Zhang et al. *Cell Death and Disease* (2020)11:580
https://doi.org/10.1038/s41419-020-02772-8

Cell Death & Disease

REVIEW ARTICLE Open Access

Crosstalk between noncoding RNAs and ferroptosis: new dawn for overcoming cancer progression

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Abstract

Cancer progression including proliferation, metastasis, and chemoresistance has become a serious hindrance to cancer therapy. This phenomenon mainly derives from the innate insensitive or acquired resistance of cancer cells to apoptosis. Ferroptosis is a newly discovered mechanism of programmed cell death characterized by peroxidation of the lipid membrane induced by reactive oxygen species. Ferroptosis has been confirmed to eliminate cancer cells in an apoptosis-independent manner, however, the specific regulatory mechanism of ferroptosis is still unknown. The use of ferroptosis for overcoming cancer progression is limited. Noncoding RNAs have been found to play an important roles in cancer. They regulate gene expression to affect biological processes of cancer cells such as proliferation, cell cycle, and cell death. Thus far, the functions of ncRNAs in ferroptosis of cancer cells have been examined, and the specific mechanisms by which noncoding RNAs regulate ferroptosis have been partially discovered. However, there is no summary of ferroptosis associated noncoding RNAs and their functions in different cancer types. In this review, we discuss the roles of ferroptosis-associated noncoding RNAs in detail. Moreover, future work regarding the interaction between noncoding RNAs and ferroptosis is proposed, the possible obstacles are predicted and associated solutions are put forward. This review will deepen our understanding of the relationship between noncoding RNAs and ferroptosis, and provide new insights in targeting noncoding RNAs in ferroptosis associated therapeutic strategies.

Facts

- Resistance to apoptosis has become the main obstacle for overcoming cancer progression.
- Ferroptosis is a type of cell death characterized by excess reactive oxygen species and intracellular iron, and is totally different from apoptosis.
- NcRNAs serve as important roles in biological processes of cancer.
- Regulation of ncRNAs to ferroptosis has been partially discovered.

Open Questions

- Can ferroptosis become the direction around which to design cancer therapy in future?
- What are the roles of ncRNAs in regulation of ferroptosis?
- Can ncRNAs become markers to filter cancer patients who are fit for ferroptosis therapy or therapeutic targets of ferroptosis inducers?

Introduction

Cancer progression including proliferation, metastasis and chemoresistance to drugs, has become serious obstacles in cancer therapy[1]. Although multiple therapeutic manners including operation, targeted therapy, chemotherapy, and radiotherapy have shown satisfactory performance, progression occurs since cancer cells

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Edited by G. Calin

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dysregulate apoptosis pathways via various manners[2,3]. Therefore, new types of cancer therapy or drugs that eliminate cancer cells are urgently needed.

Ferroptosis is a type of programmed cell death discovered in 2012[4]. Unlike apoptosis, ferroptosis is characterized by excess reactive oxygen species (ROS) and intracellular iron[5]. Superabundant ROS induces peroxidation and disintegration of lipid membrane and cell death[6]. Regulation of ferroptosis mainly depends on neutral reaction between reduced glutathione (GSH) and ROS[7]. The exchange of glutamate and cystine is mediated by systemXc$^-$, which is composed of solute carrier family 7 member 11 (SLC7A11) and solute carrier family 3 member 2 (SLC3A2), and offers the substrate cystine for GSH synthesis[8,9]. Glutathione peroxidase 4 (GPX4) catelyzes interaction between GSH and ROS to reduce intracellular oxidative stress[10]. Ferroptosis inducers can be divided into two classes based on regulation of neutral reaction to ROS. Class I ferroptosis inducers such as sorafenib, erastin and sulfasalazine, serve as blockers of systemXc$^-$ and result in a drop of GSH levels[11,12]. Class II ferroptosis inducers such as RSL3, FIN56, and ML162, inhibit function of GPX4[13,14]. Numerous studies have confirmed that ferroptosis inducers such as RSL3 and sorafenib eliminates cancer cells[15,16]. In addition, induction of ferroptosis via erastin and sulfasalazine improved effect of cytarabine and doxorubicin, and overcame cisplatin resistance of head and neck cancer[17,18]. This suggests that ferroptosis may become a new mechanism around which to design cancer therapy. However, use of ferroptosis in cancer therapy still faces obstacles. First, the specific mechanisms underlying ferroptosis and the interaction between ferroptosis and other processes, such as apoptosis, necrosis, and autophagy are not totally known, so how to control ferroptosis in cancer is in dark. Second, ferroptosis occurs in normal cells. Ferroptosis has been shown to induce the elimination of nerve cells in Parkinson's disease[19]. In addition, in acute kidney injury, ferroptosis participated in the death of renal tubular epithelial cells[20]. Therefore, use of ferroptosis inducers may generate complications. New regulatory factors should be recognized to understand the true appearance of ferroptosis in cancer.

Noncoding RNAs (ncRNAs) are RNAs that account for nearly 98% of transcriptome[21]. According to length and shapes, ncRNAs are divided into various types including microRNAs (miRNAs), PIWI-interacting RNAs (piRNAs), small nuclear RNAs (snRNAs), small nucleolar RNAs (snoRNAs), long ncRNAs (lncRNAs), circular RNAs (circRNAs), transfer RNAs (tRNAs), and ribosomal RNAs (rRNAs)[22,23]. NcRNAs participate in regulation of tumorigenesis via various biological processes such as chromatin modification, alternative splicing, competition with endogenous RNAs and interaction with proteins[24,25]. For example, *miR-675-5p* promoted the metastasis of colorectal cancer cells via modulation of P53[26]. Moreover, lncRNA *HOTAIR* served as an enhancer in epithelial-to-mesenchymal transition of breast cancer cells via competing with BRCA1[27]. In addition, *circFOXO3* enhanced progression of prostate cancer through sponging *miR-29a-3p*[28]. However, roles of ncRNAs in ferroptosis have not been fully determined.

In this review, we focus on summarizing the ncRNAs which have been found to associate with ferroptosis regulators GSH, iron, nuclear factor (erythroid-derived 2)-like 2 (NRF2) and ROS in cancer[5]. Moreover, we predict the obstacles that may limit the exploration of ncRNAs in ferroptosis in cancer therapy and offer advice for future studies. We believe that a comprehensive understanding of the interactions between ncRNAs and ferroptosis may benefit clinical therapeutics to cancer

MiRNAs and ferroptosis

MiRNAs exhibit functions by binding to the 3′-untranslated regions of target mRNAs and suppressing their expression[29]. Some studies have revealed a relationship between miRNAs and ferroptosis. In radioresistant cells, *miR-7-5p* inhibited ferroptosis via downregulating mitoferrin and thus reducing iron levels[30]. Furthermore, *miR-9* and *miR-137* enhanced ferroptosis via reduction of intracellular GSH levels, *miR-9* inhibited synthesis of GSH and *miR-137* suppressed solute carrier family 1 member 5 (SLC1A5), a component of systemXc$^-$[31]. Moreover, *miR-6852* which was regulated by lncRNA *Linc00336*, inhibited growth of lung cancer cells via promoting ferroptosis[32]. In the following sections, we will discuss the interactions between miRNAs and GSH, iron and NRF2 in cancer cells. The information of altered miRNAs in ferroptosis has been listed (Supplementary Table 1).

MiRNAs and GSH

GSH is a scavengerof ROS and protects lipid membrane[33]. Under physiological conditions, concentration of reduced GSH is about 10–100-fold more prevalent than the oxidized form. Under oxidative stress, reduced GSH is converted to oxidized form[34]. Biosynthesis of GSH involves three steps: exchange of glutamic acid and cystine induced by systemXc$^-$; synthesis of 훾-glutamylcysteine by glutamic acid and cysteine catalyzed via 훾-glutamylcysteine ligase (GCL); and synthesis of GSH via 훾-glutamylcysteine and glycine catalyzed by GSH synthetase[35]. Function of GSH includes detoxification of exogenous or endogenous dangerous compounds catalyzed by GSH-S-transferases (GSTs) and GPXs[36]. Current knowledge on relation between GSH and cancer are summarized in Table 1, and the schematic diagram of these interactions is shown in Fig. 1a. *MiR-18a* and *miR-*

Table 1 Summary of GSH associated miRNAs in cancer.

