Review Article

Non-Coding Ribonucleic Acids as Regulators of Ferroptosis in Cancer

YUN GONG, YUE LV[1], YOUCHENG XIU[1], XINTONG ZHANG[2], ZAN LIU[1], LEIHONG DENG[3] AND YINHUI LU*

Health Management Center, Jiangxi Provincial People's Hospital, The First Affiliated Hospital of Nanchang Medical College, Nanchang, Jiangxi 330006, [1]Department of Urology, The First Affiliated Hospital, Harbin Medical University, Harbin, Heilongjiang 150000, [2]Department of Neurosurgery, The Yuebei People's Hospital, Shaoguan, Guangdong 512026, [3]Department of Ultrasound Medicine, The First Affiliated Hospital of Nanchang University, Nanchang, Jiangxi 330006, China

Non-coding ribonucleic acids were thought to be non-functional transcription products decades ago. But recently they have been found to play an essential role in programmed regulation in a variety of diseases, including cancer. They include micro ribonucleic acids and their upstream long non-coding ribonucleic acids and circular ribonucleic acids. Long non-coding ribonucleic acids or circular ribonucleic acids can form a regulatory network through sponging micro ribonucleic acids. The network regulates biological functions of various tumors such as proliferation, invasion and drug resistance. In addition, other non-coding ribonucleic acids such as piwi-interacting ribonucleic acids, transfer ribonucleic acids, ribosomal ribonucleic acids, small nuclear ribonucleic acids and small nucleolar ribonucleic acids can also act as regulators of the biological characteristics of tumor cells. Ferroptosis is a programmed cell death, which is distinct from the classical caspase splicing and has received increasing attention in recent years with regard to the tumorigenesis and treatment of cancer. Interestingly, non-coding ribonucleic acids have been found to regulate ferroptosis in tumors and to maintain the biological function of tumor cells. Herein, we summarize the related research and emphasize that the regulation of ferroptosis in tumor cells by non-coding ribonucleic acids may provide a basis for future targeted cancer therapy.

Key words: Micro ribonucleic acids, long non-coding ribonucleic acid, circular ribonucleic acid, ferroptosis, cancer

In 1965, Jacob and Monod proposed a central principle of gene coding: Nuclear Deoxyribonucleic Acid (DNA) is transcribed into messenger RNA (mRNA), which is translated into proteins in the cytoplasm to enable gene expression in the body and regulate biological functions[1].

NON-CODING RIBONUCLEIC ACID (ncRNA)

With the improvement of gene sequencing technology, many unique RNA products encoded by the genome have been identified that they cannot be translated into proteins[2]. These were called non-coding RNAs (ncRNAs) where ncRNAs have previously been considered nonfunctional "junk"[3]. But this view was reversed by the Encyclopedia of DNA Elements (ENCODE) project, which revealed that the genetic code that regulated biological function was not quite as simple[4]. ncRNAs include micro RNA (miRNA or miR), long non-coding RNA (lncRNA), circular RNA (circRNA), transfer RNA (tRNA), small nuclear RNA (snRNA), small nucleolar RNA (snoRNA) and piwi-interacting RNA (piRNA)[5]. The most widely studied ncRNA is miRNA. MiRNAs are endogenous single-stranded RNAs approximately 22 nucleotides (nt) in length encoded by eukaryotic nuclear DNA[6]. MiRNAs are estimated to regulate 60 % or more genes and are involved in regulating many biological processes, including cell proliferation, apoptosis and differentiation[7]. The production of miRNAs is a strictly transcriptional process. The nuclear-coding gene, which is mostly located in intron regions are transcribed into primary transcripts (pri-miRNA) by binding to RNA Polymerase II (Pol II)[8]. Drosha and Dicer, as two types of Ribonuclease III (RNase III), play an important role in the pri-miRNA maturation. Drosha and double-

***Address for correspondence**
E-mail: 1307960615@qq.com

stranded RNA (dsRNA)-Binding Proteins (dsRBPs), for example DiGeorge Syndrome Critical Region 8 (DGCR8), bind and splice pri-miRNA transcripts to produce a ~70 nt precursor hairpin (pre-miRNA). Exportin-5 is a Ras-related nuclear protein-Guanosine Triphosphate (Ran-GTP) complex. Pre-miRNA is transforted from the nucleus to the cytoplasm by it. With the help of Trans-Activation Response (TAR) RNA-Binding Protein (TRBP), Dicer splices the pre-miRNA into a miRNA duplex in the cytoplasm[9,10]. The Argonaute (AGO) protein family is the core component of miRNA-Induced Silencing Complex (miRISC), which regulates the miRNA double-strand to a single-strand[11]. Interestingly, miRNAs recognize the miRNA Recognition Elements (mREs) of protein-coding mRNAs in order to degrade mRNAs[12]. MREs are typically located in the 3'-Untranslated Regions (UTR) of the Coding Sequences (CDS), but may also be found in the 5'-UTR and within CDS. Finally, mature single strand miRNAs can bind to mREs *via* miRISC to inhibit mRNAs translation and lead to mRNAs degradation[13] (fig. 1a). This form of genetic regulation occurs not only in normal cell populations, but also in diseases such as neurodegeneration, metabolic diseases and especially in cancer[14]. LncRNAs are RNA transcripts of more than 200 nucleotides in length which have secondary and tertiary structures. These allow them to perform functions similar to proteins[15]. They may be located in the nucleus or cytoplasm, they may be polyglandular and are usually transcribed from any strand within a protein-coding gene site[4]. The discovery of Homeobox (Hox) Antisense Intergenic RNA (HOTAIR) is a classic accomplishment of lncRNAs research[16]. The interaction between HOTAIR and Polycomb Repressive Complex 2 (PRC2) negatively regulates transcription across the Homeobox D (HoxD) site in the cis-gene[17]. Since its discovery, a growing number of researchers have become increasingly interested in exploring the function and regulation of lncRNAs. However, it may be incorrect to define lncRNAs as simply unable to encode proteins. Despite the fact that ncRNAs cannot theoretically be translated into proteins, some long strands of ncRNAs have been found to contain an Open Reading Frame (ORF) that can be translated into small peptides[18]. A lncRNA generally falls into the following five categories: Sense, overlapping at least one exon in a transcript on the same strand; antisense, overlapping at least one exon in another transcript in a complementary strand; bidirectional, reversely transcribing on a complementary chain with adjacent transcripts and sharing the same promoter; intronic, locating in the intron region of a protein-coding gene and not overlapping with exons of the transcript and intergenic, independently transcribing between two protein-coding genes[19]. The function of lncRNAs has been explored since the discovery of ncRNAs as a biological regulator, but only a small portion of these has been discovered (fig. 1b). LncRNAs can interact with one or more proteins to perform biological functions[20]. They can bind to their own transcription sites to regulate the expression of cis genes or bind to a transcription factor to prevent DNA transcription[21]. It is worth noting that lncRNAs contain predicted miRNA binding sites, which allows lncRNAs to act as negative regulators of miRNAs, reducing the number of miRNAs in the cell and thus regulating the expression of protein transcripts. This type of RNA is known as competitive endogenous RNA (ceRNA)[22] and the interaction is currently known as lncRNA-miRNA-mRNA. A ceRNA network (CeRNAnet) is gradually formed based on the lncRNA/miRNA/mRNA axis[23]. LncRNAs play an important role in many diseases including cardiovascular disease, bone disease and cancer[24-26].

CircRNA was first discovered in RNA viruses in 1976 and for a long time they were believed to be the result of RNA splicing errors[27]. Subsequently, with the development of high-throughput RNA sequencing (RNA-seq), hundreds of circRNAs were identified in a variety of eukaryotes. The mechanism of circRNAs production and gene regulation has gradually been revealed[28]. Pre-mRNA is spliced by RNA Pol II to form a covalently closed continuous loop (circRNA)[29]. Compared to linear RNAs, circRNA is usually obtained by nonstandard splicing (back-splicing) and has no 3' or 5' polarity[30]. There are three types of circRNA: Exon circRNA (ecircRNA) composed of exons; circular intronic RNA (ciRNA) composed of introns and exon-intron circRNA (elciRNA) composed of exons and introns[31]. In recent years, the search for the function of circRNA has never stopped. CircRNA is found to bind to RNA Pol II and regulates transcription efficiency at the promoter region of the parent gene. In addition to the transcriptional regulation of parental genes, it has been revealed that there is a competitive relationship between parental genes splicing and circRNAs splicing[32] (fig. 1c). Interestingly, several binding sites of miRNAs have been identified on circRNAs. Recently, circRNA has also been reported to modulate ferroptosis in tumor cells.

