIP5-AS1* functions as a miRNA sponge to silence miRNA-128-3p, stabilizing SLC7A11 mRNA and inhibiting ferroptosis. Nuclear-localized lncRNA *LINC00618* interacts with LSH to epigenetically block the expression of SLC7A11 and cause increased lipid ROS and iron, thus accelerating ferroptosis. Tumor suppressor lncRNA *P53RRA* can displace p53 to form a cytosolic *P53RRA*-G3BP1 complex, which leads to greater retention of p53 in the nucleus and blocks the expression of SLC7A11, finally causing cell-cycle arrest and ferroptosis. LncRNA *LINC00336* acts as a miRNA sponge for CBS, which acts as a marker of trans-sulphuration pathway activity and further inhibits ferroptosis by decreasing intracellular levels of iron and lipid ROS. By inhibiting the recruitment of p53 to the promoter of ELAV-like (ELAVL) RNA-binding protein, LSH promotes ELAVL1 expression and further assists the stabilization of *LINC00336*. LncRNA *RP11-89* promotes the expression of PROM2 by acting as an RNA sponge to silence the expression of miR-129-5p, which enhances the PROM2-mediated formation of ferritin-containing MVBs and the release of iron, and finally promotes ferroptosis resistance. LncRNA *MT1DP* downregulates the expression of NRF2 by stabilizing the expression of miR-365a-3p and finally promotes ferroptosis. LncRNA *GABPB1-AS1* inhibits the translation of GABPB1 by blocking its recruitment to polysomes and binding with eIF4A, and finally promotes ferroptosis of HCC cells. The right upper panel shows the critical processes involved in ferroptosis; the details can be seen in Fig. 1d. LncRNA: long noncoding RNA; *OIP5-AS1*: Opa-interacting protein 5-antisense RNA 1; miRNA: microRNA; SLC7A11: solute carrier family 7 member 11; mRNA: messenger RNA; *LINC00618*: long intergenic non-protein coding RNA 618; LSH: lymphoid-specific helicase; ROS: reactive oxygen species; *P53RRA*: p53-related lncRNA; G3BP1: GTPase-activating protein (SH3 domain)-binding protein 1; CBS: cystathionine-β-synthase; ELAV: embryonic lethal, abnormal vision; ELAVL1: ELAV-like protein 1; PROM2: prominin 2; MVBs: multivesicular bodies; *MT1DP*: metallothionein 1D pseudogene; NRF2: nuclear factor erythroid 2-related factor 2; GABPB1: GA-binding protein transcription factor subunit β1; eIF4A: eukaryotic initiation factor-4A; HCC: hepatocellular carcinoma; CoA: coenzyme A; ACSL4: acyl-CoA synthetase long-chain family member 4; LPCAT3: lysophosphatidylcholine acyltransferase 3; ALOX: arachidonate lipoxygenase; PL: phospholipid; PUFA: polyunsaturated fatty acid; PLOOH: phospholipid hydroperoxide; GCL: glutamate-cysteine ligase; GS: glutathione synthase; Glu: glutamate; Gly: glycine; GSH: glutathione; GPX4: glutathione peroxidase 4; Cfp1: CXXC finger protein 1.

Table 1 LncRNAs involved in ferroptosis

LncRNA	Cellular localization	Mechanism	Biological function	Reference
P53RRA	Cytoplasm	Interacts with G3BP1 to decrease the expression of SLC7A11	Interacts with G3BP1, displaces p53 from a G3BP1 complex, and results in p53 retention in the nucleus; decreases the expression of SLC7A11 and subsequently promotes ferroptosis	Mao et al., 2018
LINC00618	Nucleus	Interacts with LSH to decrease the expression of SLC7A11	Attenuates the expression of LSH and results in the reduced expression of SLC7A11, and then promotes ferroptosis in leukemogenesis	Wang ZL et al., 2021
OIP5-AS1	Cytoplasm	Sponge of miR-128-3p to promote the expression of SLC7A11	Acts as a miRNA sponge for miR-128-3p to promote the expression of SLC7A11, and subsequently inhibits ferroptosis in prostate cancer	Zhang YY et al., 2021
LINC00336	Nucleus	Sponge of miR6852 to promote the expression of CBS	Serves as an endogenous sponge of miR6852 to promote the expression of CBS and thereby inhibits ferroptosis	Wang et al., 2019
RP11-89	Cytoplasm	Sponge of miR-129-5p to promote the expression of PROM2	Promotes the expression of PROM2 by acting as an RNA sponge to silence the expression of miR-129-5p and further cause ferroptosis resistance	Luo et al., 2021
MT1DP	Cytoplasm	Interacts with miR-365a-3p to downregulate the expression of NRF2	Downregulates the expression of NRF2 by stabilizing the expression of miR-365a-3p, and finally promotes ferroptosis	Gai et al., 2020
GABPB1-AS1	Cytoplasm	Interacts with the mRNA of GABPB1 and blocks its translation	Inhibits the translation of GABPB1 by blocking its recruitment to polysomes and binding with eIF4A, and finally promotes the ferroptosis of HCC cells	Qi et al., 2019