Name	Associated cancer type	Target	Influence to GSH	Model of evidence	Reference
miR-27a	Bladder cancer, colorectal cancer	SLC7A11, ZBTB10	Up/Down	Cell culture, animal models	42,43
miR-143	Colorectal cancer	GPX	Up	Animal models	199
miR-17	Prostate cancer	GPX2	Up	Cell culture, animal models	56
miR-17-3p	Prostate cancer	GPX2	Up	Cell culture, animal models	57
miR-196a	Lung cancer	GPX3	Up	Cell culture, animal models	58
miR-921	Lung cancer	GPX3	Up	Cell culture	59
miR-124	Colorectal cancer	GST	Up	Cell culture, animal models	48
Let-7a-5p	Prostate cancer	GST	Up	Cell culture, animal models	49
miR-92b-3p	Prostate cancer	GST	Up	Cell culture, animal models	49
miR-129-5P	Colorectal cancer cells	GST	Up	Cell culture	50
miR-144	Prostate cancer	GST	Up	Cell culture, animal models	51
miR-153-1/2	Prostate cancer	GST	Up	Cell culture, animal models	51
miR-302c-5p	Colorectal cancer	GST	Up	Cell culture	50
miR-3664-5p	Colorectal cancer	GST	Up	Cell culture	50
miR-3714	Colorectal cancer	GST	Up	Cell culture	50
miR-513a-3p	Colorectal cancer, lung cancer	GST	Up	Cell culture	200
miR-590-3p/5p	Prostate cancer	GST	Up	Cell culture, animal models	51
miR-133a/b	Bladder cancer, lung cancer, prostate cancer, colorectal cancer, ovarian cancer, head and neck squamous cell carcinoma	GST	Up	Cell culture, animal models	52,53,201
miR-130b	Ovarian cancer	GST	Up	Cell culture	202
miR-186	Ovarian cancer	GST	Up	Cell culture	203
miR-34b	Prostate cancer	MYC	Up	Cell culture	204
miR-K12-11	Kaposi's sarcoma	xCT	Up	Cell culture	205
miR-18a	Hepatocellular carcinoma	GCL	Down	Cell culture, animal models	37
miR-218	Bladder cancer	GCL	Down	Cell culture	38
miR-21	Lung cancer	GSH	Down	Cell culture	44
miR-24-2	Colorectal cancer	GSH	Down	Clinical samples	45
miR-497	Cervical cancer	GSH	Down	Cell culture	46

Table 1 continued

Name	Associated cancer type	Target	Influence to GSH	Model of evidence	Reference
miR-503	Hepatocellular carcinoma	GSH	Down	Cell culture	47
miR-152	Hepatocellular carcinoma	GST	Down	Cell culture	39
miR-155	Lung cancer	GST	Down	Cell culture	40
miR-326	Glioma	PKM2	Down	Cell culture	41
miR-125b	Chronic lymphocytic leukemias	GSH	Unknown	Cell culture	206

218 decreased GSH levels via targeting GCL in hepatocellular carcinoma and bladder cancer[37,38]. Furthermore, in hepatocellular carcinoma and lung cancer, *miR-152* and *miR-155* decreased GSH levels via targeting GST[39,40]. In addition, *miR-326* and *miR-27a* inhibited GSH levels in cancer cells via targeting other factors such as pyruvate kinase m 2 (PKM2), SLC7A11 and zinc finger and BTB domain containing 10 (ZBTB10)[41–43]. Additionally, downregulation of GSH by miRNAs such as *miR-21*, *miR-24-2*, *miR-497* and *miR-503* has been observed in different cancer types, however, the specific mechanisms were not explored[44–47]. These findings indicate that miRNAs repress GSH levels via control of synthesis and consumption. The upregulation of GSH induced by miRNAs has been well-explored. GST was targeted by different miRNAs including *miR-124*, *let-7a-5p*, *miR-92b-3p*, *miR-129-5P*, *miR-144*, *miR-153-1/2*, *miR-302c-5p*, *miR-3664-5p*, *miR-3714*, *miR-513a-3p*, *miR-590-3p/5p*, *miR-130b*, *miR-186*, and *miR-133a/b*. These miRNAs bound to the 3′-untranslated regions of GST mRNA and inhibited GST expression, thus blocking GSH consumption and resulting in accumulation of intracellular GSH[48–51]. It is worth mentioning that *miR-133a/b* served as effective suppressors of GST in different cancer types, such as bladder cancer, lung cancer, prostate cancer, colorectal cancer, ovarian cancer and head and neck carcinoma. Inhibition of *miR-133a/b* reversed both increased GSH and insensitivity to drugs[51–54]. Furthermore, GPX family members are targeted by miRNAs and results in defect of ROS neutralization. In one report, GPX4 was decreased by *miR-181a-5p* in osteoarthritis[55]. However, the relationship between GPX4 and miRNAs in cancer is still in dark. Only GPX2 and GPX3 have been found to be modulated by miRNAs such as *miR-17*, *miR-17-3p*, *miR-196a*, and *miR-921* in colorectal cancer, prostate cancer, and lung cancer[56–59]. Overall, regulation of GSH by miRNAs occurs mainly through control of GST and GPX family members. Since GSH has been shown to participate in growth of tumors and chemoresistance to drugs which induce intracellular oxidative stress, miRNAs may regulate ferroptosis and control cancer progression via modulation of GSH.

MiRNAs and iron

Iron metabolism is another key factor in ferroptosis. Excessive iron increases ROS via Fenton reaction and ROS is neutralized by iron reversely[60]. Metabolism of iron mainly includes interaction between transferrin (TF) and its receptor (TFR), import of iron via divalent metal transporter 1 (DMT1), storage of iron as ferritin and iron-sulfur cluster (ISC), and export of iron via ferroportin (FPN)[61,62]. The specific realtion between miRNAs and iron is summarized in Table 2, and the schematic diagram of these interactions are shown in Fig. 1b. In colorectal