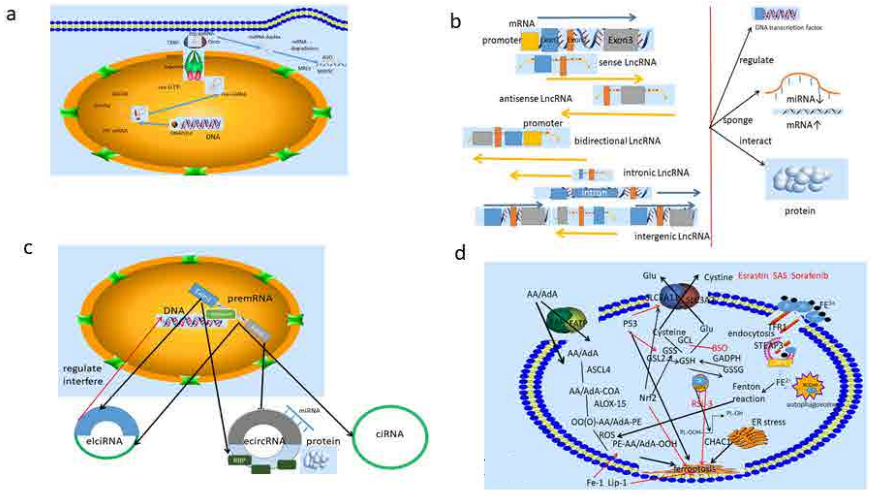

Fig. 1: (a, b and c) Formation and activity of miRNAs, lncRNAs and circRNAs; (d) The regulatory mechanisms of ferroptosis, (⟶) Promote and (⟶) Inhibit

PiRNAs are a class of small ncRNAs (sncRNAs) recently discovered in germ cells. PiRNAs consist of 24-31 nt, with a 5′-terminal uridine or a 10th position adenosine bias, lacking a clear secondary structural motif[33]. Unlike miRNAs, piRNAs are not spliced by the RNase III enzyme Dicer and are integrated into the Piwi subfamily of AGO proteins[34]. PiRNAs bind to Piwi proteins to form the piRNA-Piwi complex, which affects transposon silencing, spermatogenesis, genome rearrangement, germ cell maintenance, epigenetic and protein regulation[35]. Recently, increasing evidence has shown that piRNAs are involved in the regulation of cell proliferation and apoptosis especially in cancer cells[36]. Changes in the expression of Piwi proteins and piRNAs can increase cell proliferation, decrease apoptosis and promote the growth of lung cancer and glioma cells[37,38]. However, the role of piRNA in ferroptosis of tumor cells has not been well studied. In recent years, a new class of sncRNAs from tRNAs has been discovered. These ncRNAs derived from tRNAs are called tRNA Fragments (tRF)[39]. The tRFs can be divided into four types: 3'-trailer sequences that are removed by ElaC Ribonuclease Z 2 (ELAC2) from pre-tRNAs during tRNAs maturation, resulting in 1-tRF; 5'-tRF generated at the 5' end in the D-loop; 3'-tRF generated by the 3'-end in the T-loop; tRNA-derived stress-induced RNAs (tiRNAs) or tRNAs produced by Angiogenin (ANG) *via* the specific cleavage of the antibacterial loops of mature tRNAs under stress conditions[40,41]. Several tRNAs play an important role in the epigenetic regulation of cancer. The expression of tumor suppressor (ts) 101 and ts-46 (tRF-1s) had been associated with the survival, proliferation and apoptosis of tumor cells[42]. By binding to the mRNA of Ribosomal Protein (RP) (RPS28 and RPS15), the specific tRF-3 (LeuCAG 3' tsRNA) was inhibited to induce apoptosis *in vitro* and in xenograft mouse models and promoted protein synthesis[43]. Immunoprecipitation of the Piwi gene (Hiwi2) in Human Breast Cancer Cell Line (MDA-MB-231) cells could enrich piRNAs generated mainly from processed tRNAs, which suggested that the Piwi-piRNA pathway and tRF-5 exerted an uncharacterized function[44]. The snoRNA is a conserved nuclear RNA family of 70-200 nt in length. SnoRNAs are generally concentrated in Cajal bodies or nucleoli where they are either involved in the modification of snRNAs or rRNAs and the maturation of ribosomal subunits[45,46]. They are usually processed from debranched and excised introns by exonucleolytic trimming and form small nucleolar Ribonucleoproteins (snoRNPs) to carry out their functions in complexes with specific protein components[45,47]. Some intronic lncRNAs contain snoRNAs at the end of the region. These intron-derived snoRNA-ended RNAs are named sno-lncRNAs. The tissue and species-specific expression patterns have been identified in humans, rhesus monkeys and mice[48]. Its regulatory effect on lncRNAs may be the basis for the regulation of cancer cell apoptosis and even ferroptosis.

FERROPTOSIS

The origin of ferroptosis:

Cell death is divided into Programmed Cell Death (PCD), which is energy-dependent death with different morphological changes including apoptosis and necrosis, which is regarded as passive toxic and energy-independent process[49]. Although apoptosis, autophagy and necroptosis have previously been identified as three major types of PCD[50], a new type of PCD called ferroptosis has recently been defined.

Ferroptosis, as its name suggests, is a specific form of cell death in which iron-dependent lipid Reactive Oxygen Species (ROS) accumulate in cells. This process is not involved in apoptotic effector proteins such as cysteine-aspartic proteases (caspases) and Bcl-2-Associated X protein (BAX)[51]. ROS are composed mainly of peroxides (Hydrogen Peroxide (H_2O_2) and Hydroperoxides (ROOH)), superoxide ($O_2^{\bullet-}$) and free radicals (Hydroxyl ($HO^{\bullet}$) and Alkoxy ($RO^{\bullet}$)). Under normal circumstances, the body can transfer electrons through mitochondrial electron transport chain to produce ROS. It can also be activated during the production of uric acid in hypoxanthine and during the oxidation of fatty acids[52]. The oxidation-reduction imbalance in the body will lead to oxidative stress to produce a large number of free radicals that destroy proteins, DNA and intracellular molecules in cells. Ferrous (Fe) II in the chelatable iron transition pool can catalyze the decomposition of H_2O_2 to produce ROS such as $HO^{\bullet}$ radicals[53]. The depletion of Polyunsaturated Fatty Acids (PUFAs) and the formation of Lipid Hydroperoxide (L-OOH) provide a new inducer of iron-dependent mortality. In the presence of Fe (II), L-OOH can form lipid-free radicals that damage the cell surface and intracellular components, such as the alkoxy radical $L\text{-}O^{\bullet}$[54]. Glutamate has been used since the 1990s to treat nerve cells in mice (Immortalized mouse hippocampal cell line (HT-22)). Competing for cystine uptake, this reduces the accumulation of Glutathione (GSH) in cells and ultimately leads to oxidative cell death[55]. Cell death caused by oxidative stress is becoming increasingly more well-known. In 2007, Erastin was found to alter mitochondrial membrane permeability *via* mitochondrial Voltage-Dependent Anion Channels (VDAC), but did not promote mitochondrial release of cytochrome C or the activation of classical apoptotic-characteristic caspase-3. It had been suggested that Erastin could promote the death of cancer cells with RAS gene mutation in a non-apoptotic manner[56]. In 2008, two compounds Ras-Selective Lethal small molecule 5 (RSL5) and RSL3 were identified as having similar functions to Erastin, both of which were involved in the activation of RAS signaling pathways. RSL5, like Erastin, also plays an oxidative role through Voltage-Dependent Anion-Selective Channel protein 3 (VDAC3), participating in iron and ROS dependent cell death. They are called Type I RSLs. Type II RSLs such as RSL3 can inhibit regulatory factors leading to cell death[57]. In addition, a new activating factor of cellular oxidative stress was also discovered in 2008. Glutathione Peroxidase 4 (GPX4) gene knock-out in cells can lead to lipid peroxidation and oxidative damage leading to cell death[58]. Finally, in 2012, Dixon *et al.* formally defined Erastin-induced iron-dependent cell death as ferroptosis and found that the small molecule Ferrostatin-1 (Fer-1) not only inhibited ferroptosis in cancer cells, but also induced the same effects on glutamate-induced brain cell death in rats[51]. Through high throughput screening of small molecular libraries, it was found that Fer-1 and Liproxstatin-1 (Lip-1) could inhibit the accumulation of L-OOH, likely by preventing the deletion of GPX4 and the inhibition of the xc^- system[51,59]. Both compounds are acrylamides which are known to be a good Radical-Trapping Antioxidants (RTA). Fer-1 and Lip-1 are very effective RTAs or inhibition of autoxidation may not be the root cause of its inhibition of ferroptosis. In fact, Fer-1 and Lip-1 may be effective inhibitors of lipoxygenase[60]. In addition, a new concept has been proposed that ferrous itself reduces Fer-1 free radicals and Fer-1 forms complexes with iron to reduce the presence of labile iron[61] (fig. 1d).

