Non-coding RNAs and ferroptosis: potential implications for cancer therapy

Amar Balihodzic1,2, Felix Prinz1,2, Michael A. Dengler1, George A. Calin3, Philipp J. Jost1,4 and Martin Pichler1,2,5

© The Author(s) 2022

Ferroptosis is a recently defined form of regulated cell death, which is biochemically and morphologically distinct from traditional forms of programmed cell death such as apoptosis or necrosis. It is driven by iron, reactive oxygen species, and phospholipids that are oxidatively damaged, ultimately resulting in mitochondrial damage and breakdown of membrane integrity. Numerous cellular signaling pathways and molecules are involved in the regulation of ferroptosis, including enzymes that control the cellular redox status. Alterations in the ferroptosis-regulating network can contribute to the development of various diseases, including cancer. Evidence suggests that ferroptosis is commonly suppressed in cancer cells, allowing them to survive and progress. However, cancer cells which are resistant to common chemotherapeutic drugs seem to be highly susceptible to ferroptosis inducers, highlighting the great potential of pharmacologic modulation of ferroptosis for cancer treatment. Non-coding RNAs (ncRNAs) are considered master regulators of various cellular processes, particularly in cancer where they have been implicated in all hallmarks of cancer. Recent work also demonstrated their involvement in the molecular control of ferroptosis. Hence, ncRNA-based therapeutics represent an exciting alternative to modulate ferroptosis for cancer therapy. This review summarizes the ncRNAs implicated in the regulation of ferroptosis in cancer and highlights their underlying molecular mechanisms in the light of potential therapeutic applications.

Cell Death & Differentiation (2022) 29:1094–1106; https://doi.org/10.1038/s41418-022-00998-x

FACTS

- Ferroptosis is a unique, iron-dependent, oxidative form of regulated cell death.
- Ferroptosis is frequently suppressed in cancer supporting its growth and progression.
- Ferroptotic rich regulatory network is essentially modulated by ncRNAs.
- NcRNA-based therapeutics targeting ferroptosis is a promising novel anti-cancer therapy.

OPEN QUESTIONS

- What is the relationship between ncRNAs, ferroptosis and other forms of regulated cell death in cancer?
- Are individual ncRNAs potential molecular markers of ferroptosis that could be used in living cells and tissues?
- What are the optimal delivery systems of novel ncRNAs-therapeutics, particularly for efficient intracellular uptake and controlled release?
- Would potential combination of available drugs with novel ncRNA-therapeutics modulating ferroptosis result in an improved cancer treatment?

INTRODUCTION

Non-coding RNAs: master regulators of cellular processes

Non-coding RNAs (NcRNAs) are a miscellaneous group of non-coding transcripts with limited protein-coding potential that perform important cellular functions through different molecular mechanisms [1]. Initially, it was thought that they are functionally irrelevant. However, as a myriad of functional ncRNAs were identified and characterized, the central dogma of proteins being the functional end product of gene expression has drastically changed [2]. Broadly spoken, they can either be subdivided into short and long ncRNAs (a general cut off value is 200 nucleotides in length), or subdivided due to their biological roles [3]. Three major classes of functional ncRNAs are short microRNAs (miRNAs), long ncRNAs (lncRNAs), and circular RNAs (circRNAs). Depending on their intrinsic features, they may show tissue- and/or disease-specificity and may be detected in all body fluids making them interesting...
for their potential utilization as biomarkers [4]. In addition, ncRNAs are frequently deregulated in various diseases, including cancer [5]. In many instances their involvement in drug resistance in cancers has been reported [6–9]. Thus, targeting of ncRNAs might be a promising therapeutic option to modulate drug resistance-promoting pathways in cancer cells and improve the outcome of patients [10].

**Ferroptosis: the molecular mechanisms of a recently identified form of cell death**

Ferroptosis is an iron-dependent, oxidative form of cell death that is biochemically and morphologically different from other types of regulated cell death [11–13]. Ferroptosis is caused by excessive oxidative destruction (peroxidation) of lipids in the cellular membranes. The process relies on iron, reactive oxygen species (ROS), and phospholipids containing polyunsaturated fatty acids (PUFAs) [14–16].

Lipid peroxidation occurs when a bisallylic hydrogen atom, located between two carbon–carbon double bonds, is removed from the PUFAs in the membrane phospholipids. The result is formation of a carbon-centered phospholipid radical, phospholipid peroxyl radical, and phospholipid peroxides, a form of lipid ROS. Phospholipid peroxides can react with iron to generate free alkoxyl and peroxyl radicals [17]. The requirement of iron in this form of cell death inspired the term ferroptosis [12]. If not converted to its corresponding alcohol, phospholipid peroxides, together with phospholipid free radicals, promote further phospholipid peroxide formation via the processes of hydrogen removal and reaction with oxygen. It is the unrestrained lipid peroxidation that is considered to be the hallmark of ferroptosis [18]. Some first hints of ferroptosis-like death have been observed in the middle of 20-th century in studies investigating metabolism and neuronal cell death. The earliest reports attributed ferroptosis either to other forms of regulated cell death, or it was not recognized as being biologically significant. It was not interpreted as sufficient evidence for a distinct cell death until early 2000s when the Stockwell lab conducted screening of lethal compounds in RAS-transformed cancer cells. They identified erastin and RAS synthetic lethal 3 (RSL3) as inducers of non-apoptotic, iron-dependent cell transformation preventable by iron chelators and lipophilic antioxidants [19, 20]. The following findings, including the mechanism of action of erastin and RSL3, lead to the idea of a unique regulated cell death form. The term ferroptosis was introduced in 2012, and, thus, the field of ferroptosis research is rather officially young [12]. Despite being frequently cited as a new type of cell death, ferroptosis may actually be considered the oldest and evolutionary most conserved form of regulated cell death owing to its simple molecular requirements of iron and oxygen. In fact, ferroptosis-like death has been observed in less-complex species including protozoa, prokaryotes, fungi and plants [21–24].

**Ferroptosis initiation and regulation**

Lipid peroxidation can be initiated by non-enzymatic and enzymatic processes [25]. The non-enzymatic process is triggered by Fenton reaction, where iron and hydrogen peroxide react toward free radical formation and propagation of lipid peroxidation [15]. Numerous enzymes were implicated in the regulation of ferroptosis and are outlined in Fig. 1. Some of the key enzymes are described below.

**Ferroptosis antagonists**

Glutathione peroxidases (GPXs) protect cells from oxidative stress, and hence ferroptosis [14–16]. In fact, GPX4 is the main enzyme
Ferrostatin 1 and liproxstatin 1 are useful in experimental studies. Acyl-CoA synthetase long-chain family member 4 (ACSL4) and 
port processes [48]. In particular, NRF2 is crucial for cell survival as ferritin heavy chain 1 (FTH1), SLC7A11, and cystathionine 
during the oxidative stress. In addition to FSP1, it promotes the 
system xc
cation and oxidation of proteins, and eventual 
morphologically, ferroptotic cells have small mitochondria with increased mitochondrial membrane densities, reduced or vanishing mitochondrial cristae, and rupture of the outer mitochondrial membrane [52]. In addition, ferroptotic death may induce cell membrane rupture, release of intracellular content such as damage-associated molecular patterns (DAMPs), inducing sterile inflammation and can therefore be classified as a form of regulated necrosis [15]. Membrane repair is dependent on endosomal sorting complexes required for transport-III (ESCRT)-III (Fig. 1). This protein complex, consisting of 12 subunits, assembles into the spiral filament and mediates membrane remodeling [63].