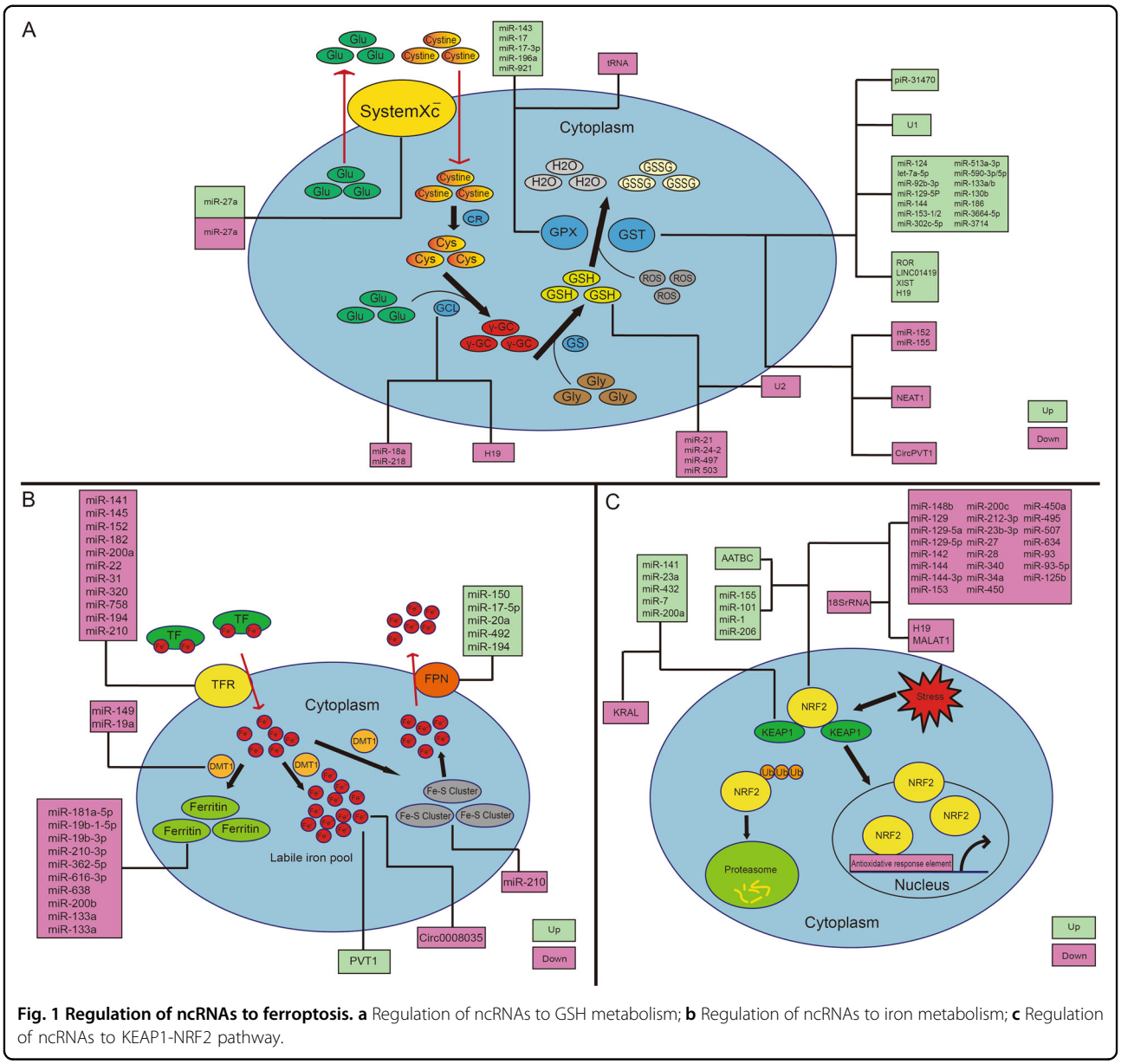

Fig. 1 Regulation of ncRNAs to ferroptosis. a Regulation of ncRNAs to GSH metabolism; **b** Regulation of ncRNAs to iron metabolism; **c** Regulation of ncRNAs to KEAP1-NRF2 pathway.

cancer, targeting of DMT1 by *miR-149* and *miR-19a* led to decreased iron import[63]. Furthermore, in colorectal cancer and hepatocellular cancer, TFR was targeted by miRNAs including *miR-141*, *miR-145*, *miR-152*, *miR-182*, *miR-200a*, *miR-22*, *miR-31*, *miR-320*, *miR-758*, and *miR-194*[63–65]. This inhibition led to disruption of interaction between TF and TFR and the following decreased iron import. Thereinto, *miR-194* suppressed the expression of both TFR and FPN in colorectal cancer[63]. FPN was also targeted by *miR-150*, *miR-17-5p*, *miR-20a*, and *miR-492* in hepatocellular carcinoma, multiple myeloma, lung cancer, and prostate cancer, respectively[66–68]. Furthermore, ferritin which is composed of ferritin heavy chain (FHC) and ferritin light chain (FLC), is controlled by miRNAs[69]. FHC could be targeted by *miR-200b*, *miR-181a-5p*, *miR-19b-1-5p*, *miR-19b-3p*, *miR-210-3p*, *miR-362-5p*, *miR-616-3p*, and *miR-638* in prostate cancer, resulting in decreased intracellular iron[65,70,71]. FLC could be targeted by *miR-133a* in colorectal cancer and breast cancer, and knockdown of *miR-133a* restored the reduced iron levels inside cancer cells[63,72]. Among the miRNAs that regulate iron levels, *miR-210* serves as an important member. In colorectal cancer cells, *miR-210* was activated by hypoxia and then targeted ISCU to alter intracellular iron homeostasis[73]. Furthermore, transfection of *miR-210* decreased the uptake of iron via TFR suppression[74]. On the contrary, miRNAs can be modulated by iron. *MiR-107*, *miR-125b*, and *miR-30d* were inhibited by iron in

Table 2 Summary of iron associated miRNAs in cancer.

Name	Associated cancer type	Target	Influence to iron	Model of evidence	Reference
miR-150	Hepatocellular carcinoma	FPN	Up	Cell culture	76
miR-17-5p	Multiple myeloma	FPN	Up	Cell culture, animal models	66
miR-20a	Lung cancer	FPN	Up	Cell culture	67
miR-492	Prostate cancer	FPN	Up	Cell culture, animal models	68
miR-194	Colorectal cancer	TFR1, FPN1	Up	Clinical samples	63
miR-449a	Glioma	CDGSH iron sulfur domain 2	Down	Cell culture, animal models	207
miR-149	Colorectal cancer	DMT1	Down	Clinical samples	63
miR-19a	Colorectal cancer	DMT1	Down	Clinical samples	63
miR-181a-5p	Prostate cancer	FHC	Down	Cell culture, animal models	70
miR-19b-1-5p	Prostate cancer	FHC	Down	Cell culture, animal models	70
miR-19b-3p	Prostate cancer	FHC	Down	Cell culture, animal models	70
miR-210-3p	Prostate cancer	FHC	Down	Cell culture, animal models	70
miR-362-5p	Prostate cancer	FHC	Down	Cell culture, animal models	70
miR-616-3p	Prostate cancer	FHC	Down	Cell culture, animal models	70
miR-638	Prostate cancer	FHC	Down	Cell culture, animal models	70
miR-200b	Hepatocellular carcinoma, breast cancer	Ferritin	Down	Cell culture	65,71
miR-133a	Colorectal cancer, breast cancer	FLC	Down	Cell culture	63,72
miR-29	Lung cancer	Iron-responsive element binding protein 2	Down	Clinical samples	208
miR-210	Renal cancer, head and neck paragangliomas, breast cancer, colorectal cancer, and oropharyngeal squamous cell carcinomas	ISCU, TFR1	Down	Cell culture, animal models	73,74,209–211
miR-126	Malignant mesothelioma	Mitochondria-destabilizing stress signals	Down	Cell culture, animal models	212
miR-7-5p	Ovarian cancer, colorectal cancer	Mitoferrin	Down	Cell culture	30
miR-122	Hepatocellular cancer	Nocturnin	Down	Cell culture, animal models	213
miR-34a	Lung cancer	P53	Down	Cell culture, animal models	214
miR-141	Colorectal cancer	TFR1	Down	Clinical samples	63
miR-145	Colorectal cancer	TFR1	Down	Clinical samples	63
miR-152	Hepatocellular carcinoma	TFR1	Down	Cell culture, animal models	64
miR-182	Colorectal cancer	TFR1	Down	Clinical samples	63
miR-200a	Hepatocellular carcinoma	TFR1	Down	Cell culture	65
miR-22	Hepatocellular cancer	TFR1	Down	Cell culture	65
miR-31	Colorectal cancer	TFR1	Down	Clinical samples	63
miR-320	Hepatocellular cancer	TFR1	Down	Cell culture	65
miR-758	Colorectal cancer	TFR1	Down	Clinical samples	63
miR-107	Hepatocellular carcinoma	–	Inhibited by iron	Cell culture, animal models	75
miR-125b	Ovarian cancer	–	Inhibited by iron	Cell culture	76
miR-30d	Hepatocellular carcinoma	–	Inhibited by iron	Cell culture, animal models	75
miR-146a	Ovarian cancer	–	Induced by iron	Cell culture	76
miR-150	Ovarian cancer	–	Induced by iron	Cell culture	76
miR-214-3p	Neuroblastoma	–	Induced by iron	Cell culture	77
miR-584	Neuroblastoma	–	Induced by iron	Cell culture	77

hepatocellular carcinoma and ovarian cancer[75,76], and *miR-146a*, *miR-150*, *miR-214-3p* and *miR-584* were increased by iron in ovarian cancer and neuroblastoma[76,77]. This phenomenon may derive from the induction of excess ROS by iron and the subsequent regulation of miRNAs transcription. Overall, different miRNAs regulate iron levels in various directions, and the imbalance of iron leads to run-away miRNA expression.