Cysteine-glutamate antiporter (system xc^-):

The antiporter system xc^- is a member of the family of heterodimeric amino acid transporters composed of light chain (xCT) and 4F2 cell-surface antigen heavy chain (4F2hc). The system can import Cysteine (Cys) into cells and transport glutamate out of cells at a 1:1 basis[62]. The thiol-containing amino acid Cys is oxidized in the form of cystine (Cys2), which is essential for resistance to cellular oxidative stress[62,63]. Solute Carrier Family 7 Member 11 (SLC7A11) (xCT) is a 12-fold transmembrane transporter that can be linked to Solute Carrier Family 3 Member 2 (SLC3A2) (4F2hc) *via* a disulfide bridge. Erastin, Sulfasalazine (SAS) and sorafenib can reduce the uptake of cystine, which can lead to lipid oxidation. SAS is an anti-inflammatory drug that eliminates ROS and is often used clinically to treat rheumatoid arthritis inflammatory bowel disease[64]. SAS was also found to inhibit leukocyte movement and the production of Interleukin (IL)-1 and IL-2 and to inhibit Nuclear Factor kappa B (NF-κB) [65,66]. Interestingly, the xc^- transporter plays an important role in pancreatic cancer by maintaining or enhancing GSH biosynthesis. SAS also effectively induces GSH depletion and enhances chemotherapy resistance of pancreatic cancer[67]. Sorafenib is the only known first line treatment for patients with advanced liver cancer[68]. Sorafenib, a multi kinase inhibitor, plays an anti-cancer role by inducing apoptosis, inhibiting cell proliferation and angiogenesis[69].

The iron-chelating agent Deferoxamine (DFO) depletes the cells iron stores to protect liver cancer cells from sorafenib's cellular oxidative stress and cytotoxicity[70]. In terms of mechanism, the study showed that sorafenib could also inhibit ferroptosis induced by SLC7A11[71]. In addition, the occurrence of ferroptosis leads to Endoplasmic Reticulum (ER) stress, which increases ChaC, Cation Transport Regulator Homolog 1 (CHAC1) significantly. It can be regarded as a marker of ferroptosis[71]. The main reason for this is the down-regulation of GSH in cells. GSH, a combination of Cys and glutamate, is an important antioxidant molecule in cells. Finally, on this basis, glycine is added to synthesize. The Sulfhydryl group (-SH) of Cys is the most important antioxidant group in GSH[72]. Buthionine Sulfoxamine (BSO) was found to inhibit glutamate-Cys ligase, a rate-limiting enzyme in GSH synthesis, leading to a reduction in GSH levels[73]. In addition, Glutathione Disulfide (GSSG) is involved in the reduction of GSH. GSSG is reduced to GSH by Nicotinamide Adenine Dinucleotide Phosphate (NADPH) and to GSSG reductase in cells to maintain the steady state level of GSH[74]. There are eight species of GPXs in mammals. GPX4 (Phospholipid Hydroperoxide Glutathione Peroxidase (PHGPx)) is a phospholipid catalase that acts to reduce the lipid peroxidation. Therefore, GPX4 plays an important role in inhibiting lipid oxidation in cells[75]. Because GPX4 is a selenoprotein, Selenium (Se) can promote the expression of GPX4 and inhibit ferroptosis induced by endoplasmic reticulum stress[76]. RSL3 does not reduce GSH expression through xc^-, but it can inhibit GPX4 enzyme activity by producing lipid ROS and promote ferroptosis[73]. In addition, ML162, ML210 and anti-cancer agent altretamine can also inhibit the activity of GPX4[77,78].

Lipid peroxidation and Transferrin (TF):

Acetyl-Coenzyme A (Acyl-CoA) Synthetase Long-chain family member 4 (ACSL4) has been found to be an important promoter of cellular lipid oxidation. The knock-out of both ACSL4 and GPX4 genes result in a marked inhibition of ferroptosis. Doll *et al.* further demonstrated that anti-diabetic medication thiazolidinediones could inhibit ferroptosis in mouse tissues by targeting ACSL4[79]. In addition, Phosphatidylethanolamines (PEs) containing Arachidonoyl Acid (AA) or Adrenoyl Acid (AdA) is the preferred substrates for oxidation involved in ferroptosis[80]. In fact, AA/ADA can enter the cell *via* the Fatty Acid Translocator (FAT), Fatty Acid Transporter Protein (FATP) or *via* free diffusion. ACSL4 catalyzes AA and AdA bonds to produce AA or AdA acyl Co-A derivatives. They are esterified into PEs (AA-PE and AdA-PE) by Lysophosphatidylcholine Acyltransferase 3 (LPCTA3). Finally, AA-PE and AdA-PE are then oxidized by 15-Lipoxygenase (15-LOX, Arachidonate 15-Lipoxygenase (ALOX15)) to produce OO(O)-AA/AdA-PE. Because some inhibitors such as RSL3 decrease the concentration or activity of GPX4, which cannot detoxify OO (O)-AA/AdA-PE, they can generate Phospholipid Hydroperoxides (PL-OOH) to execute the ferroptosis pathway[81,82]. As mentioned earlier, the formation of lipid free radicals in the presence of iron can promote cell death.

TF plays an important role in human iron metabolism. TF is mainly produced in the liver and binds up to two Fe atoms. TF loaded with Fe atoms binds to the Transferrin Receptor 1 (TFR1) and delivers the atoms to the cell by endocytosis[83]. The major binding site of TF outside the cell is Fe^{3+}, which is transported by TRF1 and is oxidized to Fe^{2+} by the Six-Transmembrane Epithelial Antigen of the Prostate 3 (STEAP3). The Divalent Metal Transporter 1 (DMT1) then transports the Fe^{2+} into the cytoplasm[84]. When iron is overloaded, ROS can be produced by the Fenton reaction, to promote the pathological changes observed in hereditary hemochromatosis and other diseases[85]. Ferritin is a 24-subunit protein complex capable of chelating more than 4500 Fe (III) iron atoms. It consists of light and heavy chains (Ferritin Light Chain (FTL), Ferritin Heavy Chain 1 (FTH1))[86]. Ferritin complex cages can oxidize Fe (II) to Fe (III) *via* FTH1 to store iron, which also results in less ROS generation[87]. When our body needs iron, ferritin can release iron in a way that relies on lysosomal degradation[88]. Furthermore, the Nuclear Coactivator 4 (NCOA4) receptor co-exists with ferritin in autophagosomes and lysosomes. Reducing the expression of NCOA4 blocks the transfer of ferritin to lysosomes, which in turn inhibits the degradation of ferritin. Two subunits of ferritin (FTL, FTH1) of the E3 ubiquitin ligase complex (HECT and RLD Domain Containing E3 Ubiquitin Protein Ligase 2 (HERC2) and Neuralized E3 Ubiquitin Protein Ligase 4 (NEURL4)) can interact to keep iron levels stable[89]. Therefore, changes in NCOA4 expression affect the sensitivity of ferroptosis in cells[90]. In addition, two subunits of ferritin can also play an indirect role. Iron chelation treatment with DFO affects the availability of iron in living organisms to inhibit the sensitivity of ferroptosis[51].

Tumor Protein P53 and Nuclear Factor Erythroid 2-Related Factor 2 (NRF2):

As an important tumor suppressor gene, P53 can inhibit tumor proliferation and growth by mediating oxidative stress and ferroptosis[91]. The P53 gene has been found to inhibit the expression of SLC7A11 and thus promote ferroptosis in tumor cells[92]. Glutamine is another important factor involved in iron-induced mortality. Glutaminase 2 (GSL2) can increase the expression of GSH in cancer cells and inhibit the onset of ferroptosis. P53 has been found to regulate the expression of GSL2, which is closely related to mitochondrial respiration and Adenosine Triphosphate (ATP) production in cancer cells[93]. Therefore, P53 is a starting point for promoting the occurrence of ferroptosis in a variety of cancers and warrants further study.