Ferroptosis, metabolic and cellular signaling pathways

The regulation of ferroptosis is strongly connected to various essential cellular processes, including metabolic pathways (iron, lipids, amino acids, and glucose metabolism), mitochondrial activity, maintenance of redox status, or response to radiation exposure. Furthermore, several key mediators of cell signaling pathways have been implicated in the regulation of ferroptosis, including multiple oncogenic and tumor-suppressive proteins (e.g., p53) [14, 16].

Iron metabolism plays a central role in ferroptosis. For example, transferrin and its receptor import iron into the cells and promote ferroptosis [64]. In contrast, mechanisms that export cellular iron have been shown to reduce ferroptosis [65, 66]. Autophagic degradation of major iron-storage protein ferritin promotes ferroptosis due to increased iron availability (Fig. 1). This process is named ferritinophagy [67]. Other types of autophagy, such as lipophagy, clockophagy and chaperone-mediated autophagy may also contribute to induction of ferroptosis via degradation of negative regulators of ferroptosis [68–70]. Indeed, there is growing evidence asserting the interaction between ferroptotic and autophagic machinery [71]. For example, lipid peroxidation products (i.e., 4-HNE) may induce autophagosome formation [72]. Heme oxygenase-1 (HO-1), a source of intracellular iron, is found to promote macroautophagy [73]. Erasin also promotes chaperone-mediated autophagy via upregulation of lysosome-associated membrane protein 2a (LAMP-2A), that may also degrade GPX4 [74]. In contrast, overexpression of GPX4 has been shown to inhibit ROS-mediated autophagy [75].

The activity of several metabolic pathways can affect the generation of ROS and are therefore strongly associated with the induction of ferroptosis. For example, glutamine can replenish tricarboxylic acid (TCA) cycle through the generation of α-ketoglutarate [64]. High glutamine uptake and metabolism can result in increased TCA cycle activity and increased rate of mitochondrial respiration, leading to ROS formation and loss of the mitochondrial membrane potential. High extracellular concentration of glutamate impedes system xψ function due to inhibition of cystine uptake, and eventual intracellular glutathione synthesis, therefore leading to the ferroptosis induction [12].
Hypoxia promotes ferroptosis by increasing ROS production which can directly contribute to lipid peroxidation and activation of hypoxia-inducible factors (HIFs) [14]. HIFs have been shown to drive ferroptosis in clear cell renal carcinoma [76]. Even though glucose starvation increases ROS generation, it actually suppresses ferroptosis through the activation of energy sensor AMPK. AMPK, an important regulator of autophagy and apoptosis, promotes ferroptosis by inhibiting system x_c activity in energy-sufficient AMPK-mediated manner [79].

Tumor suppressor proteins may sensitize cells to ferroptosis. P53, an important regulator of apoptosis and autophagy, enhances ferroptosis and prevents tumor development via suppressing the transcription of system x_c component SLC7A11 [80]. In addition, BRCA1-associated protein 1 (BAP1) also promotes ferroptosis by SLC7A11 downregulation [81]. Involvement of oncogenes in ferroptosis is best illustrated through the initial discovery of stronger lethality of erastin and RSL3 in RAS-mutated cancer cells, suggesting determining role of RAS-RAF-MEK pathway in ferroptosis [82].

Furthermore, ionizing radiation has been shown to upregulate ACSL4 expression in cancer leading to increased lipid peroxidation and ferroptosis [83]. Clearly, many more regulators of ferroptosis are yet to be discovered and characterized. As mentioned, and exemplified earlier in text, ncRNAs as versatile master regulators of cellular processes have also recently been linked to the regulation of ferroptosis (Fig. 2). The following sections will systematically summarize the current knowledge on the involvement ncRNAs in regulation of ferroptosis and their role in cancer.

**The role of miRNAs in the regulation of ferroptosis in cancer**

miRNAs are a class of small evolutionarily conserved ncRNAs with a length of approximately 22 nucleotides. Their main function is post-transcriptional regulation of gene expression through binding to complementary target mRNA sequences, leading to translational inhibition or mRNA degradation. The final result is halted protein synthesis [84, 85]. In addition, it has been reported that miRNAs may also induce gene sensitization by binding to target sequence and act as translational activator [86]. While they were completely unknown less than three decades ago, nowadays it has been estimated that miRNAs control the expression of over 60% of all protein-coding genes [87]. Given their substantial regulatory capacity, it seems obvious that deregulation of this tightly controlled miRNA network is frequently linked to cardiovascular, autoimmune, infectious, and neurodegenerative diseases [84]. In fact, they are increasingly recognized as major mediators of disease. The first link between miRNA and human cancer was reported in 2002 by Calin and colleagues [88]. Since then, thousands of miRNAs have been discovered, their deregulation in virtually every type of cancer has been confirmed, and their involvement in all hallmarks of cancer has been revealed [89]. Their regulatory roles in ferroptosis in cancer are not well understood yet, but there is strong evidence that miRNAs are also involved in this crucial process in cancer cells (Fig. 2). Some prominent examples are outlined below and a broader overview is provided in Table 1.

**Ferroptosis-stimulating miRNAs**

MiR-214-3p promotes ferroptosis in hepatocellular carcinoma (HCC) by downregulating the expression of activating transcription factor 4 (ATF4) [35]. ATF4 is induced by stress signals and prevents ferroptosis through the induction of SLC7A11 [90]. In addition, ATF4 regulates the expression of genes involved in differentiation, metastasis and angiogenesis [91]. In gliomas, ATF4 promotes tumor angiogenesis which can be diminished in vitro with ferroptosis inducers [92].

In lung cancer, miR-101-3p is found to be downregulated [26]. When available, this miRNA targets oncogenic transducin beta-like 1X-linked (TBLR1) protein. Low expression of miR-101-3p and high expression of TBLR1 result in enhanced activity of the transcription factor nuclear factor kappa B (NF-kB), which regulates ferroptosis through GPX4 and prostaglandin-endoperoxide synthase 2 (PTGS2). Interestingly, appealing results on tumor growth reduction were observed in in vivo experiments when miR-101-3p was delivered in the form of nanoparticles [26].