MiRNAs and NRF2

NRF2 serves as a transcriptional factor and activates downstream antioxidant factors. The expression of NRF2 mainly depends on Kelch-like ECh-Associated Protein 1 (KEAP1), which assembles Cullin3 to form the Cullin-E3 ligase complex and then degrades NRF2 protein via the ubiquitin-proteasome route[78]. Inhibition of NRF2 has been confirmed to enhance ferroptosis[79]. The specific information regarding interaction between miRNAs and NRF2 is listed in Table 3, and the schematic diagram is shown in Fig. 1c. In esophageal cancer, *miR-129*, *miR-142*, *miR-144-3p*, *miR-450*, *miR-507*, and *miR-634* targeted the 3′-untranslated region of NRF2 mRNA and decreased NRF2 expression, resulting in an increase of ROS[80–85]. Among these miRNAs, *miR-144-3p* played an important role in the regulation of NRF2. Targeting NRF2 by *miR-144-3p* inhibited tumor progression in melanoma and acute myeloid leukemia[86], and increased the sensitivity of lung cancer cells to cisplatin[87], indicating the role of *miR-144-3p* in oxidative homeostasis. Other miRNAs that targeted NRF2 include *miR-144*, *miR-153*, *miR-200c*, and *miR-212-3p*, although their effects have not been explored[82,88–90]. Moreover, miRNAs regulate NRF2 via targeting KEAP1. In hepatocellular carcinoma, ovarian cancer, leukemia, and neuroblastoma cells, KEAP1 was targeted by *miR-141*, *miR-23a*, *miR-432*, *miR-7*, and *miR-200a*[88,91–95]. Thereinto, *miR-200a* served as an active role. In esophageal squamous cell carcinoma, methylseleninic acid activated KEAP1/NRF2 pathway via upregulating *miR-200a*, the latter inhibited KEAP1 expression and induced expression of NRF2[96]. In breast cancer and pancreatic adenocarcinoma, *miR-200a* suppression reverted expression of KEAP1 and then inhibited NRF2 and promoted the anchorage-independent cell growth in vitro[97]. In turn, NRF2 enhances miRNAs expression via binding to the antioxidative response element box. In myelocytic leukemia, *miR-125b* driven by NRF2 promoted leukemic cells survival. Inhibition of *miR-125b* enhanced responsiveness of leukemic cells towards chemotherapy[98]. However, in oral squamous cell carcinoma, repression of *miR-125b* by peroxiredoxin like 2A (PRXL2A) protected cancer cells from drug-induced oxidative stress in an NRF2-depedent manner[99], indicating the mutual regulation between *miR-125b* and NRF2. In addition, expression of *miR-29B1*, *miR-129-3p*, and *miR-380-3p* was induced by NRF2 in acute myelocytic leukemia, hepatocellular carcinoma, and neuroblastoma[98,100,101]. Conversely, *miR-181c*, *miR-378*, *miR-122*, *miR-17-5p*, *miR-1*, and *miR-206* were repressed by NRF2 in various cancer types[66,102–107]. Thereinto, inhibition of *miR-1* and *miR-206* was mediated by SOD1 induced by NRF2 but not the role of NRF2 as a transcriptional factor. In summary, miRNAs regulate NRF2 pathway through targeting KEAP1 and NRF2 mRNAs. Conversely, NRF2 controls miRNAs via transcription or downstream factor SOD1.

MiRNAs and ROS

In addition to factors above, miRNAs regulate ROS via other mechanisms. The information of miRNAs that are related to ROS in cancer is listed in Table 4. MiRNAs can positively regulate ROS levels. For example, *miR-21* whose expression increased with tumor grade, has been identified to enhance ROS level in lung cancer, colorectal cancer, gastric cancer, hepatocellular carcinoma, ovarian cancer, and prostate cancer[108–113]. Mechanically, *miR-21* targeted STAT3, proline oxidase (POX), and programmed cell death 4 (PDCD4) to induce oxidative stress[114–116]. Moreover, *miR-146a* has attracted much attention. In ovarian cancer, *miR-146a* repressed SOD2 expression and inhibited proliferation of cancer cells and enhanced chemosensitivity to drugs[117]. In lung cancer, suppression of *miR-146a* restored catalase and inhibited ROS induction, and protected cancer cells from cisplatin-induced cytotoxicity[118]. In addition, overexpression of *miR-124*, *miR-526b*, and *miR-655* led to excess ROS via thioredoxin reductase 1 in breast cancer[119,120]. Furthermore, the antioxidant enzyme SOD1 was downregulated by stable expression of *miR-143* or *miR-145* in colorectal cancer[121]. This indicates that miRNAs enhance intracellular ROS via different manners. On the other hand, in lung cancer, *miR-99* suppressed the invasion and migration of cancer cells via targeting NOX4-mediated ROS production[122]. Additionally, *miR-520* and *miR-373* reduced ROS via targeting NF-κB and TGF-β signaling pathways and repressed growth and lymph node metastasis of breast cancer[123]. Other miRNAs such as *let-7*, *miR-137*, *miR-193b*, *miR-199*, and *miR-26a*, have been found to decrease ROS level in cancer cells via diverse targets such as heme oxygenase-1, C-MYC, and triglyceride[124–128], indicating that miRNAs inhibit ROS level. Conversely, *miR-133a*, *miR-150-3p*, *miR-1915-3p*, *miR-206*, *miR-34*, *miR-638*, and *miR-182* were activated by oxidative stress and then played a role in the subsequent biological processes[129–133]. Moreover, *miR-125*, *miR-145-5p*, *miR-17-5p*, *miR-199*, and *miR-17-92*, were decreased by excess intracellular ROS[134–137]. Among them, *miR-125b* plays a dual role in oxidative homeostasis. As discussed above, *miR-125b* serves as a regulator of NRF2. In addition, *miR-125b* could be inhibited by ROS via a DNMT1-dependent DNA

Table 3 Summary of NRF2 associated miRNAs in cancer.

Name	Associated cancer type	Target	Influence to NRF2	Model of evidence	Reference
miR-141	Hepatocellular carcinoma, ovarian cancer	KEAP1	Up	Cell culture	88,91–93
miR-23a	Leukemic	KEAP1	Up	Cell culture, animal models	94
miR-432	Esophageal cancer	KEAP1	Up	Cell culture	92,95
miR-7	Neuroblastoma cells	KEAP1	Up	Cell culture	92
miR-200a	Breast cancer, esophageal cancer, hepatocellular carcinoma, and pancreatic adenocarcinomas	KEAP1,	Up	Cell culture, animal models	81,92,96,97,215,216
miR-155	Lung cancer	NRF2	Up	Cell culture	217
miR-101	Hepatocellular carcinoma, prostate cancer	NRF2, SOD1	Up/Down	Cell culture, animal models	88,105,218
miR-1	Lung cancer, prostate cancer	NRF2, SOD1	Up/Inhibited by NRF2	Cell culture, animal models	105,107
miR-206	Lung cancer, prostate cancer	NRF2, SOD1	Up/Inhibited by NRF2	Cell culture, animal models	105–107
miR-148b	Endometrial cancer	ERMP1	Down	Cell culture	219
miR-129	Esophageal cancer	NRF2	Down	Cell culture, animal models	80
miR-129-5a	Esophageal cancer	NRF2	Down	Cell culture, animal models	80,81
miR-129-5p	Esophageal cancer	NRF2	Down	Cell culture, animal models	80
miR-142	Esophageal cancer	NRF2	Down	Cell culture	82
miR-144	Hepatocellular carcinoma, leukemia, hepatocellular carcinoma, neuroblastoma	NRF2	Down	Cell culture	88,89
miR-144-3p	Melanoma, lung cancer, and acute myeloid leukemia	NRF2	Down	Cell culture	86,87,220,221
miR-153	Neuroblastoma, breast cancer, and oral squamous cell carcinoma	NRF2	Down	Cell culture	82,90
miR-200c	Lung cancer	NRF2	Down	Cell culture, animal models	222
miR-212-3p	Melanoma	NRF2	Down	Cell culture	86
miR-23b-3p	Melanoma	NRF2	Down	Cell culture	86
miR-27	Neuroblastoma	NRF2	Down	Cell culture, animal models	223
miR-28	Breast cancer, esophageal cancer	NRF2	Down	Cell culture	81,224
miR-340	Hepatocellular carcinoma, esophageal cancer	NRF2	Down	Cell culture	85,88,92
miR-34a	Breast cancer, colon cancer, ovarian cancer, and lung cancer	NRF2	Down	Cell culture	225,226
miR-450	Esophageal cancer	NRF2	Down	Cell culture	83
miR-450a	Esophageal cancer	NRF2	Down	Cell culture, animal models	80,81
miR-495	Nonsmall-cell lung cancer	NRF2	Down	Cell culture	227
miR-507	Esophageal cancer	NRF2	Down	Cell culture, animal models	80,81,84