NRF2 is a transcription factor that plays a crucial role in the oxidative stress response. The harmful effects of ROS and some electrophiles are counteracted by NRF2[94]. Under normal conditions, NRF2 can bind to Kelch-like ECH-associated protein 1 (Keap1) and is subjected to ubiquitination and proteasome degradation. In conditions of oxidative stress, NRF2 enters the nucleus and binds to the Antioxidant Response Element (ARE) on DNA to promote the transcription and expression of anti-oxidative genes[95]. Interestingly, NRF2 can regulate two subunits of ferritin (FTL/FTH1) to regulate the level of iron in cells[96]. Several enzymes are regulated by NRF2 during GSH metabolism, such as Glutathione Synthase (GSS) and a subunit of the Cys glutamate transporter xCT, SLC7A11[97]. In addition, NRF2 plays a fundamental role in maintaining cellular redox homeostasis by regulating antioxidant systems such as GSH and Thioredoxin (TXN) and involves NADPH regeneration as well as heme metabolism[98]. Obviously, NRF2 not only plays an essential role in oxidative stress, but also plays a regulatory role in the mechanism of ferroptosis.

Ferroptosis and diseases:

Many diseases have been found to be associated with ferroptosis. By inhibiting or promoting enzymes or genes involved in ferroptosis, this has an impact on the course of diseases, such as liver disease, renal injury or cardiovascular disease and neurodegeneration[99]. NcRNAs, especially miRNAs, can alter disease progression by modulating ferroptosis. Ding *et al.* found that miR-182-5p and miR-378A-3p could promote ferroptosis by inhibiting GPX4 and SLC7A11 expression in models of ischemia-reperfusion renal injury[100]. In murine model with intracerebral hemorrhage, miR-124 was found to modulate Ferroportin 1 (FPN1) and inhibit ferroptosis and apoptosis[101]. Interestingly, the role of ferroptosis in cancer is not quite the same as in other diseases. Ferroptosis can inhibit the proliferation and cell cycle of cancer cells, which suggests that we should focus on ferroptosis-based therapies for cancer that escape other forms of cell death, such as apoptosis or autophagy[102]. The role of ncRNAs in cancer has been extensively studied. Their role in regulating ferroptosis in cancer cells has also recently been discovered and will be reviewed below.

ncRNAS AND FERROPTOSIS IN CANCERS

MiRNAs and ferroptosis:

The differential expression of the GPX family of genes in Acute Myeloid Leukemia (AML) might be involved in the regulation of ferroptosis in tumor cells by influencing the expression of miR-202, miR-381, miR-181 and many other miRNAs, and related transcription factors (Serum Response Factor (SRF) and E2F Transcription Factor 1 (E2F1)) or tumor-associated kinases (Death Associated Protein Kinase 1 (DAPK1) and proto-oncogene c-Src (SRC)). This provides a new direction for exploring the mechanisms of cell proliferation and the cell cycle of AML cells[103]. Tomita *et al.* found that the expression of miR-7-5p was significantly increased in Radiation-Resistant Cells (CRR) and decreased with the time of irradiation. Interestingly, the study also showed that miR-7-5p could reduce the content of Fe^{2+} in hepatoma cells and inhibit the occurrence of ferroptosis[104].

Erastin could increase ferroptosis of liver hepatocellular carcinoma cell line (HePG2 and Hep3B) cells and inhibit the proliferation of liver cancer cells. Pre-miR-214 was revealed to increase the sensitivity to Erastin of liver cancer cells and could promote ferroptosis by targeting Activating Transcription Factor 4 (ATF4). In addition, the role of miR-214 in promoting ferroptosis might also be associated with increased levels of Malondialdehyde (MDA) and ROS[105]. Sorafenib-resistant hepatoma cells showed miR-23a-3p transcriptional regulation of ACSL4 expression in an ETS Proto-Oncogene 1 (ETS1) manner. MiR-23a-3p inhibitors could promote cell ferroptosis and improve drug resistance[106]. This suggests that radiation-induced ferroptosis in liver cancer cells is regulated by miRNAs. It is worth exploring whether other treatments, such as chemotherapy, are also regulated by miRNAs.

Zhang *et al.* found that miR-9 could target Glutamic-Oxaloacetic Transaminase 1 (GOT1) to inhibit Erastin and RSL3 sensitivity to ferroptosis in melanoma cells. GOT1 was a key enzyme in glutaminolysis, which was inhibited by miR-9. Silencing miR-9 could increase the expression of GOT1 and promote ferroptosis in cancer cells[107]. SLC1A5 is a cell membrane surface protein that mediates glutamine uptake. Recently, it was reported that miR-137 overexpression and Glutamyl-P-Nitroanilide (GPNA) could decrease the expression of SLC1A5 and inhibit the breakdown of glutamine and the ferroptosis of melanoma cells[108]. Glutamine metabolism and uptake play an essential role in the occurrence of ferroptosis in cancer cells.

LOXs play a key role in the lipid metabolism of tumors and the development of many cancers. The decrease of Epidermis-type Lipoxygenase 3 (ALOXE3) expressions might inhibit the occurrence of ferroptosis by decreasing the inhibitory effects of P53 on SLC7A11. Furthermore, miR-18a was found to be an upstream gene of ALOXE3 and could inhibit its role in ferroptosis in glioma cells. In addition, ALOXE3 could promote the migration of glioma cells by stimulating the secretion of 12-Hydroxyeicosatetraenoic Acids (12-HETE) and further activating the Phosphatidylinositol 3-Kinase/Protein Kinase B (PI3K/AKT) pathway[109].

Kirsten Rat Sarcoma Viral Oncogene Homologue (KRAS) mutations are common in the progression, metastasis and drug resistance of colorectal cancer[110]. Park *et al.* found that Achaete-Scute Family BHLH Transcription Factor 4 (ASCL-4) was significantly up-regulated in KRAS mutant colorectal cancer cells and when bromelain was used to treat colorectal cancer cells, ASCL-4 was significantly down-regulated and ferroptosis was evidenced by MDA and ROS generation. In addition, the differential expression of miRNAs in human colorectal adenocarcinoma cell line (Caco-2 and DLD-1) cells treated with bromelain was analyzed. It was found that miR-19b-3p, miR-130A-3p, miR-150-5p, miR-144-3p, miR-16-5p, miR-7A-5p and miR-17-5p were differentially expressed and could target ASCL-4 to regulate ferroptosis[111]. Angius *et al.* found that the epigenetic regulation of TP53 and SLC7A11 expression played an essential role in the regulation of ferroptosis in colorectal cancer cells. It was worth noting that let-7c, let-7e and miR-150-5p genes could regulate TP53. These miRNAs are worthy of further study in the cell death of colorectal cancer[112].

Aurora Kinase A (AURKA) is a serine/threonine kinase that regulates cell division and proliferation and is up-regulated in many cancers. MiR-4715-3p was found to inhibit AURKA expression in upper gastrointestinal cancers and inhibit GPX4 expression to promote ferroptosis in tumor cells. The expression of Poly (ADP-ribose) Polymerase 1 (PARP) and caspase-3 was also regulated by miR-4715-3p, indicating that the apoptosis of tumor cells was also regulated. There is a link between cell death of various types, apoptosis, autophagy and ferroptosis[113]. Lee *et al.* found that Epithelial-Mesenchymal Transition (EMT) could play a regulatory role in ferroptosis sensitivity of head and neck tumors. Interestingly, inhibiting miR-200 family expression might promote ferroptosis sensitivity by modulating EMT epigenetics in head and neck tumors[114]. Physcion 8-O-Glucopyranoside (PG) has anti-cancer effects in a variety of cancers[114]. It enhanced GLS2 expression by down-regulating miR-103A-3p, increased the levels of Fe^{2+} and MDA in cells and significantly promoted ferroptosis[115]. Cancer-Associated Fibroblasts (CAFs) can secrete a variety of biologically active regulatory genes or substances to promote the development and proliferation of tumor cells. Recently, Zhang *et al.* found that CAF secreted miR-522 could regulate the drug resistance and proliferation of gastric cancer cells. MiR-522 was also found to inhibit ferroptosis of gastric cancer cells by targeting ALOX15[116].

Nanomedicine combined with related mechanisms for targeted delivery and treatment of tumors has attracted increasing attention[117]. Luo *et al.* used POPO-3 as a fluorescent dye to label miR-101-3p, a miRNA reported to modulate biological characteristics of various tumor cells, to inhibit the progression of A549 lung cancer cells *via* nanocarriers. MiR-101-3p had also been found to promote tumor cell apoptosis and ferroptosis to inhibit tumor cell proliferation by targeting Transducin (Beta)-like 1X Related protein 1 (TBLR1)[118].