Moreover, miR-324-3p is significantly downregulated in lung adenocarcinoma (LUAD) cell lines when compared to healthy cells. When overexpressed, miR-324-3p induces ferroptosis by targeting GPX4, and enhances cisplatin sensitivity [27]. This miRNA is additionally upregulated by metformin in breast cancer cell lines,
Table 1. Examples of miRNAs implicated in ferroptosis regulation in cancer.

| miRNA    | Role in ferroptosis | Mechanism of action                                           | Reference |
|----------|---------------------|----------------------------------------------------------------|-----------|
| miR-375  | Induces ferroptosis in gastric cancer | Downregulates SLC7A11                                           | [34]      |
| miR-4715-3p | Induces ferroptosis in gastric and esophageal carcinomas | Downregulates AURKA and GPX4 expression                         | [170]     |
| miR-214-3p | Induces ferroptosis in HCC     | Downregulates ATF4 and SLC7A11                                  | [35]      |
| miR-101-3p | Induces ferroptosis in lung cancer | Downregulates TBLR1, NF-κB, GPX4 and PTGS2 expression            | [26]      |
| miR-324-3p | Induces ferroptosis in LUAD  | Downregulates GPX4                                              | [27]      |
| miR-324-3p | Induces ferroptosis in breast cancer | Downregulates GPX4                                              | [28]      |
| miR-5096  | Induces ferroptosis in breast cancer | Downregulates SLC7A11                                           | [36]      |
| miR-1287-5p | Induces ferroptosis in osteosarcoma | Downregulates GPX4                                              | [171]     |
| miR-137   | Inhibits ferroptosis in melanoma | Downregulates SLC1A5                                            | [93]      |
| miR-9     | Inhibits ferroptosis in melanoma | Downregulates GOT1, inhibits glutaminolysis                      | [172]     |
| miR-130b-3p | Inhibits ferroptosis in melanoma | Downregulates DKK1, upregulates NRF2 and HO-1 expression        | [173]     |
| miR-103a-3p | Inhibits ferroptosis in gastric cancer | Downregulates GLS2, prevents hydrolysis of glutamine to glutamate | [174]     |
| miR-522   | Inhibits ferroptosis in gastric cancer | Downregulates ALOX15                                            | [60]      |
| miR-23a-3p | Inhibits ferroptosis in HCC     | Downregulates ACSL4                                             | [54]      |
| miR-4443  | Inhibits ferroptosis in NSCLC   | Downregulates m6A, upregulates FSP1                              | [46]      |
| miR-424-5p | Inhibits ferroptosis in ovarian cancer | Downregulates ACSL4                                             | [55]      |
| miR-7-5p  | Inhibits ferroptosis in ovarian, oral squamous cell and HCC | Downregulates mitoferrin, reduces mitochondrial iron levels | [99]      |
| miR-7-5p  | Inhibits ferroptosis in cervical and oral squamous carcinomas | Upregulates ferritin, downregulates ALOX12 expression            | [59]      |

and in vivo experiments lead to GPX4 downregulation and ferroptosis induction [28].

Ferroptosis-inhibitory miRNAs

It has been shown in melanoma cells that miR-137 inhibits lipid peroxidation and iron accumulation in vitro and in vivo by directly targeting solute carrier family 1 member 5 (SLC1A5) [93]. SLC1A5, a non-member of system x−, is a neutral amino acid transporter of alanine, serine, cysteine, and glutamine [94]. As a consequence, reduced levels of this important glutamine transporter lead to decreased glutamate uptake, glutaminolysis, and MDA accumulation [93]. Under physiological conditions, glutamine uptake and its metabolism induce lipid ROS generation and ferroptotic cell death [64]. In addition, miR-137 is associated with TNM stage, metastasis and drug resistance in various cancers through different pathways [95–98].

In addition, miR-7-5p is highly expressed in radioresistant cell lines of ovarian, oral squamous cell and HCC. miR-7-5p downregulates mitoferrin, a protein responsible for transporting iron into mitochondria. Ferroptosis is diminished as a result of reduced iron levels [99]. This miRNA is also upregulated in radioresistant cervical cancer [59]. The observed radio-resistance in cervical and oral squamous carcinoma cell lines is, at least partly, due to miR-7-5p effect on ferroptosis. Knockdown of miR-7-5p is shown to increase ROS levels, mitochondrial membrane potential, intracellular Fe2+ content, as well as downregulation of the iron storage protein ferritin, and upregulation ALOX12 expression [59].

MiR-4443 is upregulated in non-small cell lung cancer (NSCLC) where it contributes to cisplatin resistance [46]. In addition, this miRNA may be transferred to the sensitive cells via exosomes and make them resistant. Mechanistically, miR-4443 inhibits ferroptosis via regulation of FSP1 expression in an N6-methyladenosine (m6A) manner by directly targeting its gene METTL3 [46].

MiRNAs have extremely diverse regulatory roles. In addition to direct regulation of ferroptotic key players, as outlined in the above section, miRNAs may indirectly regulate this cell death process via interaction with other ncRNAs, as illustrated in the following sections.

The role of IncRNAs in the regulation of ferroptosis in cancer

LncRNAs are a class of heterogeneous ncRNAs that are more than 200 nucleotides in length. They share many features with mRNA regarding transcriptional and post-transcriptional processing [100]. Despite being classified as ncRNA, the relevance of the protein-coding potential of IncRNAs is growing [101]. Nevertheless, current evidence infers that IncRNAs mainly regulate cellular processes through the interaction with various other molecules, such as DNA, RNA, and proteins [102, 103]. Having a much broader interactome than miRNAs, IncRNAs can also control chromatin structure, methylation status, sequestration of miRNAs, assembly or disruption of protein complexes, and post-translational modifications [100, 103]. Another feature of IncRNAs is their tissue- and condition-specific (e.g., cancer-specific) expression pattern [100]. The first IncRNAs, H19 and Xist, were discovered in 1980s and 1990s, but they remained exceptions until the early 2000s when characterization of ncRNAs started to outpace protein-coding genes [104]. Dysregulated IncRNAs are involved in all hallmarks of cancers, including sustained angiogenesis and deregulated cellular metabolism [105, 106]. In addition, mounting evidence suggest their importance in ferroptosis regulation, as outlined below (Fig. 2).

Ferroptosis-stimulating IncRNAs

Tumor suppressive IncRNA P53RRA, also known as LINC00472, is downregulated in various cancers including lung, liver, colon, renal and breast cancers [107–111]. In lung cancer, it interacts with Ras GTPase-activating protein-binding protein 1 (G3BP1) in the cytosol [38]. This cytosolic P53RRA–G3BP1 interaction displaces p53 from the G3BP1 complex. In turn, p53 is retained in the nucleus, leading to cell-cycle arrest, apoptosis, and ferroptosis. P53RRA promotes ferroptosis and apoptosis by affecting transcription of several metabolic genes, including the
downregulation of SCL7A11. Additionally, P53RRA increases erastin-induced ferroptosis, lipid ROS and iron concentrations [38].

Furthermore, IncRNA GA binding protein transcription factor beta subunit 1 antisense RNA 1 (GABPB1-AS1) is upregulated by erastin in HCC cells. It inhibits the translation of GA binding protein transcription factor subunit beta 1 (GABPB1) protein, which acts as an activation subunit of transcription activator nuclear respiratory factor 2, also called GA-binding protein (GABP). Downregulated GABPB1 protein leads to the downregulation of peroxiredoxin-5 peroxidase (PRDX5). The resulting suppression of the cellular antioxidant capacity causes accumulation of ROS and MDA, and reduction in cell viability [112].

Metallothionein 1D pseudogene (MT1DP) is an IncRNA that regulates erastin-induced ferroptosis through NRF2 [113]. Ectopic MT1DP expression in NSCLC upregulates ROS and MDA levels, increases intracellular ferrous iron concentration, and reduces glutathione levels in cancer cells exposed to erastin. These effects are achieved through downregulation of NRF2, indirectly via stabilization of miR-365a-3p that normally targets NRF2 mRNA. Interestingly, Gai and colleagues designed folate-modified liposome nanoparticles to enhance the bioavailability and the efficiency of the targeted delivery of both erastin and MT1DP. In vivo mice studies have shown promising results for erastin-induced ferroptosis through this particular pathway in NSCLC [113].