Table 3 continued

Name	Associated cancer type	Target	Influence to NRF2	Model of evidence	Reference
miR-634	Esophageal cancer	NRF2	Down	Cell culture, animal models	80,81,85
miR-93	Pancreatic adenocarcinomas, breast cancer	NRF2	Down	Cell culture, animal models	97,221
miR-93-5p	Melanoma	NRF2	Down	Clinical samples	86
miR-125b	Acute myelocytic leukemia, oral squamous cell carcinoma, and renal cancer	NRF2	Down/Induced by NRF2	Cell culture, animal models	98,99,228
miR-181c	Colorectal cancer	–	Inhibited by NRF2	Cell culture, animal models	102
miR-378	Mucoepidermoid carcinoma	–	Inhibited by NRF2	Cell culture, animal models	103
miR-122	Hepatocellular carcinoma	–	Inhibited by NRF2	Cell culture	104
miR-17-5p	Multiple myeloma	–	Inhibited by NRF2	Cell culture, animal models	66
miR-29B1	Acute myelocytic leukemia	–	Induced by NRF2	Cell culture	98
miR-129-3p	Hepatocellular carcinoma	–	Induced by NRF2	Cell culture, animal models	100
miR-380-3p	Neuroblastoma	–	Induced by NRF2	Cell culture, animal models	101

methylation in ovarian cancer[140]. Moreover, although *miR-21* has been discussed as the enhancer of ROS in breast cancer, DNA damage induced by ROS led to activation of *miR-21* via NF-κB, indicating the interaction between miRNAs and ROS[138]. In total, we can infer that altered levels of GSH, iron, and NRF2 are not the only methods by which miRNAs regulate ROS and vice versa in, miRNAs and ROS can also regulate each other in various pathways.

LncRNAs and ferroptosis

LncRNAs mainly serve as regulators of transcription factors in nucleus or as sponges of miRNAs in cytoplasm[139]. *Linc00336* was promoted by lymphoid-specific helicase in lung cancer and inhibited ferroptosis via sponging *miR-6852*[32]. Furthermore, in breast cancer and lung cancer, lncRNA *P53rra* bound to Ras GTPase-activating protein-(SH3domain)-Binding Protein 1 (G3BP1) and displaced P53 from a G3BP1 complex, resulting in retention of P53 in nucleus and downregulation of SLC7A11[140]. In addition, ferroptosis inducer erastin upregulated lncRNA GA binding protein transcription factor subunit beta 1 (GABPB1) antisense RNA 1 (*Gabpb1-AS1*), which suppressed GABPB1 and led to downregulation of peroxiredoxin-5 peroxidase and suppression of cellular antioxidant capacity in hepatocellular carcinoma[141]. Interaction between lncRNAs and ferroptosis has been listed (Supplementary Table 1), and the relationship between lncRNAs and ferroptosis associated factors is summarized in Table 5. The schematic diagram of these interactions is shown in Fig. 1.

LncRNAs and ferroptosis associated factors

Since there are only a few studies about lncRNAs and ferroptosis factors, we will discuss them together. Regulation of GSH by lncRNAs in cancer mainly depends on GST and GCL[46]. In breast cancer, knockdown of lncRNA *Ror* led to reduced multidrug resistance-associated P-glycoprotein and GST expression, resulting in restored sensitivity of breast cancer cells to tamoxifen[142]. Similarly, in colorectal cancer, knockdown of lncRNA *Xist* inhibited doxorubicin resistance via suppressing GST and increasing GSH[48]. Furthermore, in hepatocellular carcinoma cells, silencing lncRNA *Neat1* inhibited IL-6-induced STAT3 phosphorylation which contributed to the increase of GST[143]. In addition, lncRNA *Linc01419* bound to the promoter region of *GSTP1* and recruited DNA methyltransferase, increasing promoter methylation and decreasing GST expression in esophageal squamous cell carcinoma[144]. Moreover, knockdown of lncRNA *H19* resulted in recovery of cisplatin sensitivity via reduction of GCL and GST[145]. In total, regulation of GSH by lncRNAs mainly depends on GST and GCL. Moreover, in hepatocellular carcinoma, silencing of lncRNA *Pvt1* inhibited

Table 4 Summary of ROS associated miRNAs in cancer.

Name	Associated cancer type	Target	Influence to ROS	Model of evidence	Reference
miR-124	Non-small cell lung cancer	TXNRD1	Up	Cell culture	120
miR-125a	Osteosarcoma	Estrogen-related receptor alpha	Up	Cell culture	229
miR-128a	Medulloblastoma	BMI-1	Up	Cell culture	230
miR-139-5p	Breast cancer	Unknown	Up	Cell culture, animal models	231
miR-143	Colorectal cancer	SOD1	Up	Cell culture	121
miR-146a	Lung cancer, ovarian Cancer	Catalase, SOD2	Up	Cell culture, animal models	117,118
miR-146b-5p	Leukemic	Unknown	Up	Cell culture	232
miR-15	Colorectal cancer, cancer stem cells	C-MYC	Up	Cell culture, animal models	233
miR-155	Glioma, pancreatic cancer	MAPK13, MAPK14, and Foxo3a	Up	Cell culture, animal models	234,235
miR-15a-3p	Lung cancer	P53	Up	Cell culture	236
miR-16	Colorectal cancer, cancer stem cells	C-MYC	Up	Cell culture, animal models	233
miR-186	Colorectal cancer	CKII	Up	Cell culture	237
miR-193a-3p	Glioma	γH2AX	Up	Cell culture	238
miR-210	Cancer stem cells, glioma	P53	Up	Cell culture, animal models	239
miR-212	Colorectal cancer	MnSOD	Up	Clinical samples	240
miR-216b	Colorectal cancer	CKII	Up	Cell culture	237
miR-22	Hepatocellular carcinoma	SIRT-1	Up	Cell culture	241
miR-223	Breast cancer	HAX-1	Up	Cell culture	242
miR-23b-3p	Acute myeloid leukemia	PrxIII	Up	Cell culture	243
miR-25-5p	Colorectal cancer	SOX10	Up	Cell culture	244
miR-26a-5p	Acute myeloid leukemia	PrxIII	Up	Cell culture	243
miR-26b	Small cell lung cancer	Myeloid cell leukemia 1 protein	Up	Cell culture, animal models	245
miR-30	Gastric cancer	P53	Up	Cell culture	246
miR-337-3p	Colorectal cancer	CKII	Up	Cell culture	237
miR-34c	Nonsmall cell lung cancer	HMGB1	Up	Cell culture	247
miR-371-3p	Lung cancer	PRDX6	Up	Cell culture, animal models	248
miR-422a	Gastric cancer	PDK2	Up	Cell culture, animal models	249
miR-4485	Breast cancer	Mitochondrial protein	Up	Cell culture, animal models	133
miR-4673	Lung cancer	8-Oxoguanine-DNA Glycosylase-1	Up	Cell culture	250
miR-504	Lung cancer	P53	Up	Cell culture	251
miR-506	Lung cancer	P53, NF-κB	Up	Cell culture, animal models	252
miR-509	Breast cancer	P53	Up	Cell culture	253
miR-526b	Breast cancer	Thioredoxin Reductase 1	Up	Cell culture	119
miR-551b	Lung cancer	MUC1	Up	Cell culture	254
miR-655	Breast cancer	Thioredoxin Reductase 1	Up	Cell culture	119
miR-661	Colorectal cancer	Hexose-6-phosphate dehydrogenase, pyruvate kinase M2	Up	Cell culture	255
miR-760	Colorectal cancer	CKII	Up	Cell culture	237
miR-92	Hepatocellular carcinoma	Unknown	Up	Clinical samples	256
miR-128	Glioma, hepatocellular carcinoma	PKM2	Up/Down	Cell culture	257