Interestingly, miR-324-3p was revealed to directly target GPX4 and regulate ferroptosis and cisplatin sensitivity in A549 cells[119]. In addition, miR-324-3p/GPX4 had been shown to modulate ferroptosis not only in lung cancer, but also in breast cancer. Metformin, a drug used to treat hypoglycemia, could promote ferroptosis in breast cancer cells by regulating miR-324-3p to suppress GPX4 expression[120], whether the same mechanism exists in other cancers remains to be further studied.

Cisplatin is a first-line chemotherapy drug for many tumors, including lung cancer. Cisplatin could induce Fibroblast-Specific Protein 1 (FSP1) expression and promote ferroptosis in lung cancer cells. In addition, the expression of miR-4443 was increased in cisplatin-resistant cell lines and inhibited the expression of FSP1 *via* Methyltransferase-Like 3 (METTL3) regulation of N6-methyladenosine (m^6A) and interfered with ferroptosis in A549 cells[121].

Erastin and RSL3 could induce ferroptosis of ovarian cancer cells. Ma *et al.* determined that miR-424-5P could target ACSL4 to promote ferroptosis. MiR-424-5p activity as a tumor inhibitor might represent a novel potential therapeutic strategy for ovarian cancer[122]. MiR-15a and miR-1287-5p could promote ferroptosis in prostate cancer and osteosarcoma cells by inhibiting the expression of GPX4[123,124] (fig. 2 and Table 1).

LncRNA and ferroptosis:

Wang *et al.* found that the expression of Long Intergenic Non-Protein Coding RNA 618 (LINC00618) was down-regulated in leukemia and was significantly inhibited by Vincristine (VCR). In addition, LINC00618 increased the expression of BAX and the cleavage of caspase-3 to enhance apoptosis in leukemic cells. Interestingly, LINC00618 had also been shown to be associated with lipid oxidation of ferroptosis in leukemia cells by detecting ROS levels and intracellular iron deposition.

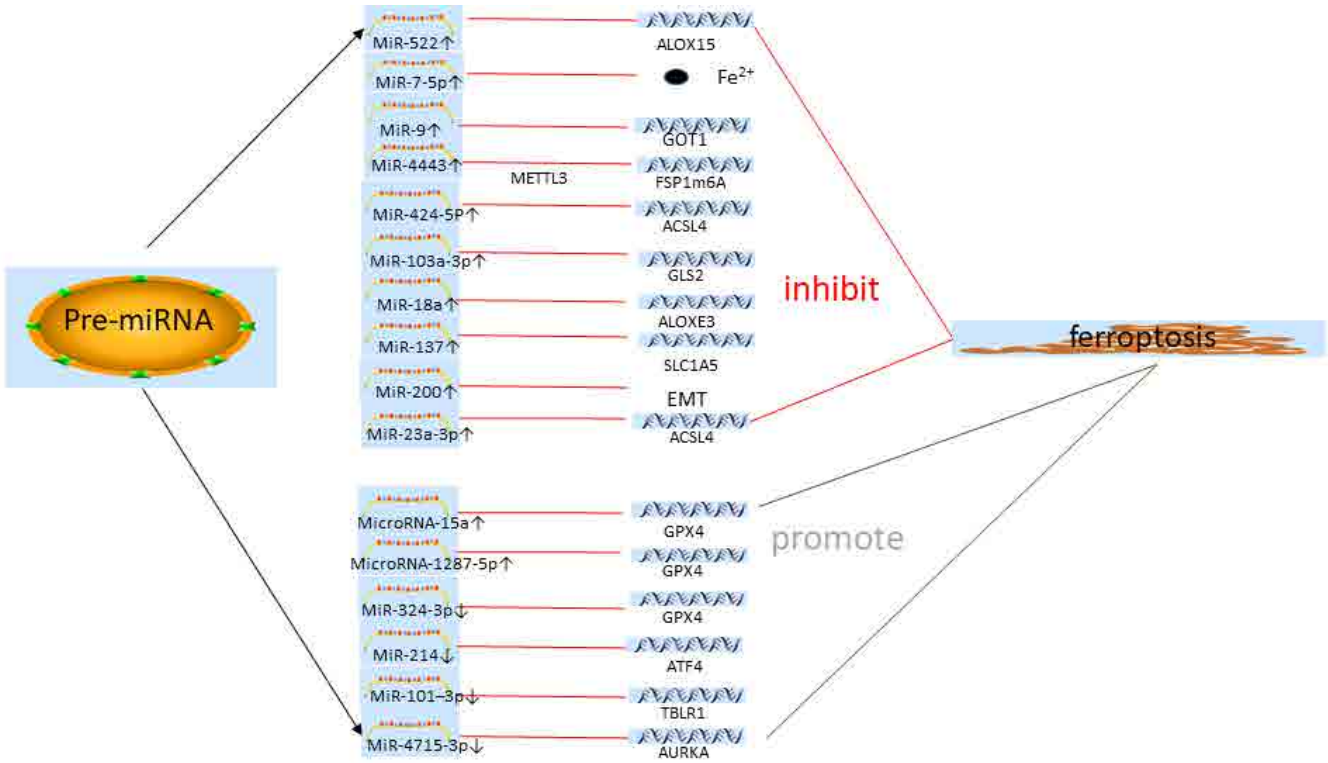

Fig. 2: miRNAs and ferroptosis in cancers

TABLE 1: miRNAs AND FERROPTOSIS IN CANCERS

miRNAs	References	Expression	Target/Mechanisms	Cancers
miR-202/miR-181/miR-381	[103]	/	GPX	AML
miR-7-5p	[104]	↑	Fe^{2+}	HCC
miR-214	[105]	↑	ATF4	HCC
miR-23a-3p	[106]	↑	ACSL4	HCC
miR-9	[107]	↑	GOT1	Melanoma
miR-137	[108]	↑	SLC1A5	Melanoma
miR-18a	[109]	↑	ALOXE3	Glioblastoma

miR-19b-3p/miR-130A-3P/ miR-150-5p/miR-144-3p/miR -16-5p/miR-7A-5P/miR-17-5p	[111]	↓	ASCL-4	Colorectal cancer
Let-7c, let-7e, miR-150-5p	[112]	↑	TP53	colorectal cancer
miR-4715-3p	[113]	↓	AURKA	Upper gastrointestinal cancers
miR-200	[114]	↑	EMT	Head and neck cancer
miR-103a-3p	[115]	↑	GLS2	Gastric cancer
miR-522	[116]	↑	ALOX15	Gastric cancer
miR-101-3p	[118]	↓	TBLR1	Lung cancer
miR-324-3p	[119]	↓	GPX4	Lung cancer
miR-324-3p	[120]	↓	GPX4	Breast cancer
miR-15a				
miR-4443	[121]	↑	FSP1	Lung cancer
miR-424-5P	[122]	↑	ACSL4	Ovarian cancer
miR-15a	[123]	↑	GPX4	Prostate cancer
miR-1287-5p	[124]	↑	GPX4	Osteosarcoma

It could also inhibit the expression of Lymphoid-Specific Helicase (LSH) to inhibit the xc– system-related gene SLC7A11 and promote ferroptosis in leukemia cells[125].

In 2016, He *et al.* reported that LINC00336 was associated with poor prognosis in renal cell carcinoma[126] and also played an important role in ferroptosis of lung cancer cells. LINC00336 could inhibit ferroptosis by binding to ELAV-like RNA binding protein 1 (ELAVL1). In addition, LSH promoted the expression of ELAVL1 and LINC00336 *via* the P53 signaling pathway. Interestingly, miR6852, a downstream target gene of LINC00336, was found to regulate the ferroptosis-related marker Cystathionine Beta-Synthase (CBS). Thus, there seems to be a regulatory network involving LSH/P53/ELAVL1/ LINC00336 and miR6852/CBS in lung cancer cells[127].

The lncRNA Metallothionein 1D Pseudogene (MT1DP) could interact with miR-365 to enhance cadmium-induced oxidative stress by inhibiting NRF2 expression[128]. Recently, Gai *et al.* also reported a role for the MT1DP/miR-365a-3p/NRF2 axis in cellular oxidative stress in Non-Small Cell Lung Carcinoma (NSCLC)[129]. Folic acid is widely used as targeted therapy and as optical imaging therapy of tumors. Cancer-targeted optical diagnostics are performed by loading folic acid onto the surfaces of a variety of nanoparticles, including liposomes[130,131]. By detecting MDA and ROS levels, intracellular iron concentrations and GSH, the upregulation of MT1DP could promote NSCLC ferroptosis by inhibiting the expression of NRF2[129].