Ferroptosis-inhibitory IncRNAs

LINC00336 is a nuclear IncRNA with oncogenic functions in lung cancer, including the regulation of ferroptosis [114]. It interacts with RNA-binding protein ELAV-like RNA-binding protein 1 (ELAVL1), which stabilizes the LINC00336 via binding adenylate and uridylic (AU)-rich elements (AREs), the signal regions that determine RNA stability. In addition, it is indirectly upregulated through the p53 signaling pathway since LSH increases ELAVL1 expression. When upregulated, LINC00336 acts as an endogenous sponge of miR-6852, thus preventing miRNA-induced downregulation of CBS. The result is inhibited ferroptosis in lung cancer cells, leading to enhanced cell proliferation, colony formation, and tumor formation. LINC00336 has been shown to decrease iron concentration, lipid ROS, and mitochondrial superoxide, and increases mitochondrial membrane potential [114].

Zhang et al. investigated the effects of chronic cadmium exposure - one of the causative factors of prostate cancer - on cellular growth and ferroptosis resistance in vitro and in vivo. After the cadmium exposure, the expression of ferroptosis-related proteins (particularly GPX4, FTH1 and SCL7A11) was increased, suggesting that cadmium exposure confers ferroptosis resistance. These effects were preceded by upregulation of IncRNA OIP5-AS1 expression. OIP5-AS1 acts as an endogenous sponge of miR-128-3p to regulate the expression of SCL7A11 [39].

Nuclear enriched transcript 1 (NEAT1) is a well-known oncogenic perinuclear IncRNA that has significant roles in non-cancerous diseases as well [115, 116]. It is associated with several hallmarks of cancers including proliferation, cell cycle, invasion, migration and apoptosis [117]. Wu et al. found that NEAT1 is capable of binding to ACSL4 mRNA, thus reducing the expression level of this pro-ferroptotic enzyme in NSCLC [56]. While NEAT1 contributes to apoptosis, its role in ferroptosis in NSCLC seems to be independent from it. Also, its contribution to ferroptosis is mediated exclusively via ACSL4 as erastin induction does not significantly affect other ferroptotic players, such as SCL7A11, GPX4, and TFR1 levels [56].

Table 2 provides additional IncRNAs involved in ferroptosis regulation in cancer.

| IncRNA | Role in ferroptosis | Mechanism of action | Reference |
|--------|---------------------|---------------------|-----------|
| P53RRA (LINC00472) | Induces ferroptosis in lung cancer | Downregulates SCL7A11 | [38] |
| MT1DP | Induces ferroptosis in NSCLC | Stabilizes miR-365a-3p, downregulates NRF2 | [113] |
| GABPB1-AS1 | Induces ferroptosis in HCC | Inhibits GABPB1 translation, downregulates GABPB1 and PRDX5 | [112] |
| LINC00618 | Induces ferroptosis in leukemias | Downregulates SLC7A11 via attenuation of LSH expression | [37] |
| LINC00336 | Inhibits ferroptosis in lung cancer | Stabilized by ELAVL1 and LSH. Sponges miR6852, upregulates CBS | [114] |
| NEAT1 | Inhibits ferroptosis in NSCLC | Downregulates ACSL4 expression | [56] |
| H19 | Inhibits ferroptosis in breast cancer | Inhibits production of lipid ROS and induces production of GSH | [175] |
| IncPVT1 | Inhibits ferroptosis in HCC | Sponges miR-214-3p, upregulates GPX4 | [29] |
| OIP5-AS1 | Inhibits ferroptosis in prostate cancer | Sponges miR-128-3p, upregulates SLC7A11 expression | [39] |
| RP11-89 | Inhibits ferroptosis in bladder cancer | Sponges miR-129-5p, upregulates PROM2 which induces iron export | [176] |
| MEG8 | Inhibits ferroptosis in benign hemangioma | Sponged by miR-497-5p. Upregulates SLC7A11 and GPX4 expression | [177] |

In the first study investigating the roles of ferroptosis-associated IncRNAs in the prognosis of head and neck cancer (HNSCC), a total of 25 differentially expressed IncRNAs were found to be...
individual circRNAs can bind to multiple miRNAs that regulate ferroptosis in cancer [124, 125]. Due to their increased stability, circRNAs can be found in the cytoplasm [125]. There they usually function as miRNA sponges.

transcription regulation, most circRNAs are located in the nuclear matrix, which is believed to be a nucleocytoplasmic barrier. However, recent studies have shown that some circRNAs (e.g., intron-containing circRNAs) are present in the cytoplasm and can function as miRNA sponges. Individual circRNAs can bind to multiple miRNAs that regulate different pathways [124, 125]. This feature is of particular importance for the potential therapeutic purposes. Importantly, miRNA-circRNA interactions might not always result in miRNA suppression, but also vice versa. Therefore, circRNAs may also function as miRNA transportation or reservoir agents [124, 130].

While some circRNAs (e.g., intron-containing circRNAs) are found only in the nucleus where they might play a role in transcription regulation, most circRNAs are located in the cytoplasm [125]. There they usually function as miRNA sponges. Individual circRNAs can bind to multiple miRNAs that regulate different pathways [124, 125]. This feature is of particular importance for the potential therapeutic purposes. Importantly, miRNA-circRNA interactions might not always result in miRNA suppression, but also vice versa. Therefore, circRNAs may also function as miRNA transportation or reservoir agents [124, 130].

Moreover, mathematical models assert that optimal ceRNA activity requires supraphysiologic concentrations of their natural counterparts. This clearly suggests an overestimation of ceRNA activity and demand for better molecular models. Lastly, ceRNA as the appealing and straightforward approach in ncRNA studying may potentially hinder researchers’ consideration of other confirmed ncRNAs’ mechanisms of action. Nevertheless, circRNAs are important regulators of numerous normal and pathological cellular processes and diseases, including cancer [138]. So far, circRNAs have been associated with several hallmarks of cancers, including sustained proliferative signaling, evasion of growth suppressors, angiogenesis, invasion and metastasis, and evading cell death and senescence [124, 138]. Growing evidence associate them with ferroptosis (Fig. 2).

### Ferroptosis-stimulating circRNAs
Three circRNAs capable of ferroptosis induction are cIARS, circKDM4C and circ_0000190. cIARS is derived from the IARS gene, and it is found to be highly expressed in HCC after sorafenib treatment.
treatment. Liu et al. found that it promotes ferroptosis after sorafenib treatment through, at least partially, activation of autophagy and ferritinophagy. This circRNA physically interacts with RNA binding protein AlkB Homolog 5 (ALKBH5) [139]. ALKBH5 is known for the improvement of Bcl-2 mRNA stability by catalyzing m6A demethylation, thus enhancing Bcl-2/BECN1 interactions. It is also known as autophagy inhibitor in cancer [140]. Sorafenib administration increases cIARS–ALKBH5 interaction, which is probably due to sorafenib-induced expression of cIARS as this kinase inhibitor has no influence on the ALKBH5 protein levels. Consequently, cIARS represses negative role of ALKBH5 in autophagy leading to enhanced autophagy, ferritinophagy and ferroptosis [139]. Up to date, cIARS is the only circRNA that regulates ferroptosis via interaction with a formed protein.