Table 4 continued

Name	Associated cancer type	Target	Influence to ROS	Model of evidence	Reference
miR-145	Colorectal cancer, hepatocellular carcinoma	SOD1, PKM2	Up/Down	Cell culture	121,258
miR-211	Myeloma, oral carcinoma	PRKAA1, TCF12	Up/Down	Cell culture, animal models	259,260
miR-222	Hepatocellular carcinoma, breast cancer	NF-κB, TGF-β	Up/Down	Cell culture, animal models	261,262
miR-23a/b	Myeloma, renal cancer	C-MYC, POX	Up/Down	Cell culture, animal models	263,264
miR-29	Ovarian cancer, lung cancer, and lymphoma	C-MYC, SIRT1	Up/Down	Cell culture, animal models	265,266
miR-34a	Gastric cancer, glioma	NOX2	Up/Down	Cell culture	267
Let-7	Hepatocellular carcinoma, prostate cancer, and pancreatic cancer	Heme oxygenase-1, P53	Up/Down	Cell culture, animal models	123,268
miR-33a	Glioma, hepatocellular carcinoma	SIRT6	Up/Down	Cell culture, animal models	269
miR-221	Hepatocellular carcinoma, breast cancer	NF-κB, TGF-β, and DICER	Up/Down/Induced by ROS	Cell culture, animal models	261,262,270
miR-21	Lung cancer, colorectal cancer, gastric cancer, hepatocellular carcinoma, ovarian cancer, and prostate cancer	SOD, MAPK, SOD2, Glucose, NFκB, STAT3, POX, and PDCD4	Up/Down/Induced by ROS	Cell culture, animal models	108,112,114,271
miR-17-92	Gastric cancer, lung cancer	C-MYC, P53, and NFκB	Up/Down/Inhibited by ROS	Cell culture	137,272,273
miR-181	Hepatocellular carcinoma, uterine leiomyoma	Unknown	Up/Induced by ROS	Cell culture	132,274
miR-200	Breast cancer, cancer stem cells, hepatocellular carcinoma, and lung cancer	P53, PRDX2, GAPB/NRF2, SESN1	Up/Induced by ROS	Cell culture, animal models	222,275–277
miR-34	Cancer stem cells, bladder cancer, lung cancer	C-MYC, P53	Up/Induced by ROS	Cell culture	278,279
miR-182	Uterine leiomyoma, lung cancer	PDK4	Up/Induced by ROS	Cell culture, animal models	132,133
miR-199	Gastric cancer, ovarian cancer	DNMT1	Up/Inhibited by ROS	Cell culture	134
miR-20a	Breast cancer, pancreatic cancer	BECN1, ATG16L1, and SQSTM1	Up/Inhibited by ROS	Cell culture, animal models	136,280
miR-125b	Hepatocellular carcinoma, ovarian cancer, and breast cancer	Hexokinase 2, DNMT1, and HAX-1	Up/Inhibited by ROS	Cell culture, animal models	228,281
miR-1246	Breast cancer	NF-κB, TGF-β	Down	Cell culture	124
miR-137	Ovarian cancer	C-MYC	Down	Cell culture, animal models	125
miR-193b	Liposarcoma	Antioxidant methionine sulfoxide reductase A	Down	Cell culture, animal models	127
miR-199a-3p	Testicular cancer	Transcription factor specificity protein 1	Down	Cell culture	126
miR-26a	Hepatocellular carcinoma	Triglyceride, totalcholesterol, malondialdehyde	Down	Cell culture	128
miR-30c-2-3p	Breast cancer	NF-κB, TGF-β	Down	Cell culture	282
miR-346	Ovarian cancer	GSK3B	Down	Cell culture	283
miR-373	Breast cancer	NF-κB, TGF-β	Down	Cell culture, animal models	123
miR-520	Breast cancer	NF-κB, TGF-β	Down	Cell culture, animal models	123
miR-7	Nonsmall cell lung cancer	MAFG	Down	Cell culture	284
miR-885-5p	Hepatocellular carcinoma	TIGAR	Down	Cell culture	285
miR-99a	Lung cancer	NOX4	Down	Cell culture, animal models	122
miR-133a	Rhabdomyosarcoma	9	Induced by ROS	Cell culture, animal models	129
miR-150-3p	Hepatocellular carcinoma	–	Induced by ROS	Cell culture	130
miR-1915-3p	Hepatocellular Carcinoma	–	Induced by ROS	Cell culture	130
miR-206	Rhabdomyosarcoma	–	Induced by ROS	Cell culture, animal models	131
miR-34a-3p	Hepatocellular carcinoma	–	Induced by ROS	Cell culture, animal models	129
miR-34a-5p	Hepatocellular carcinoma	–	Induced by ROS	Cell culture	130
miR-638	Hepatocellular carcinoma	–	Induced by ROS	Cell culture	130
miR-125	Gastric cancer	–	Inhibited by ROS	Cell culture	134

Table 4 continued

Name	Associated cancer type	Target	Influence to ROS	Model of evidence	Reference
miR-145-5p	Gastric cancer	–	Inhibited by ROS	Cell culture, animal models	135
miR-17-5p	Pancreatic cancer	–	Inhibited by ROS	Cell culture, animal models	136
miR-27a	Pancreatic cancer, colorectal cancer	–	Inhibited by ROS	Cell culture, animal models	286
miR-328	Gastric cancer	–	Inhibited by ROS	Cell culture, animal models	287
miR-329	Breast cancer	–	Inhibited by ROS	Cell culture, animal models	288
miR-362-3p	Breast cancer	–	Inhibited by ROS	Cell culture, animal models	288

TFR expression and obstructed iron uptake via *miR-150*[146]. Furthermore, silencing of FHC in leukemia cells induced production of ROS and altered downstream genes via increasing *H19* and *miR-657* expression[147]. This means that lncRNAs are associated with iron metabolism in cancer cells. Moreover, in bladder cancer, suppression of NRF2 by lncRNA associated transcript in bladder cancer (*Aatbc*) resulted in apoptosis[148]. In multiple myeloma, metastasis associated lung adenocarcinoma transcript 1 (*Malat1*) which has been proved to play a role in various cancers, inhibited NRF2 via activation of their negative regulator KEAP1[149]. Furthermore, overexpression of Keap1 regulation-associated lncRNA (*Kral*) inhibited NRF2 via increasing KEAP1 expression, and reversed the resistance of hepatocellular carcinoma cells to 5-fluorouracil[91]. Therefore, lncRNAs regulate NRF2 expression via direct and indirect manners. On the contrary, NRF2 participates in regulation of lncRNAs. In gallbladder cancer, downregulation of lncRNA *loc344887* suppressed cell proliferation and decreased migration and invasion. Further studies found that *loc344887* was upregulated after ectopic expression of NRF2[150]. In a recent study, NRF2 activated smoke and cancer-associated lncRNA 1 (*Scal1*) and induced oxidative stress protection. Knockdown of NRF2 suppressed *Scal1* and alleviated the proliferation of lung cancer cells[92]. In sum, lncRNAs can regulate NRF2 by directly controlling expression or modulating KEAP1 indirectly, and NRF2 can regulate lncRNAs expression reversely.