XAV939, a Tankyrase inhibitor that targets Wnt/beta (β)-catenin signaling was found to act as a small molecule inhibitor by shortening telomeres to promote tumor cell apoptosis[132]. The lncRNA miR503HG might be down-regulated by XAV939 to inhibit the proliferation and development of NSCLC by sponging the miR1273c/ SOX4 axis. Furthermore, XAV939 could also inhibit SLC7A11 expression and promote ferroptosis in NSCLC[133]. However, the search for lncRNAs between XAV939 and SLC7A11 able to promote the ferroptosis process has not been confirmed and warrants further exploration.

In lung cancer cells, Wang *et al.* found that lncRNA Nuclear Paraspeckle Assembly Transcript 1 (lncNEAT1) could inhibit cell ferroptosis by sponging ACSL4. In addition, the levels of ACSL4, SLC7A11 and GPX4 were significantly decreased following silencing of NEAT1 silencing and Erastin co-processing in lung cancer cells, which suggested that this mechanism might facilitate the occurrence of ferroptosis[134].

The role of Erastin in the induction of ferroptosis in Hepatocellular Carcinoma (HCC) cells is well established. Qi *et al.* found that Erastin promoted the up-regulation of lncRNA GA-Binding Protein Transcription Factor Subunit Beta 1-Antisense RNA 1 (GABPB1-AS1) and inhibited the expression of GABPB1. Down-regulation of GABPB1 translation also resulted in the down-regulation of the gene encoding Peroxiredoxin-5 (PRDX5) peroxidase, which in turn reduced the cell antioxidant capacity and increased the susceptibility to ferroptosis in HCC cells[135].

LncRNA P53RRA was down-regulated in cancer cells and had been associated with the inhibition of cancer progression. P53RRA interacted with Ras GTPase-activating protein-Binding Protein 1 (G3BP1) to induce the translocation of P53 from the G3BP1 complex and the retention of P53 in the nucleus, which led to lung cancer cells apoptosis and ferroptosis[136].

Recently, several studies had begun to identify lncRNAs associated with ferroptosis in different cancer types. For colon cancer, Cai *et al.* used RNA-seq results to query the Ferroptosis-Disease associations database (FerrDb) and The Cancer Genome Atlas (TGCA) database. Cox model analysis was used to construct a seven ferroptosis-related lncRNAs-signature (LINC01503, ARRDC1 Antisense RNA 1 (ARRDC1-AS1), OIP5 Antisense RNA 1 (OIP5-AS1), AC004687.1, AC010973.2, AP001189.3 and NCK1 Divergent Transcript (NCK1-DT)). The results also revealed the potential molecular mechanisms involving ferroptosis-related lncRNAs, including the Mitogen-Activated Protein Kinase (MAPK), mammalian Target of Rapamycin (mTOR) and GSH pathways[137]. Furthermore, Tang *et al.* analyzed the TGCA database and found that 25 significantly different expressed lncRNAs, such as LINC01963, were associated with ferroptosis in head and neck tumors. The related mechanisms such as Notch pathway and phagocytosis mediated by FC gamma R were analyzed by Gene Set Enrichment Analysis (GSEA)[138]. High expression of lncRNA Brain-Derived Neurotrophic Factor Antisense (BDNF-AS) was revealed in Gastric Cancer (GC) and Peritoneal Metastasis (PM). LncRNA BDNF-AS could recruit WD repeat-containing protein 5 (WDR5) to modulate F-box and WD repeat domain containing 7 (FBXW7) expression to protect GC cells from ferroptosis[139]. LncRNA SLC16A1-AS1 was overexpressed in renal cell carcinoma and could inhibit ferroptosis *via* miR-143-3P/SLC7A11 axis[140]. LncRNA RP11-89 could promote iron export through miR-129-5P/Prominin2 (PROM2) axis and inhibit ferroptosis in bladder cancer cells[141].

Recently some compounds have been found to modulate the biological characteristics of cancer cells and the occurrence of ferroptosis by regulating lncRNA. Wenyujin's effective ingredient, curcumenol, has been found to have anti-cancer potential. Curcumenol was revealed to induce cells ferroptosis and inhibit cells proliferation in lung cancer cells *via* lncRNA Imprinted Maternally Expressed Transcript (H19)/miR-19B-3P/FTH1 signal transduction[142]. In addition, the researchers found that metformin inhibits autophagy and growth in breast cancer by inducing ferroptosis through lncRNA H19[143] (fig. 3 and Table 2).

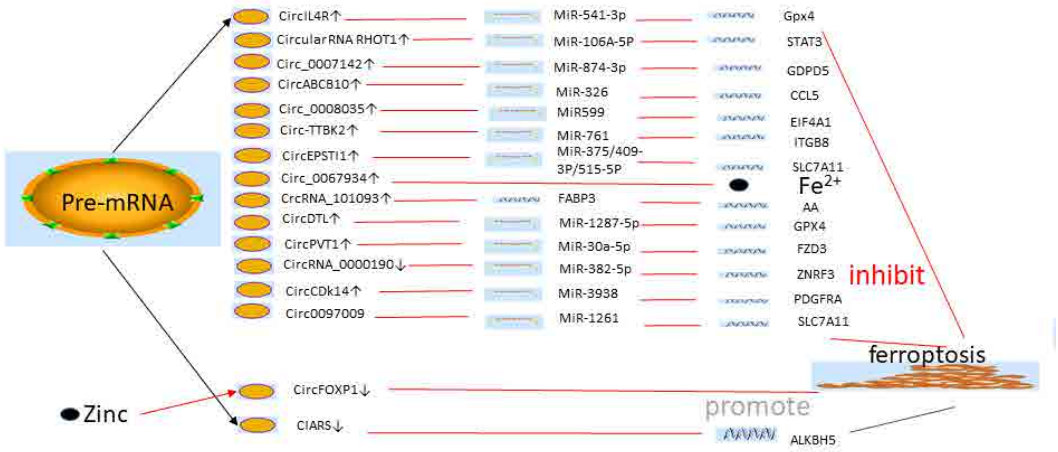

Fig. 3: LncRNAs and ferroptosis in cancers

TABLE 2: LncRNAs AND FERROPTOSIS IN CANCERS

LncRNAs	References	Expression	Target/Mechanisms	Cancers
LINC00618	[125]	↓	SLC7A11	AML
LINC00336	[127]	↑	miR6852/CBS	Lung cancer
MT1DP	[129]	↓	miR-365a-3p/NRF2	Lung cancer
LncRNA miR503HG	[133]	↑	miR1273c/SOX4	Lung cancer
LncNEAT1	[134]	↑	ACSL4, SLC7A11 and GPX4	Lung cancer
LncRNA GABPB1-AS1	[135]	↓	GABPB1/PRDX5	HCC
LncRNA P53RRA	[136]	↓	G3BP1/P53	Lung cancer
LINC01503, ARRDC1-AS1, OIP5-AS1, AC004687.1, AC010973.2, AP001189.3 and NCK1-DT	[137]	↑	MAPK, mTOR and GSH pathways	Colon cancer
LINC01963	[138]	/	Notch pathway	Head and neck cancer
LncRNA BDNF-AS	[139]	↑	WDR5/FBXW7	Gastric cancer
LncRNA SLC16A1-AS1	[140]	↑	miR143-3P/SLC7A11	Renal cell carcinoma
LncRNA RP11-89	[141]	↑	miR-129-5P/PROM2	Bladder cancer
Metformin/Curcumenol/lncRNAH19	[142,143]	↓	miR-19b-3p/FTH1	Lung cancer/breast cancer

CircRNA and ferroptosis:

Sorafenib, a commonly used chemotherapy drug for advanced HCC, had been found to promote ferroptosis in liver cancer cells. Further, the inhibition of ferroptosis was also associated with the promotion of sorafenib resistance[144]. Analysis of three sorafenib-treated HCC cell lines by RNA-seq and Sanger sequencing revealed that cIARS (Human Serum Albumin (HSA_circ_0008367)) was highly expressed in hepatoma cells. cIARS could bind with as Alpha (α)-Ketoglutarate-Dependent Dioxygenase (ALKB) Homolog 5 (ALKBH5) to inhibit the expression of P62 and increase levels of the lipidation of autophagy-related gene (LC3). cIARS could increase the level of MDA and Fe^{2+} and decrease the expression of GSH by promoting sorafenib and Erastin-mediated ferroptosis. Interestingly, cIARS also modulated ferroptosis in HCC cells by inhibiting ALKBH5 expression[145]. Circ0097009 are significantly up-regulated in HCC tissues and cell lines. The knock-down of circ0097009 could inhibit the proliferation and invasion of HCC cells and promote ferroptosis through the miR-1261/SLC7A11 axis[146].