Further, circKDM4C is downregulated in AML. Normally, it sponges miRNA let-7b-5p which targets p53. In addition to indirect upregulation of p53, circKDM4C, when not retrieved from the circRNA pool, is capable of ferroptosis induction via increasing cellular iron content, upregulation of ACSL4 and PTGS2, and downregulation of GPX4 and FTH1 [32].

Fig. 3  NcRNA-based therapeutics and delivery systems. Several ncRNA-based therapeutics exist, including antisense oligonucleotides, siRNAs, shRNAs, miRNA mimics, anti-miRNAs, miRNA sponges, and therapeutic circRNAs (box 1). Their major limitations and side effects can be overcome by usage of unique delivery systems that include lipid and polymer nanoparticles, antibodies, bacteriophages, exosomes and viral vectors (box 2). Newer generation of ncRNA therapeutics with convenient clinical administration (box 3) are awaited candidates due to their numerous advantages, including utilization of existing cellular processing mechanisms, capability of multiple signaling pathway targeting and promising cost-effective production (box 4). siRNA, small interfering RNA; shRNA, short hairpin RNA; antimiRs, anti-microRNAs; circRNAs, circular RNAs. Created with BioRender.
CircKIF4A, upregulated in papillary thyroid cancer, acts as a sponge of miR-1231, leading to GPX4 overexpression [146]. Table 3 provides an overview of additional circRNAs involved in ferroptosis regulation in cancer.

**Ferroptosis and ncRNAs interplay: therapeutic potential in cancer**

Remarkably, this form of cell death has been associated with numerous pathologic processes including neurodegeneration, liver and lung fibrosis, ischemia-reperfusion injuries in brain, heart, kidneys and organ transplantation [14, 16]. Nevertheless, there is major evidence of its particular relevance in cancer. It has been shown that mesenchymal and dedifferentiated cancer cells, which are resistant to cancer therapeutics and apoptosis, are highly susceptible to ferroptosis inducers [147, 148]. Hence, inducing ferroptotic cell death (e.g., by pharmacologic manipulation) may help to overcome resistance of malignant cells to chemotherapy and therefore has great potential for cancer treatment. Several strategies to specifically induce ferroptosis are already being tested. One option is to target key enzymes involved in ferroptosis in cancer cells. For example, pharmacologic and genetic inhibition of system x_{c} by blocking SLC3A2 and SLC7A11 have shown promising results in mouse models with low toxicity [149–152]. Similarly, targeting FSP1 is a promising approach due to its irrelevance in normal mice development indicating a potential broad therapeutic window [42, 153].

While GPX4 is expressed in most cancer cell lines, it is essential for various organs, including kidneys and neurons [145, 154, 155]. Therefore, GPX4 inhibitors (e.g., RSL3) should be delivered specifically to the cancer cells to prevent side effects. Indirect ferroptosis inducers such as erastin may have low solubility and labile metabolism in the complex human body [156]. Incorporation of ferroptotic inducer compounds into protective delivery systems, such as nanoparticles, may overcome this problem. In addition, nanoparticles delivering iron, peroxides, and ncRNAs targeting key inhibitors of ferroptosis into cancer cells are already actively being tested in vitro and in vivo studies. NcRNAs are notably emerging as they ultimately carry several advantages. They are naturally occurring molecules in cells meaning their therapeutic counterparts may utilize existing cellular metabolic pathways. Additionally, ncRNAs frequently target multiple genes within one and/or more pathways causing a broader yet specific anti-cancer response, such as the case with miR-15 and miR-16 cluster that regulates various anti-apoptotic and cell cycle players, including bcl-2, mcl1 and c-JUN [157]. Lastly, ncRNA therapeutics can be fairly easy chemically synthesized shaping them as cost-effective medications of the future.

Indeed, several ncRNA-based therapies are currently developed, including antisense oligonucleotides, small interfering RNAs, short hairpin RNAs, miRNA mimics, miRNA sponges, anti-microRNAs (antimiRs), and therapeutic circular RNAs (Fig. 3) [158, 159]. Some of them are targeting up-regulated oncogenic molecules, while others replenish downregulated tumor suppressors. Although majority are still being tested in clinical studies, eleven ncRNA-based therapeutics have already been approved for several other disease entities [159]. Major current limitations of ncRNA-based therapeutics are specificity, delivery, and tolerability. Issues with specificity and off-target effects occur due to uptake by the...
Particular advances have been made with chemical modifications and optimization of delivery methods that include lipid nanoparticles, polymers, antibodies, bacteriophages, and exosomes (Fig. 3) [159]. Furthermore, immune checkpoint inhibitors, radiotherapies, polymers, antibodies, bacteriophages, and exosomes occur if ncRNAs are recognized as foreign viral nucleic acids [158].

These findings propose the potential drug repositioning and synergistic combinatorial therapeutic regimens in the future. Figure 4 highlights the compounds, including available therapeutics, with their suggested roles in ferroptosis.

CONCLUSION
Recently characterized as unique form of regulated cell death, ferroptosis has already been associated with numerous diseases—above all with cancer. However, our knowledge about ferroptosis is still fairly limited and many open questions remain. We still do not know the complete relationship between ferroptosis and other forms of regulated cell death that share some common upstream mechanisms, such as p53. In addition, redox-independent roles of iron as well as the roles of other metals (e.g., copper) are not completely ruled out in ferroptosis induction. In addition, the exact molecular events responsible for the execution of cell death via ferroptosis are not fully understood. This is particularly pronounced in our ignorance of molecular events that occur downstream of lipid peroxidation including crucial moment(s) when activated ferroptosis cannot longer be suppressed. Finally, specific markers of ferroptosis suitable for application in live cells and intact tissues are still lacking. Furthermore, ncRNAs are a heterogeneous group of non-coding transcripts with exceptional regulatory and biomarker capacities. Only a fraction of annotated ncRNAs have been investigated in the context of ferroptosis and cancer. Nevertheless, current evidence suggests that ferroptosis is frequently inhibited in cancer through the deregulation of usually tightly controlled ncRNA networks, thereby aiding cancer cell survival and progression. Hence, artificial induction of ferroptosis carries a great therapeutic potential. Albeit in their infancies, emerging innovative therapeutics in both fields are paving the exciting path toward the successful utilization of novel ferroptosis-modulating ncRNA-therapeutics in cancer.

DATA AVAILABILITY
Correspondence and requests for materials should be addressed to Martin Pichler.