Other than the factors above, lncRNAs regulate ROS levels via various mechanisms. In bladder cancer, lncRNA urothelial cancer associated 1 (*Uca1*) decreased ROS level via targeting *miR-16* which led to decreased GSH synthetase[151]. Furthermore, in hepatocellular carcinoma, downregulation of *H19* increased ROS via MAPK/ERK signaling pathway and reversed chemotherapy resistance[152]. Moreover, knockdown of lncRNA growth arrest specific 5 (*Gas5*) in melanoma enhanced intracellular ROS via increased superoxide anion and NADPH oxidase 4 (NOX4)-oxidized GSH[153]. In lung cancer cells, the intracellular oxidative stress induced by paclitaxel was attenuated by knockdown of maternally expressed 3 (*Meg3*), and *Meg3* overexpression induced cell death and increased sensitivity to paclitaxel in an ROS-dependent manner[154]. In total, lncRNAs influence ROS metabolism via control of GSH, iron, NRF2 and other factors, and these factors can regulate lncRNAs expression reversely.

Other ncRNAs and ferroptosis

CircRNAs, tRNAs, rRNAs, piRNAs, snRNAs, and snoRNAs are also contained in family of noncoding RNAs[21]. However, studies on the relations between these ncRNAs and ferroptosis are few. The interactions have

Table 5 Summary of GSH, iron, NRF2, and ROS associated lncRNAs in cancer.

Control point	Name	Associated cancer type	Target	Influence to control point	Model of evidence	Reference
GSH	*Linc01419*	Esophageal squamous cell carcinoma	GST	Up	Clinical samples	144
	Neat1	Hepatocellular carcinoma	GST	Up	Cell culture	143
	H19	Ovarian cancer	GCLC, GCLM, GST	Up/Down	Cell culture, animal models	145
	Xist	Colorectal cancer	GST	Down	Cell culture, animal models	48
	Ror	Breast cancer	GST	Down	Cell culture, animal models	142
Iron	*Pvt1*	Hepatocellular carcinoma	*miR-150*/HIG2	Up	Cell culture, animal models	146
	H19	Myeloid leukemia	*miR-675*	Inhibited by iron	Cell culture	147
NRF2	*Aatbc*	Bladder cancer	NRF2	Down	Cell culture, animal models	148
	Kral	Hepatocellular carcinoma	KEAP1	Down	Cell culture	91
	Malat1	Multiple myeloma	KEAP1	Down	Cell culture, animal models	149
	H19	Ovarian cancer	NRF2	Down	Cell culture, animal models	145
	Scal1	Lung cancer	–	Induced by NRF2	Cell culture	92
	Loc344887	Gallbladder cancer	–	Induced by NRF2	Cell culture	150
ROS	*Meg3*	Lung cancer	P53	Up	Cell culture	154
	Uca1	Bladder cancer	*miR-16*	Down	Cell culture	151
	Gas5	Melanoma	G6PD	Down	Cell culture	153
	H19	Hepatocellular carcinoma	MAPK/ERK signaling pathway	Down	Cell culture	152
	Miat	Neuroblastoma, glioblastoma	MAPK7, FUT8, and MCL1	Unknown	Cell culture	289–295

been listed (Supplementary Table 2). The schematic diagram of these interactions is shown in Fig. 1.

CircRNAs

CircRNAs are covalently closed, single-stranded RNA molecules derive from exons via alternative mRNA splicing[22]. Several studies have uncovered function of circRNAs in ferroptosis. In glioma, *circ-TTBK2* enhanced cell proliferation and invasion and inhibited ferroptosis via sponging *miR-761* and subsequent ITGB8 activation, knockdown of *circ-TTBK2* promoted erastin-induced ferroptosis[155]. Furthermore, *circ0008035* inhibited ferroptosis in gastric cancer via *miR-599*/EIF4A1 axis. Knockdown of *circ0008035* enhanced anticancer effect of erastin and RSL3 via increased iron accumulation and lipid peroxidation[156]. According to ferroptosis associated factors, in gastric cancer, *circPVT1* promoted multidrug resistance by enhancing P-gp and GSTP. MRNA levels of P-gp and GSTP were obviously repressed after downregulation of *circ-PVT1* in paclitaxel-resistant gastric cancer cells[157]. Moreover, high-throughout microarray-based circRNA profiling revealed that 526 circRNAs were dysregulated in cervical cancer cells, and bioinformatic analyses indicated that these circRNAs participated mainly in GSH metabolism[158]. However, associated miRNAs and downstream factors were not screened. Thus, further studies on the modulation of ferroptosis by circRNAs are needed.

TRNAs

TRNAs serve as adapter molecules between mRNAs and proteins. The interaction between tRNAs and ferroptosis includes two possible manners. First, tRNAs are required in the synthesis of ferroptosis associated factors such as SLC7A11, GPX4, and IREB2, thus the mutation of tRNAs may alter the expression of these factors and then influence ferroptosis[217]. Second, tRNAs have multiple interaction partners including aminoacyl-tRNA-synthetases, mRNAs, ribosomes and translation factors[159]. Among them, cysteinyl-tRNA synthetase plays a role in ferroptosis. In fibrosarcoma, rhabdomyosarcoma and pancreatic carcinoma, loss of cysteinyl-tRNA synthetase suppressed erastin-induced ferroptosis via increasing intracellular GSH and transsulfuration, and inhibition of the transsulfuration pathway resensitized cells to erastin[160]. Interestingly, tRNAs mutation may control ferroptosis in an opposite manner. Selenocysteine which is formed from serine at the respective tRNA, is a component of GPXs. However, in hepatoma, colorectal cancer and breast cancer, the mutation of tRNA led to decline of selenoprotein expression except GPX4 and GPX1, and weak ferroptosis alteration[161–163]. This indicates that tRNAs modulate GSH levels mainly via synthesis but not metabolism. In addition, tRNAs influence ROS levels via various manners. Lung cancer mouse model with deletion of selenocysteine-tRNA gene exhibited ROS accumulation and increased susceptibility to lymph nodules metastasis[164]. Additionally, Queuine-modified tRNAs promoted cellular antioxidant defense via catalase, SOD, GPX, and GSH reductase and inhibited lymphoma[165]. In total, tRNAs decrease GSH synthesis and increase ferroptosis without modulating GPX4, while on the other hand, tRNAs enhance the antioxidant defense system and then inhibit ferroptosis.

RRNAs

RRNAs constitute the structural and functional core of ribosomes[166]. Some reports have provided clues for role of rRNAs in ferroptosis. In cervical cancer, NRF2 was found to contain a highly conserved 18S rRNA binding site on 5′ untranslated region that is required for internal initiation. Deletion of this site remarkably enhanced translation, indicating that the 18S rRNA regulates NRF2 expression[167]. In another study, hepatoma cells treated with ethidium bromide exhibited a 70% decrease in the 16S/18S rRNA ratio and enhanced NRF2 expression[168]. However, whether NRF2 and 18S rRNA are mutually regulated remains unclear. Regarding ROS, nuclear mitotic apparatus protein (NuMA) is involved in cellular events such as DNA damage response, apoptosis, and P53-mediated growth arrest. In breast cancer cells, NuMA bound to 18S and 28S rRNAs and localized to rDNA promoter regions. Downregulation of NuMA expression triggered nucleolar oxidative stress and decreased pre-rRNA synthesis[169]. Furthermore, in leukemia HL-60 cells treated with iron chelator deferoxamine, rRNA synthesis in nucleoli was inhibited[170]. In conclusion, interaction between rRNAs and ferroptosis has not been completely uncovered. Role of ribosomes as the place in which proteins related to ferroptosis are synthesized may provide clues for further studies.