CircIL4R was also differentially expressed in HCC tissues and cells. Low expression of circIL4R not only inhibited the proliferation of HCC, but also promoted the ferroptosis of HCC cells. In addition, it was found that circIL4R could promote the expression of GPX4, a ferroptosis suppressor gene, by sponging miR-541-3p[147], which modulated the biological characteristics of prostate cancer[148]. The role of circIL4R in regulating ferroptosis in cancer cells is rarely reported, but it is worth of further study. In addition, quantitative Reverse Transcription Polymerase Chain Reaction (qRT-PCR) and luciferase assays showed that circIL4R was overexpressed in HCC and could also sponge miRNA-541-3p. GPX4 had been identified as a downstream target gene for miR-541-3p. It is well known that GPX4 is a key regulator of ferroptosis. CircIL4R was also found to promote GPX4 expression and inhibit the role of ferroptosis in HCC[147].

SLC7A11 is an essential subunit of the xc^- system as mentioned above. Knocking down the expression of SLC7A11 could promote the occurrence of ferroptosis. Wu *et al.* found that circRNA Epithelial Stromal Interaction 1 (circEPSTI1) could promote SLC7A11-mediated the production of GSH and inhibit ferroptosis in cervical cancer cells using the GSH/GSSG assay. MiR-375/409-3p/515-5p were downstream genes of circEPSTI1 and might regulate ferroptosis of cervical cancer cells[149]. CircRNA Tau Tubulin Kinase 2 (circ-TTBK2) was revealed to promote the proliferation and invasion of glioma cells *via* the miR-761/Integrin Subunit Beta 8 (ITGB8) axis. At the same time, the involvement of circ-TTBK2 in ferroptosis inhibition of glioma was determined by analyzing the content of Fe^{2+} and the generation of ROS in cells[150].

circRNA Cyclin Dependent Kinase 14 (CircCDK14) could promote glioma progression by regulating the miR-3938/Platelet-Derived Growth Factor Receptor Alpha (PDGFRA) axis and protect against ferroptosis[151]. qRT-PCR revealed that circ_0008035 expression was significantly higher in gastric cancer cells and tissues and its expression was inversely proportional to Overall Survival (OS). Circ_0008035 could promote proliferation and inhibit apoptosis of gastric cancer cells by regulating the miR-599/ Eukaryotic Translation Initiation Factor 4A1 (EIF4A1) axis. Further, silencing circ_0008035 expression using small interfering (si)-circ_0008035 could promote Erastin or RSL3-mediated cell death of gastric cancer. Knocking down circ_0008035 also increased the production of MDA and lipid ROS by promoting the occurrence of ferroptosis[152]. In addition, circRNA_0000190 has been shown to further regulate Zinc and Ring Finger 3 (ZNRF3) in gastric cancer cells by sponging miR-382-5p to promote ferroptosis[153]. CircRNA ATP Binding Cassette Subfamily B Member 10 (CircABCB10) had been reported to regulate the proliferation, invasion and metastasis of tumor cells in several tumors, including lung and breast cancer[154,155]. Further, circABCB10 also modulated the apoptosis and ferroptosis of rectal cancer cells *via* the miR-326/ Chemokine (C-C motif) Ligand 5 (CCL5) axis[156].

Circ_0007142 was revealed to be highly expressed in colorectal cancer. Circ_0007142 could promote Glycerophosphodiester Phosphodiesterase Domain Containing 5 (GDPD5) expression by sponging miR-874-3p to inhibit colorectal cancer cell apoptosis and ferroptosis[157], thus, providing further support that there is a direct correlation between the types of cell death.

In addition, circRNA Ras Homolog Family Member T1 (RHOT1) was reported to promote breast cancer proliferation, invasion and migration. Further, circRNA RHOT1 also inhibited ferroptosis in breast cancer cells by regulating the miR-106A-5P/Signal Transducer and Activator of Transcription 3 (STAT3) axis[158]. It has been reported that there is a close relationship between STAT3 expression and genes involved in ferroptosis, such as NRF2 and GPX4[159]. Thus, there are good prospects for identifying a regulatory mechanism of ferroptosis by targeting the STAT3 gene.

Circ_0067934 has been found to act as a regulator of thyroid cancer. Circ_0067934 silence could raise the level of iron and ROS in cells[160]. Recently, exosome circRNA_101093 could interact with Fatty Acid-Binding Protein 3 (FABP3) and increase the reaction of arachidonic acid with taurine, which was critical for desensitization of lung adenocarcinoma cells to ferroptosis[161]. In addition, circRNA (Denticleless E3 Ubiquitin Protein Ligase Homolog) circDTL could act as a oncogene in lung cancer cells. The researchers found that knockdown of circDTL promoted apoptosis and ferroptosis in NSCLC cells through the miR-1287-5P/GPX4 axis[162]. Zinc acts as a regulator of a key gene for ferroptosis. Zinc could inhibit the proliferation of lung cancer cells and promote ferroptosis in lung cancer cells with high expression of circRNA Forkhead Box P1 (circFOXP1)[163].

Recently, researchers have found that circPVT1 Oncogene (PVT1) could upregulate and increase the expression of multidrug resistance-related proteins (including Multidrug Resistance Protein 1 (MRP1) and P-Glycoprotein (P-GP)) in 5-Fluorouracil (5-FU) resistant Esophageal Squamous Cell Carcinoma (ESCC) cells. The knockdown of circPVT1 was revealed to enhance chemical sensitivity to 5-FU by miR-30a-5p/Frizzled Class Receptor 3 (FZD3) axis and the occurrence of ferroptosis[164] (fig. 4 and Table 3).

Fig. 4: CircRNAs and ferroptosis in cancer

TABLE 3: CircRNAs AND FERROPTOSIS IN CANCERS

CircRNAs	References	Expression	Target/Mechanisms	Cancers
cIARS	[145]	↓	ALKBH5	HCC
CircIL4R	[147]	↑	miR-541-3p/GPX4	HCC
Circ0097009	[146]	↑	miR-1261/SLC7A11	HCC
CircEPSTI1	[149]	↑	miR-375/409-3P/515-5P/SLC7A11	Cervical cancer
Circ-TTBK2	[150]	↑	miR-761/ITGB8	Glioma
CircCDk14	[151]	↑	miR-3938/PDGFRA	Glioma
Circ_0008035	[152]	↑	miR599/EIF4A1	Gastric cancer
CircRNA_0000190	[153]	↓	miR-382-5p/ZNRF3	Gastric cancer
CircABCB10	[156]	↑	miR-326/CCL5	Colorectal cancer
Circ_0007142	[157]	↑	miR-874-3p/GDPD5	Colorectal cancer
CircRNA RHOT1	[158]	↑	miR-106A-5P/STAT3	Breast cancer
Circ_0067934	[160]	↑	miR-545-3p/SLC7A11	Thyroid cancer
Eosome CircRNA_101093	[161]	↑	FABP3	Lung adenocarcinoma
CircDTL	[162]	↑	miR-1287-5p/GPX4	Lung cancer
Zinc/CircFOXP1	[163]	↓	/	Lung cancer
CircPVT1	[164]	↑	miR-30a-5p/FZD3	ESCC
Zinc/CircFOXP1	[163]	↓	/	Lung cancer
CircPVT1	[164]	↑	miR-30a-5p/FZD3	ESCC

Other ncRNAs and ferroptosis:

To date, there are no reports evaluating the role of piRNA in ferroptosis. In breast cancer, piRNA-36712 was found to be significantly less expressed than in normal breast cells. RNAs produced by SEPW1 Pseudogene (SEPW1P) interacted with piRNA-36712 to inhibit the expression of P53[165]. PiRNA is known to associate with Piwi proteins to form effector complexes and regulate gene expression through epigenetics. Piwi-like protein 2 (Piwil2) was reported to form a Piwil2/STAT3/c-Src triple protein complex by directly associating with STAT3 protein *via* its Piwi Argonaut and Zwille (PAZ) domain. In addition, STAT3 is phosphorylated by c-Src and translocates to the nucleus, where it represses P53 gene transcription by binding to its promoter region of target genes in tumor cells[166]. Jiang *et al.* also reported that Piwil2 could inhibit tumor cell apoptosis by repressing P53 phosphorylation *via* P38[167]. These findings indicate that that Piwil2 may or may not inhibit ferroptosis in tumor cells. As a piRNA-like small RNA, piR-L-138 might interact with p60-MDM2 Proto-Oncogene (MDM2) to inhibit apoptosis and promote cisplatin resistance in P53-mutated lung cancer[168]. Recently, it had been reported that overexpression of piR-31470 could inhibit the levels of Glutathione S-Transferase Pi 1 (GSTP1) through DNA methylation modification and increase the vulnerability of RWPE1 cells (human prostate epithelial cells) to DNA damage and oxidative stress[169]. Overall, these finding suggest that piR-31470 might promote ferroptosis in cancer cells.