REFERENCES
1. Qu Z, Adelson DL. Evolutionary conservation and functional roles of ncRNA. Front Genet. 2012;3:205.
2. Cech TR, Steitz JA. The noncoding RNA revolution—trashing old rules to forge new ones. Cell. 2014;157:77–94.
3. Ling H, Vincent K, Pichler M, Fodde R, Berindan-Neagoe I, Slack FJ, et al. Junk DNA and the long non-coding RNA twist in cancer genetics. Oncogene. 2015;34:5003–11.
4. Kim T, Reitmair A. Non-Coding RNAs: functional aspects and diagnostic utility in oncology. Int J Mol Sci. 2013;14:4934–68.
5. Esteller M. Non-coding RNAs in human disease. Nat Rev Genet. 2011;12:861–74.
6. Sarkar FH, Li Y, Wang Z, Kong D, Ali S. Implication of microRNAs in drug resistance for designing novel cancer therapy. Drug Resist Updat. 2010;13:57–66.
7. Jiang W, Xia J, Xie S, Zou R, Pan S, Wang ZW, et al. Long non-coding RNAs as a determinant of cancer drug resistance: Towards the overcoming of chemoresistance via modulation of IncRNAs. Drug Resist Updat. 2020;50:100683.
8. Hua X, Sun Y, Chen J, Wu Y, Sha J, Han S, et al. Circular RNAs in drug resistant tumors. Biomed Pharmacother. 2019;118:109233.
9. Posch F, Prinz F, Balihodzic A, Mayr C, Kieslich T, Klec C, et al. MiR-200c-3p regulates cisplatin resistance in biliary tract cancer by ZEB1-independent mechanisms. Cancers. 2021;13:3996.
10. Matsui M, Corey DR. Non-coding RNAs as drug targets. Nat Rev Drug Disco. 2017;16:167–79.
11. Bedou I, Herold MJ, Strasser A. Emerging connectivity of programmed cell death pathways and its physiological implications. Nat Rev Mol Cell Biol. 2020;21:678–95.
12. Dixon SJ, Lembregt KM, Lamprecht MR, Skouta R, Zaitsev EM, Gleason CE, et al. Ferroptosis: an iron-dependent form of nonapoptotic cell death. Cell. 2012;149:1060–72.
13. Galluzzi L, Vitale I, Aaronsen SA, Abrams JM, Adam D, Agostini P, et al. Molecular mechanisms of cell death: recommendations of the Nomenclature Committee on Cell Death 2018. Cell Death Differ. 2018;25:456–511.
14. Jiang X, Stockwell BR, Conrad M. Ferroptosis: mechanisms, biology and role in disease. Nat Rev Mol Cell Biol. 2021;22:266–82.
15. Huang F, Liu J, Tang D, Kang R. Oxidative damage and antioxidant defense in ferroptosis. Front Cell Dev Biol. 2020;8:586578.
16. Li J, Cao F, Yin H, Huang Z, Lin Z, Mao N, et al. Ferroptosis: past, present and future. Cell Death Dis. 2020;11:88.
17. Collin F. Chemical basis of reactive oxygen species reactivity and involvement in neurodegenerative diseases. Int J Mol Sci. 2019;20:2407.
18. Rishi G, Huang G, Subramaniam VN. Cancer therapeutics: role of ferroptosis and ferroptosis. Int J Biochem Cell Biol. 2021;141:106094.
19. Yang WS, Stockwell BR. Synthetic lethal screening identifies compounds activating iron-dependent, nonapoptotic cell death in oncogenic-RAS-harboring cancer cells. Chem Biol. 2008;15:324–45.
20. Yagoda N, von Rechenberg M, Zaganjar E, Bauer AJ, Yang WS, Fridman DJ, et al. RAS-RAF-MEK-dependent oxidative cell death involving voltage-dependent anion channels. Nature. 2007;447:864–8.
21. Aldrovandi M, Banthiya S, Meckelmann S, Zhou Y, Heydecker D, O’Donnell VB, et al. Specific oxygenation of plasma membrane phospholipids by Pseudomonas aeruginosa lipoxynase generates structural and functional alterations in mammalian cells. Biochim Biophys Acta. 2018;1863:152–64.
22. Dar HH, Tuyrina YY, Mikulska-Ruminska K, Shirvastava I, Ting HC, Tjurin VA, et al. Pseudomonas aeruginosa utilizes host polyunsaturated phosphatidylethanolamines to trigger theft-ferroptosis in bronchial epithelium. J Clin Invest. 2018;128:4639–53.
23. Bogacz M, Krauth-Siegel RL. Trypanosomadoxin peroxidase-deficiency commits trypanosomes to ferroptosis-type cell death. Elife. 2018;7:e37503.
24. Distefano AM, Martin MV, Cordoba JP, Bellido AM, D’ippolito S, Colman SL, et al. Heat stress induces ferroptosis-like cell death in plants. J Cell Biol. 2017;216:463–76.
25. Zheng J, Conrad M. The metabolic underpinnings of ferroptosis. Cell Metab. 2020;32:920–37.
26. Luo Y, Xu G, Yi H, Li Q, Wu Z, Wang J, et al. Nanomedicine promotes ferroptosis to inhibit tumour proliferation in vivo. Redox Biol. 2021;42:101908.
27. Deng SH, Wu DM, Li L, Liu T, Zhang T, Li J, et al. mir-324-3p reverses cisplatin resistance by inducing GPX4-mediated ferroptosis in lung adenocarcinoma cell line A549. Biochem Pharmacol Res Commun. 2021;549:54–60.
28. Hou Y, Cai S, Yu S, Lin H. Metformin induces ferroptosis by targeting miR-324-3p/GPX4 axis in breast cancer. Acta Biochim Biophys Sin. 2021;53:333–41.
29. He QN, Bao NR, Wang S, Xi M, Zhang TH, Chen FS. Ketamine induces ferroptosis of liver cancer cells by targeting IncRNA PVT1/miR-214-3p/GPX4. Drug Des Devel Ther. 2021;15:3965–78.
30. Chen S, Zhang Z, Zhang B, Huang Q, Liu Y, Qiu Y, et al. CircCDK14 promotes tumor progression and resists ferroptosis in glioma by regulating PDGFRα. Int J Biol Sci. 2022;18:8481–57.
31. Jiang W, Xia J, Xie S, Zou R, Pan S, Wang ZW, et al. Long non-coding RNAs as drug targets in cancer. Front Genet. 2022;13:841.
32. Jiang W, Xia J, Xie S, Zou R, Pan S, Wang ZW, et al. Long non-coding RNAs as drug targets in cancer. Front Genet. 2022;13:841.
33. He QN, Bao NR, Wang S, Xi M, Zhang TH, Chen FS. Ketamine induces ferroptosis of liver cancer cells by targeting IncRNA PVT1/miR-214-3p/GPX4. Drug Des Devel Ther. 2021;15:3965–78.
34. Chen S, Zhang Z, Zhang B, Huang Q, Liu Y, Qiu Y, et al. CircCDK14 promotes tumor progression and resists ferroptosis in glioma by regulating PDGFRα. Int J Biol Sci. 2022;18:8481–57.
35. Shanshan W, Hongying M, Jingfeng J, Yiming Y, Rui R, Rui Y. CircDTL functions as an oncogene and regulates both apoptosis and ferroptosis in non-small lung cancer cells. Front Genet. 2021;12:743505.
36. Dong LH, Huang JJ, Zu P, Liu J, Gao X, Du JW, et al. CircKDMAC4 upregulates P53 by sponging hsa-let-7b-5p to induce ferroptosis in acute myeloid leukemia. Environ Toxicol. 2021;36:1288–302.
37. Liu M, Zhu W, Pei D. System Xc−: a key regulatory target of ferroptosis in cancer. Investig N. Drugs. 2021;39:1233–31.
38. Ni H, Qin H, Sun C, Liu Y, Ruan G, Guo Q, et al. Mir-375 reduces the stemness of gastric cancer cells through triggering ferroptosis. Stem Cell Res Ther. 2021;12:3235.
39. Bai T, Liang R, Zhu R, Wang W, Zhou L, Sun Y. MicroRNA-214-3p enhances erastin-induced ferroptosis by targeting ATP4A in hepatoma cells. J Cell Physiol. 2020;235:5637–48.
36. Yadav P, Sharma P, Sundaram S, Venkatraman G, Bera AK, Karunaganad D. SLC7A11/\textit{xct} is a target of miR-5096 and its restoration partially rescues miR-5096-mediated ferroptosis and anti-tumor effects in human breast cancer cells. Cancer Lett. 2021;522:21–24.