LncRNA: long noncoding RNA; *P53RRA*: p53-related lncRNA; *LINC00618*: long intergenic non-protein coding RNA 618; *OIP5*: Opa-interacting protein 5; *AS1*: antisense RNA 1; *MT1DP*: metallothionein 1D pseudogene; GABPB1: GA-binding protein transcription factor subunit β1; G3BP1: GTPase-activating protein (SH3 domain) binding protein 1; SLC7A11: solute carrier family 7 member 11; LSH: lymphoid-specific helicase; CBS: cystathionine-β-synthase; PROM2: prominin 2; NRF2: nuclear factor erythroid 2-related factor 2; mRNA: messenger RNA; miRNA: microRNA; eIF4A: eukaryotic initiation factor-4A; HCC: hepatocellular carcinoma.

cells. Nano-particles encapsulated with lncRNA *MT1DP* can be a therapeutic target for cancer treatment (Gai et al., 2020). LncRNA *GABPB1-AS1* is the antisense RNA of GABPB1 mRNA. In HCC, lncRNA *GABPB1-AS1* is upregulated by erastin and inhibits the translation of GABPB1, further promoting the ferroptosis of HCC cells. Mechanistically, lncRNA *GABPB1-AS1* directly interacts with the mRNA of GABPB1, blocking its recruitment to polysomes and binding with eukaryotic initiation factor-4A (eIF4A) (Qi et al., 2019). Diverse meta-analyses have also reported that ferroptosis-related lncRNAs have the potential to predict the prognosis and outcome of breast cancer (Zhang KM et al., 2021), lung cancer (Lu et al., 2021; Zheng et al., 2021), and HCC (Chen ZA et al., 2021). This provides further insights regarding the role of lncRNAs and suggests clinical targets for cancer treatment. However, the detailed mechanism of action of lncRNAs in cellular iron metabolism and ferroptosis still needs to be clarified. Given the diverse functions of lncRNAs in cellular metabolism and the great potential of targeting ferroptosis in cancer therapy, in-depth exploration of the exact mechanism of ferroptosis, especially the functional roles of lncRNAs in ferroptosis and iron metabolism, will help accelerate the application of lncRNAs in combination with ferroptosis targets in clinical cancer treatment.

5 Perspectives

Cellular iron homeostasis is vital for various cellular biological processes. However, iron metabolism reprogramming is found in many cancers and is a hallmark for rapid cell proliferation and cancer malignancy. Cancer cells prefer to stockpile intracellular iron by upregulating diverse genes involved in iron transport, uptake, and storage, and downregulating genes related to iron efflux. Thus, methods that decrease the intracellular iron concentration, including genetically modulating gene-related iron metabolism, administering iron chelators, and using neutralized antibodies, are promising approaches to cancer treatment. However, given the universal biological function of iron in the

cell cycle, DNA synthesis, oxygen transport, and the electron transfer chain in both normal cells and cancer cells, how to specifically target cancer cells to reduce their cellular iron and increase the adverse effects brought about by therapeutic methods needs to be further investigated.

Moreover, the excessive iron makes cancer cells that show little response to traditional necroptosis more vulnerable to iron-catalyzed ferroptosis, which raises expectations for the potential of ferroptosis as a promising strategy for treating therapy-resistant cancers. Thus, deeply exploring the mechanisms and key factors modulating ferroptosis will shed light on precision cancer therapy. Targeting the disrupted expression of system Xc^-, GPX4, and antioxidant-related genes is also a promising method for triggering the ferroptosis of cancer cells with an iron overdose. However, it raises many questions. For example, what is the plasticity of the iron metabolism of cancer cells for triggering ferroptosis? Simultaneously, cancer cells could use excessive iron to promote cells to iron-dependent cell death, namely ferroptosis. Excessive iron contributes to both tumor growth and ferroptosis-induced tumor inhibition. Thus, how to use this "double-edged sword" for cancer treatment is an urgent problem to be solved.

LncRNAs play a versatile role in tumorigenesis, cancer cell proliferation, invasion, angiogenesis, and metastasis via various mechanisms. LncRNAs are positively involved in regulating ferroptosis-related processes, including modulating the iron concentration, GSH metabolism, and the activity of system Xc^-. In particular, lncRNAs cooperate with diverse typical signaling pathways, such as p53 and NRF2, to regulate the expression of ferroptosis-related genes. Thus, the collective actions of lncRNAs, iron metabolism and ferroptosis in cancer development need further study. A deeper understanding of lncRNA modulation in iron metabolism will widen the knowledge of cancer metabolism and provide promising new cancer therapeutic strategies.

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Author contributions

Aifu LIN and Jian LIU contributed to the study design and data analysis, and edited the manuscript. Lei QU and Xinyu HE wrote the manuscript. Lei QU, Qian TANG, and Xiao FAN contributed to the figure and table design. All authors have read and approved the final version.

Compliance with ethics guidelines

Lei QU, Xinyu HE, Qian TANG, Xiao FAN, Jian LIU, and Aifu LIN declare that they have no conflict of interest.

This review does not contain any studies with human or animal subjects performed by any authors.

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