Loss of Cysteinyl-tRNA Synthetase (CARS) could inhibit ferroptosis by promoting transport in the xc^- system and induction of the transsulfuration pathway[170]. In addition, Shimada *et al.* found that inhibition of tRNA synthetase might compensate for the loss of Cys in tumor cells, promote endogenous Cys biosynthesis and subsequently inhibit ferroptosis[171], tRNAs may regulate the formation of the cytochrome C-mediated apoptosome and further alter the apoptotic sensitivity of tumor cells[172].

The prospect of N^6-methyladenosine (m^6A) regulation:

With the development of high-throughput sequencing, over 170 types of RNA modifications have been discovered, of which methylation is the most common in eukaryotes. RNA modifications make RNA more complex and diverse, and are involved in the regulation of a variety of biological functions[173]. m^6A was

first reported to modulate mRNA expression in Novikoff hepatoma cells[174]. Since then, over 7000 mRNA types have been identified that are regulated by m^{6}A in mammals, and a new type of epigenetics emerged. m^{6}A is considered the most common methylation modification[175]. In addition, m^{6}A modification has been identified in ncRNAs including miRNA, lncRNA, circRNA, ribosomal RNA (rRNA) and tRNA[176]. m^{6}A modification occurs mainly in adenosine-rich RRACH sequences and is achieved by RNA methyltransferase (writers) such as METTL3 and METTL14; RNA demethylase (erasers) such as ALKBH5 and m^{6}A binding protein (readers) such as YTH N6-Methyladenosine RNA Binding Protein 1 (YTHDF1) and YTHDF2. Likewise, m^{6}A plays a key role in regulating the stability or splicing of cancer genes[177]. Two subunits SLC7A11 and SLC3A2 in the xc^- system, which are important regulatory mechanisms of ferroptosis, are regulated by the m^{6}A reader YT521-B Homology Containing 2 (YTHDC2) in lung adenocarcinoma. YTHDC2 could inhibit the expression of SLC3A2 by enhancing the m^{6}A modification of the Homeo Box A13 (HOXA13) mRNA 3'-UTR and promote the ferroptosis of lung cancer cells[178]. Recently, METTL3 was identified as the target gene of miR-4443. Interestingly, miR-4443 could regulate FSP1 m^{6}A modification *via* METLL3, which inhibited ferroptosis and promoted NSCLC cisplatin resistance[121]. Both writers and readers can modify the function and death of cancer cells, including ferroptosis *via* the regulation of target genes. Bioinformatics analysis identified the upstream ncRNAs of YTHDC2 and METLL3 could regulate the ferroptosis of cancer cells *via* mRNA m^{6}A. FSP1, SLC3A2 and SLC7A11 are essential regulatory genes for ferroptosis. Whether their m^{6}A modification is regulated by other ncRNAs is worth further study. The role of m^{6}A modification of ncRNAs in ferroptosis has not been reported. However, it has recent reports indicate that m^{6}A regulates ncRNAs expression in apoptosis and autophagy. Sorafenib has been shown to be a promoter of ferroptosis. The stability of circRNA-SORE in sorafenib-resistant hepatoma cells was regulated by m^{6}A and might inhibit cells apoptosis *via* the β-catenin signaling pathway[179]. The m^{6}A modification of Forkhead box O3 (FOXO3) was revealed to maintain the stability of FOXO3 mRNA *via* METLL3 activity and promote the sensitivity of sorafenib in hepatoma cells by inhibiting autophagy[180]. Further studies had validated the role of circRNA-SORE m^{6}A in regulating ferroptosis in sorafenib-resistant hepatoma cells and searched for upstream ncRNAs of FOXO3. The interaction between cIARS (HSA) and ALKBH5 might modulate ferroptosis in hepatoma cells through autophagy and apoptosis, although the authors only used ALKBH5 as an autophagy inhibitor. ALKBH5 can be used as an eraser of m^{6}A activity to explore the role of mRNAs methylation or of ncRNAs demethylation in ferroptosis.

The prospect of immunotherapy:

In the past few decades, cancer immunotherapy has made great progress from scientific exploration to clinical practice. Immune checkpoint therapy and the use of blocking antibodies have produced clinically significant efficacy[181]. Inhibition or activation of T cell function is directly controlled by certain immune checkpoint molecules, these include Programmed Cell Death protein 1 (PD-1) and its corresponding ligand PD-L1, Cytotoxic T Lymphocyte Associated Antigen 4 (CTLA-4), T Cell Membrane Protein 3 (TIM3), B and T Lymphocyte Attenuator (BTLA) and Lymphocyte Activating Gene 3 (LAG3)[182]. In the tumor's microenvironment, these molecules are often expressed abnormally, which can induce excessive cellular immune tolerance and immune escape[183]. In the study of lncRNA-mediated ferroptosis in head and neck cancer, there were also differences in the expression of PD-1, CTLA4 and LAG3 between the high and low-risk groups[138]. It is suggested that lncRNA may modulate the occurrence of ferroptosis and change the immune escape of tumor cells. In addition, tumor cells are also regulated by intrapacket or vesicular ncRNAs in the process of tumor immune escape[184]. Circ-Carboxypeptidase A4 (CPA4) was found to inhibit apoptosis of NSCLC cells *via* let-7 miRNA/PD-L1 axis and promote tumor immune escape through inactivated CD8 T cells[185]. However, immunotherapy for cancer has been found to restore or enhance the effect of CD8 T cells to enhance the specific lipid peroxidation of ferroptosis in the tumor microenvironment. The release of Interferon gamma (IFNγ) from CD8 T cells could decrease the expression of SLC7A11 and SLC3A2[186]. NcRNAs may inhibit immune escape and become an important target of immunotherapy while regulating tumor cell death (ferroptosis).

DISCUSSION

As a type of cell death, ferroptosis is closely associated with other forms of cell death. The correlation between ferroptosis, apoptosis or autophagy can be identified by detecting the related proteins or by observing changes in mitochondria. Ferroptosis is also a genetically regulated form of cell death.

The role of ncRNAs in the regulation of gene expression represents a novel direction to be explored in ferroptosis. There is no doubt that the most studied ncRNAs have focused on miRNA and its upstream lncRNA and circRNA. These form a network called the CeRNAnet, which regulates gene expression, especially in various cancers. But most ceRNA network regulation mechanisms investigated are still limited to apoptosis, autophagy or other metastatic pathways and drug resistance in cancer cells. We should continue to explore the occurrence of ferroptosis in different cancer types for the following reasons: Due to their potential role in apoptosis and autophagy; to identify marker genes associated with ferroptosis; and to search for upstream genes such as lncRNAs and circRNAs based on known miRNAs. For other ncRNAs such as piRNAs and tRNAs, there is still much to be explored in terms of tumor cell ferroptosis. PiRNA has been found to play a regulatory role in many mechanisms of ferroptosis. Further research could be carried out to investigate piRNA interacting proteins such as Piwil1 or Piwil2. We can also study the role of ferroptosis in tumor cells apoptosis by piRNAs. The regulatory networks involving ncRNAs such as tRNAs, rRNAs and piRNAs are still relatively unknown, and further research is needed to identify the differential expression of these ncRNAs based on gene sequencing and the functional role of ferroptosis. m^6A, a type of gene editing, can promote the stability and maturation of mRNAs or ncRNAs. This suggests that there is a critical role for gene regulation of PCD including ferroptosis in cancer. Readers, writers and erasers of m^6A may be the potential regulators of ferroptosis.

Current ncRNAs and ferroptosis researches are still lacking in terms of improving cancer chemoresistance. Further studies should address genes or pathways associated with chemoresistance such as ATP-Binding Cassette (ABC) transporters, DNA damage repair, exosomes, KRAS signaling pathways. These mechanisms could be combined with ncRNAs regulation of ferroptosis to modulate the resistance towards chemotherapeutic drugs such as cisplatin and sorafenib. The use of bioinformatics will easily approach to screening of ncRNAs and at the same time, in future studies, ferroptosis activators and inhibitors such as Fe-1 or Erastin should be investigated for their role on ncRNAs. In addition, we wish to see further exploration of gene therapy (ncRNAs) and immunotherapy in tumor PCD to improve chemotherapy resistance.

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Yun Gong and Yue Lv contributed equally to this work and share first authorship.

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