37. Wang Z, Chen X, Liu N, Shi Y, Liu Y, Ouyang L, et al. A nuclear long non-coding RNA LINC00618 accelerates ferroptosis in a manner dependent upon apoptosis. Mol Ther. 2021;30:256–274.

38. Mao C, Wang X, Liu Y, Wang M, Yan B, Jiang Y, et al. A G3BP1-Interacting IncRNA promotes ferroptosis and apoptosis in cancer via nuclear sequestration of p53. Cancer Res. 2018;78:3848–96.

39. Zhang Y, Guo S, Wang S, Li X, Hou D, Li H, et al. LncRNA OIPS-A51 inhibits ferroptosis in prostate cancer with long-term cadmium exposure through miR-128-5p/STK38A/SLC7A11 signaling. Ecotoxicol Environ Saf. 2022;210:113276.

40. Yao W, Wang J, Meng F, Zhu J, Xia J, Lu L, et al. Circular RNA CircPTPT1 inhibits 5-fluorouracil chemosensitivity by regulating ferroptosis through miR-30a-5p/FDZ3 axis in esophageal cancer cells. Front Oncol. 2021;11:780938.

41. Wu P, Li C, Ye Dmei, Yu K, Li Y, Tang H, et al. Circular RNA circEPSTI1 accelerates cervical cancer progression via miR-375/409-3P/515-5p/SLC7A11 axis. Aging. 2021;13:4663–73.

42. Doll S, Freitas FP, Shah R, Aldrovandi M, da Silva MC, Ingold I, et al. FSP1 is a glutathione-independent ferroptosis suppressor. Nature. 2019;575:693–8.

43. Kraft VAN, Bezjian CT, Pfeiffer S, Ringelstetter L, Muller C, Zandkarimi F, et al. GTP cyclohydrolase 1/tetrahydrobiopterin counteracts ferroptosis through lipid remodeling. ACS Cent Sci. 2020;6:41–53.

44. Bersuker K, Hendricks JM, Li Z, Magatong L, Ford B, Tang PH, et al. The Coq oxidoreductase FSP1 acts parallel to GPX4 to inhibit ferroptosis. Nature. 2019;575:688–92.

45. Klein EA, Thompson IM, Tangen CM, Crowley JJ, Lucia MS, Goodman PJ, et al. Vitamin E and the risk of prostate cancer: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). JAMA. 2011;306:1549–56.

46. Song Z, Jia G, Ma P, Cang S. Exosomal miR-4434 promotes cisplatin resistance in non-small cell lung cancer by regulating FSP1 in m6A modification-mediated ferroptosis. Life Sci. 2021;276:119399.

47. Chorley BN, Campbell MR, Wang X, Karaca M, Sambandam D, Bangura F, et al. Identification of novel NRF2-regulated genes by ChIP-seq: influence on retinoid X receptor alpha. Nucleic Acids Res. 2012;40:7416–29.

48. Wu S, Lu H, Bai Y. MiR in cancers: A double-edged sword. Cancer Med. 2019;8:2252–67.

49. Sun X, Ou Z, Chen R, Niu X, Chen D, Kang R, et al. Activation of the p62-Keap1-NRF2 pathway protects against ferroptosis in hepatocellular carcinoma cells. Histochemistry. 2016;65:173–84.

50. Chen D, Tavana O, Chu B, Erber L, Chen Y, Baer R, et al. NRF2 is a major target of ARF in p53-independent tumor suppression. Mol Cell. 2017;68:224–32.

51. Liu N, Lin X, Huang C. Activation of the reverse transsulfuration pathway of ROS in Radioresistant HeLa and SAS Cell Lines. Int J Mol Sci. 2021;22:8300.

52. Xie Y, Hou W, Song X, Sun X, Lotze MT III, Zeh HJ, et al. Autophagy promotes ferroptosis by degradation of ferritin. Autophagy. 2016;12:1425–8.

53. Zhao Q, Lei P, Jackman KA, Li XL, Xiong H, Li XL, et al. Tau-modified iron export prevents ferroptotic damage after ischemic stroke. Mol Psychiatry. 2017;22:1520–30.

54. Brown CW, Amante JJ, Chihoy P, Elaimy AL, Liu H, Zhu LJ, et al. Prominin2 drives ferroptosis resistance by stimulating iron export. Dev Cell. 2019;51:575–86.

55. Hou W, Xie Y, Song X, Sun X, Lotze MT III, Zeh HJ, et al. Autophagy promotes ferroptosis by degradation of ferritin. Autophagy. 2016;12:1425–8.

56. Amy K, Harris AL. Activating transcription factor 4. Int J Biochem Cell Biol. 2016;78:3005.
Ye Y, Yang S, Han Y, Sun J, Xu L, Wu L, et al. Linc00472 suppresses proliferation by targeting glutamine transporter SLC1A5 in melanoma. Cell Death Differ. 2018;25:1457–71.

Balihodzic A, Barth DA, Prinz F, Pichler M. Involvement of long non-coding RNAs in cancer: mechanisms of action and technological advancements. Mol Cancer. 2016;15:1–10.

Prensner JR, Chinnaiyan AM. The emergence of lncRNAs in cancer biology. Nat Rev Cancer. 2014;14:655–67.

Statello L, Guo C-J, Chen L-L, Huarte M. Gene regulation by long non-coding RNAs. Nat Rev Mol Cell Biol. 2009;10:92–104.

Gao S, Wang Z. Comprehensive analysis of regulatory network for LINC00472 in hepatocellular carcinoma cell proliferation, migration and invasion through miR-365a-3p/NRF2 axis in non-small cell lung cancer cells. Cell Death Dis. 2020;11:751.

Chen D, Fan Z, Rauh M, Buchfelder M, Eyupoglu IY, Savaskan N. ATF4 promotes angiogenesis and neuronal cell death and confers ferroptosis in a xCT-dependent manner. Oncogene. 2017;36:5593–608.

Lou M, Wu L, Zhang K, Wang H, Zhang T, Gutierrez L, et al. miR-137 regulates ferroptosis by targeting glutamine transporter SLC1A5 in melanoma. Cell Death Differ. 2018;25:1457–71.

Scalli M, Pochini C, Console L, Losso MA, Indiveri C. The Human SLC1A5 (ASCT2) Amino Acid Transporter: from function to structure and role in cell biology. Front Cell Dev Biol. 2018;6:96.

Yin F, Zhang Q, Dong Z, Hu J, Ma Z. LncRNA HOTTIP participates in cisplatin resistance of tumor cells by regulating miR-137 expression in pancreatic cancer. Onco Targets Ther. 2020;13:26689.

Hu TM, Chen Q-D, Wei G-W, Wei J, Yin J-X, He J-H, et al. Hypoxia-Induced miR-137 inhibition increased glioblastoma multiforme growth and chemoresistance through LRPs6. Front Oncol. 2020;10:611699.

Li D-M, Chen Q-D, Wei G-N, Wei J, Yin J-X, He J-H, et al. Hypoxia-Induced miR-137 contributes to cisplatin resistance via repressing CAP3 in lung adenocarcinoma. Am J Cancer Res. 2016;6:1317.