PiRNAs, snRNAs, and snoRNAs

PiRNAs are the class of small ncRNA molecules distinct from miRNAs in that they are larger, lack sequence conservation, and are more complex[171]. PiRNAs are involved in tumorigenesis of variety cancers[172]. However, studies on piRNAs and ferroptosis are few. In prostate cancer, piR-31470 formed a complex with piwi-like RNA-mediated gene silencing 4 (PIWIL4). This complex recruited DNMT1, DNA methyltransferase 3 alpha, and methyl-CpG binding domain protein 2 to initiate and maintain the hypermethylation and inactivation of GSTP1. Overexpression of piR-31470 inhibited GSTP1 expression and increased vulnerability to oxidative stress and DNA damage in human prostate epithelial RWPE1 cells, resulting in tumorigenesis[173]. However, the GSTP1 inactivation may inhibit tumor growth via

induction of ferroptosis once the tumors are formed. Clearly, further studies are needed to explore the roles of piRNAs in different stages of cancer. SnoRNAs are a class of small RNA molecules that mediate modifications of rRNAs, tRNAs, and snRNAs. The snoRNA ACA11 was overexpressed in multiple myeloma cells, increasing ROS and resulting in protein production and cell proliferation[174]. There are currently no reports on ferroptosis and snRNAs which mediate post-transcriptional splicing in gene expression. In cervical cancer and osteosarcoma, assembly chaperones and core proteins devoted to snRNA maturation contributed to recruiting trimethylguanosine synthase 1 to selenoprotein mRNAs including GPX1 for cap hypermethylation[175]. Future studies should focus on the possible regulation of snRNAs towards GPX families. In sum, further studies are needed to explore functions of circRNAs, tRNA, rRNAs, piRNAs, snoRNAs and snRNAs in ferroptosis. Furthermore, the network of factors modulating ferroptosis remains to be established. As ferroptosis is a process of dynamic equilibrium, any alteration of the associated factors may intersect with others. For example, GSH maintains the cytosolic labile iron pool via formation of iron-GSH complexes[176]. In addition, GSH regulates iron trafficking, and inhibition of GSH synthesis leads to diminished iron efflux following nitric oxide exposure[177]. Moreover, iron is exported via multidrug resistant protein 1 (MRP1), a known transporter of GSH conjugates[178]. GSH depletion, MRP1 inhibition or MRP1 knock-out leads to decreased iron release upon nitric oxide treatment[179]. Conversely, the secondary increase in ROS induced by iron stimulates GSH production, indicating that iron and GSH are interconnected[46]. Moreover, targets of NRF2 play a critical role in mediating iron/heme metabolism. Both FTL and FTH, the key iron storage protein, as well as FPN, which is responsible for cellular iron efflux, are controlled by NRF2[180,181]. In addition, a number of integral GSH synthesis and metabolism related enzymes including both the catalytic and modulatory subunits of GCLC, GCLM, GSS, and SLC7A11, are under the control of NRF2[182–184]. In total, regulation of ferroptosis are linked together, modulation of GSH, iron and NRF2 by ncRNAs may result in further change of each other, and finally alter ferroptosis process.

Clinical application potential of ncRNA-associated ferroptosis

Targeting ncRNAs in cancer has yielded some promising results, however, application of ferroptosis via an ncRNA-dependent manner in clinic is facing obstacles. Inadequate understanding of specific mechanisms results in the limited use of ncRNA modifiers in ferroptosis. Furthermore, cell death occurs in a variety of ways, and numerous ncRNAs may be simultaneously regulated, thus how to ensure that the alteration of associated ncRNAs leads to ferroptosis is another problem. Moreover, ncRNAs act in various ways that may intersect with ferroptosis. For example, ferroptosis inducer *miR-210* and *H19* could modulate autophagy via targeting BECN1, ATG7, SIRT1, and HIF-1α[185–188]. In addition, *miR-146a* could regulat ROS modulator catalase and SOD2 which repressed mitochondrial function[189,190]. Alteration of autophagy or mitochondrial function resulted in multiple pathologic changes such as neuroinflammation, neurodegeneration, vessel remodeling and myocardial fibrosis, thus how to overcome these possible complications should be considered[191–194]. In addition, some pathways such as the KEAP1-NRF2 axis, is inhibited by multiple miRNAs and lncRNAs and promotes ferroptosis. Nevertheless, the repression of KEAP1-NRF2 results in the defect in cleaning of ROS and leads to susceptibility to DNA damage and tumorigenesis[195,196]. To solve these problems, future studies should address the following points. First, more ncRNAs should be identified. A ferroptosis-associated ncRNA screening platform should be established to identify the spectrum of ferroptosis associated ncRNAs and those specific to certain cancers. Second, more intensive studies using complex molecular biological experiments, such as chromosome immunoprecipitation, RNA immunoprecipitation, RNA pull-down, luciferase assays, and RNA truncation should be performed to explore the precise roles of ncRNAs in ferroptosis. Third, in order to translate fundamental experimental results into clinic, functions of ncRNAs in ferroptosis should be tested in animal models. Transgenic mouse models should be established to verify the function of ncRNAs more clearly. Fourth, in order to ensure whether ferroptosis is modulated by ncRNAs, accurate detection of ROS and iron levels, and observation of mitochondrial morphology in tumor tissues are needed. Furthermore, primary culture of tumor cells from patients should be performed to explore whether the proliferation of cancer cells is enhanced by Fer-1, which is the specific inhibitor of ferroptosis. The involvement of ncRNAs in ferroptosis in cancer can be verified in knockdown or overexpression studies. Finally, since ferroptosis occurs in not only tumors but also normal tissues, and as above, ferroptosis regulation by ncRNAs may activate other biological processes and even increase the susceptibility to tumorigenesis. Thus, both ferroptosis-related ncRNAs and associated markers of cell death, senescence, and remodeling should be assessed in patients who are suitable for ferroptosis-associated therapy. In addition, adverse events, dose-limiting toxicities and therapeutic effects should be carefully monitored through rigorous detection of organ functions, imaging of vital organs and tumors, and hematological changes during the application of ferroptosis inducers in clinic. After all, as cancer is a developmental process, the collaboration between

multidisciplinary teams should be made to obtain rational therapy regimens to enhance therapeutic effect and alleviate complications.

Conclusions and perspectives

Cancer cells may be intrinsically insensitive or evolve and develop resistance to apoptosis, resulting in cancer progression[197]. Under the development of molecular biological technologies, identification of new targets or methods to eliminate cancer cells has attracted substantial attention. Ferroptosis is a recently recognized form of programmed cell death that relies on excess intracellular ROS and consequent lipid peroxidation[198]. Ferroptosis has been successfully applied to limit tumor growth and overcome the resistance of cancer cells to apoptosis, indicating that it may be useful as a new therapeutic approach[3]. Nevertheless, the application of ferroptosis inducers in cancer therapy is limited, mainly because the specific mechanisms underlying ferroptosis remain unexplored.

NcRNAs have been proved to regulate gene expression by various manners. Numerous ncRNAs have been found to regulate behaviors of cancer cells. In recent years, researchers have examined some ferroptosis-associated ncRNAs in cancer cells. Nevertheless, the specific regulatory mechanisms have not been explored. Therefore, wider and deeper studies to explore the function of ncRNAs in ferroptosis are needed. In this review, the landscape of ncRNAs associated with ferroptosis in cancer thus far is summarized. In addition, possible obstacles during application of ncRNA-associated ferroptosis in clinic are put forward and associated solutions are suggested. However, the information summarized in this review is not sufficient to support the application of ferroptosis inducers in cancer, more ncRNAs should be identified and deeper researches should be performed. In conclusion, ncRNAs may become markers to filter cancer patients who are fit for ferroptosis therapy and become therapeutic targets of ferroptosis inducers.

Acknowledgements

The authors thank the personnel at Harbin Medical University Cancer Hospital for their generous help. This study was financially supported by the National Natural Science Foundation of China (grant numbers LH2019H099), Youth Project of Haiyan Foundation of Harbin Medical University Cancer Hospital (grant numbers JJQN2018-15).

Conflict of interest

The authors declare that they have no conflict of interest.

Supplementary Information accompanies this paper at (https://doi.org/10.1038/s41419-020-02772-8).

Received: 6 March 2020 Revised: 6 July 2020 Accepted: 10 July 2020
Published online: 24 July 2020

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