Tokiita M, Fukumoto M, Itoh K, Kuwahara Y, Igarashi K, Nagasawa T, et al. MiR-7-5p is a key factor that controls radiosensitivity via intracellular Fe2+ content in clinically relevant radioresistant cells. Biochem Biophys Res Commun. 2019;518:712–8.

Stallero L, Guo C-J, Chen L-L, Huarte M. Gene regulation by long non-coding RNAs and its biological functions. Nat Rev Mol Cell Biol. 2020;21:96–109.

Bartonicek N, Maag JLV, Dinger ME. Long noncoding RNAs in cancer: mechanisms of action and technological advancements. Mol Cancer. 2016;15:1–10.

Premr Jun Jhih chained AM. The emergence of IncRNAs in cancer biology. Cancer Disc. 2011;1:391–407.

Teppan J, Barth DA, Prinz F, Jonas K, Pichler M, Klec C. Involvement of long non-coding RNAs (IncRNAs) in tumor angiogenesis. Non-Coding RNA. 2020;6:42.

Baliatskii A, Barth DA, Prinz F, Pichler M. Involvement of long non-coding RNAs in glucose metabolism in cancer. Cancers. 2021;13:977.

Deng X, Xiong W, Jiang X, Zhang S, Li Z, Zhu Y, et al. LncRNA LINC00472 regulates cell stiffness and inhibits the migration and invasion of lung adenocarcinoma by binding to YBX1. Cell Death Dis. 2020;11:945.

Chen C, Zheng Q, Kang W, Yu C. Long non-coding RNA LINC00472 suppresses hepatocellular carcinoma cell proliferation, migration and invasion through miR-93-5p/PCD4 pathway. Clin Res Hepatol Gastroenterol. 2019;43:436–45.

Ye Y, Yang S, Han Y, Sun J, Xv L, Wu L, et al. LINC00472 suppresses proliferation and promotes apoptosis by elevating PCBD4 expression by sponging mir-196a in colorectal cancer. Aging. 2018;10:1523–33.

Gao S, Wang Z. Comprehensive analysis of regulatory network for LINC00472 in clear cell renal cell carcinoma cells. Sci Rep. 2019;9:16185.

Shen Y, Katsaros D, Luo LWM, Hernandez BY, Chong C, Canuto EM, et al. Prognostic and predictive values of long non-coding RNA LINC00472 in breast cancer. Oncotarget. 2015;6:8579–92.

Qi W, Li Z, Xia L, Dai J, Zhang Q, Wu C, et al. LncRNA GABPB1-AS1 and GABPB1 regulate oxidative stress during estrogen-induced ferroptosis in HepG2 hepatocellular carcinoma cells. J Cell Physiol. 2021;2021:1–20.

Gai C, Liu C, Wu X, Yu M, Zheng J, Zhang W, et al. MITD1P loaded by folate-modified liposomes sensitizes estrogen-induced ferroptosis via regulating miR-365a-3p/NRF2 axis in non-small cell lung cancer cells. Cell Death Dis. 2020;11:751.

Wang M, Mao C, Duyang L, Liu Y, Lai W, Liu N, et al. Long noncoding RNA LINC00336 inhibits ferroptosis in lung cancer by functioning as a competing endogenous RNA. Cell Death Differ. 2019;26:2329.

Yu X, Li Z, Zheng H, Chan MTV, Wu WKK. NEAT1: A novel cancer-related long non-coding RNA. Cell Prolif. 2017;50:e12329.

Prinz F, Kapeller A, Pichler M, Klec C. The implications of the long non-coding RNA NEAT1 in non-cancerous diseases. Int J Mol Sci. 2019;20:6027.

Klec C, Prinz F, Pichler M. Involvement of the long noncoding RNA NEAT1 in carcinogenesis. Mol Oncol. 2019;13:46–60.

Wu Zh, Tang Y, Hu H. The role of ferroptosis in breast cancer patients: a comprehensive analysis. Cell Death Dis. 2021;7:93.

Zhang K, Ping L, Du T, Liang G, Huang Y, Li Z, et al. A ferroptosis-related lncRNAs signature predicts prognosis and immune microenvironment in breast cancer. Front Oncol. 2021;8:678877.
1106

Zhang Y, Tan H, Daniels JD, Zandkarimi F, Liu H, Brown LM, et al. Idazoxan Ketone Estarin Induces Ferroptosis and Slows Tumor Growth in a Mouse Lymphoma Model. Cell Chem Biol. 2019;26:623–33. e9

Savaskan NE, Heckel A, Hahnen E, Engelhorn T, Doerfler A, Ganslandt O, et al. Small interfering RNA-mediated xCAT silencing in gliomas inhibits neurodegeneration and alleviates brain edema. Nat Med. 2008;14:629–32.

Badgley MA, Kremer DM, Mauret HC, DelGiorno KE, Lee HJ, Purohit V, et al. Cysteine depletion induces pancreatic tumor ferroptosis in mice. Science. 2020;368:85–9.

Sato M, Onuma K, Domon M, Hasegawa S, Suzuki A, Kusumi R, et al. Loss of the cysteine/glutamate antiporter in melanoma abrogates tumor metastasis and markedly increases survival rates of mice. Int J Cancer. 2020;147:3224–35.

Chen J, Qin C, Zhou Y, Chen Y, Mao M, Yang J. Metformin may induce ferroptosis management of cancer and other diseases. Nat Rev Drug Discov. 2017;16:203–7.

Slaby O, Laga R, Sediouc O. Therapeutic targeting of non-coding RNAs in cancer. Biochem J. 2017;474:219–51.

Hagiwara K, Homma M, Harumoto T, Harada K, Savada T, Yamamoto J, et al. Development of prodrg type circular siRNA for in vivo knockdown by systemic administration. Nucleic Acid Ther. 2020;30:346–64.

Wang W, Green M, Choi JE, Gijon M, Kennedy PD, Johnson JK, et al. CD8+ T cells regulate tumour ferroptosis during cancer immunotherapy. Nature. 2019;569:270–8.

Xu Q, Zhou L, Yang G, Meng F, Wan Y, Wang L, et al. CircL4F4L facilitates the tumor progression and alleviates brain edema. Nat Med. 2008;14:629–32.

Chen J, Qin C, Zhou Y, Chen Y, Mao M, Yang J. Metformin may induce ferroptosis by inhibiting autophagy via lncRNA H19 in breast cancer. FEBS Open Bio. 2022;12:146–53.

© The Author(s) 2022

SPRINGER NATURE

Cell Death & Differentiation (2022) 29:1094 – 1106

This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons license, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons license and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this license, visit http://creativecommons.org/licenses/by/4.0/.

© The Author(s) 2022

AUTHOR CONTRIBUTIONS

AB, FP, MD, GAC, PJ and MP wrote the manuscript, and all authors approved the submitted version.

FUNDING

This work was supported by BioTechMed-Graz (Lab Rotation Program 2020, to AB). The research of MP was supported by the Austrian Science Fund FWF (DK-MCD, W 1226).

COMPETING INTERESTS

The authors declare no competing interests.

CONSENT FOR PUBLICATION

All authors agree to publish.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Martin Pichler. Reprints and permission information is available at http://www.nature.com/reprints

Publisher’s note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.