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 role 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 therapy¹. Although multiple therapeutic manners including operation, targeted therapy, chemotherapy, and radiotherapy have shown satisfactory performance, progression occurs since cancer cells...
dysregulate apoptosis pathways via various manners. 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. Unlike apoptosis, ferroptosis is characterized by excess reactive oxygen species (ROS) and intracellular iron. Superabundant ROS induces peroxidation and disintegration of lipid membrane and cell death. Regulation of ferroptosis mainly depends on neutral reaction between reduced glutathione (GSH) and ROS. 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. Glutathione peroxidase 4 (GPX4) catalyzes interaction between GSH and ROS to reduce intracellular oxidative stress. 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. Class II ferroptosis inducers such as RSL3, FINS6, and ML162, inhibit function of GPX4. Numerous studies have confirmed that ferroptosis inducers such as RSL3 and sorafenib eliminates cancer cells. In addition, induction of ferroptosis via erastin and sulfasalazine improved effect of cytarabine and doxorubicin, and overcame cisplatin resistance of head and neck cancer. 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. In addition, in acute kidney injury, ferroptosis participated in the death of renal tubular epithelial cells. 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. 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). NcRNAs participate in regulation of tumorigenesis via various biological processes such as chromatin modification, alternative splicing, competition with endogenous RNAs and interaction with proteins.

For example, miR-675-5p promoted the metastasis of colorectal cancer cells via modulation of P53. Moreover, lncRNA HOTAIR served as an enhancer in epithelial-to-mesenchymal transition of breast cancer cells via competing with BRCA1. In addition, circFOXO3 enhanced progression of prostate cancer through sponging miR-29a-3p. 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. 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 miRNAs and suppressing their expression. Some studies have revealed a relationship between microRNAs and ferroptosis. In radio-resistant cells, miR-7-5p inhibited ferroptosis via downregulating mitoferrin and thus reducing iron levels. 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−. Moreover, miR-6852 which was regulated by lncRNA Linc00336, inhibited growth of lung cancer cells via promoting ferroptosis. In the following sections, we will discuss the interactions between miRNAs and GSH, iron and NRF2 in cancer cells. The information of altered microRNAs in ferroptosis has been listed (Supplementary Table 1).

MiRNAs and GSH

GSH is a scavenger of ROS and protects lipid membrane. 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. Biosynthesis of GSH involves three steps: exchange of glutamic acid and cystine induced by systemXc−; synthesis of γ-glutamylcysteine by glutamic acid and cysteine catalyzed via γ-glutamylcysteine ligase (GCL); and synthesis of GSH via γ-glutamylcysteine and glycine catalyzed by GSH synthetase. Function of GSH includes detoxification of exogenous or endogenous dangerous compounds catalyzed by GSH-S-transferases (GSTs) and GPXs. 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-
| 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      | 36         |
| 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      | 31         |
| miR-302c-5p| Colorectal cancer                                                                       | GST         | Up               | Cell culture                     | 51         |
| 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      | 31         |
| 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      | 32,33,34    |
| 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         |
decreased GSH levels via targeting GCL in hepatocellular carcinoma and bladder cancer\textsuperscript{37,38}. Furthermore, in hepatocellular carcinoma and lung cancer, \textit{miR-152} and \textit{miR-155} decreased GSH levels via targeting GST\textsuperscript{39,40}. In addition, \textit{miR-326} and \textit{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)\textsuperscript{41–43}. Additionally, downregulation of GSH by miRNAs such as \textit{miR-21}, \textit{miR-24-2}, \textit{miR-497} and \textit{miR-503} has been observed in different cancer types, however, the specific mechanisms were not explored\textsuperscript{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 \textit{miR-124}, \textit{let-7a-5p}, \textit{miR-92b-3p}, \textit{miR-129-5P}, \textit{miR-144}, \textit{miR-153-1/2}, \textit{miR-302c-5p}, \textit{miR-3664-5p}, \textit{miR-3714}, \textit{miR-513a-5p}, \textit{miR-590-3p/5p}, \textit{miR-130b}, \textit{miR-186}, and \textit{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\textsuperscript{48–51}. It is worth mentioning that \textit{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 \textit{miR-133a/b} reversed both increased GSH and insensitivity to drugs\textsuperscript{51–54}. Furthermore, GPX family members are targeted by miRNAs and results in defect of ROS neutralization. In one report, GPX4 was decreased by \textit{miR-181a-5p} in osteoarthritis\textsuperscript{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 \textit{miR-17}, \textit{miR-17-3p}, \textit{miR-196a}, and \textit{miR-921} in colorectal cancer, prostate cancer, and lung cancer\textsuperscript{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\textsuperscript{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)\textsuperscript{61,62}. The specific reaction between miRNAs and iron is summarized in Table 2, and the schematic diagram of these interactions are shown in Fig. 1b. In colorectal cancer...
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\(^{65}\). 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-210-5p, 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

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**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.
| 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                | Cell culture, animal models | 63        |
| miR-449-5p | 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                                            | PWC                     | Down              | Cell culture, animal models | 70        |
| miR-19b-1-5p| Prostate cancer                                       | PWC, FPN                | Down              | Cell culture, animal models | 70        |
| miR-19b-3p | Prostate cancer                                            | PWC                     | Down              | Cell culture, animal models | 70        |
| miR-210-3p | Prostate cancer                                            | PWC                     | Down              | Cell culture, animal models | 70        |
| miR-362-5p | Prostate cancer                                            | PWC                     | Down              | Cell culture, animal models | 70        |
| miR-616-3p | Prostate cancer                                            | PWC                     | Down              | Cell culture, animal models | 70        |
| miR-638    | Prostate cancer                                            | PWC                     | 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                                                | PWC                     | Down              | Cell culture      | 213       |
| miR-210    | Renal cancer, head and neck parangliomas, 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                          | Miroferrin              | Down              | Cell culture      | 30        |
| miR-122    | Hepatocellular cancer                                      | Nocturnin               | Down              | Cell culture, animal models | 213       |
| miR-23a    | 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              | Cell culture, animal models | 63        |
| miR-200a   | Hepatocellular carcinoma                                  | TFR1                    | Down              | Cell culture      | 65        |
| miR-22     | Hepatocellular carcinoma                                  | TFR1                    | Down              | Cell culture      | 65        |
| miR-31     | Colorectal cancer                                          | TFR1                    | Down              | Clinical samples  | 63        |
| miR-120    | Hepatocellular carcinoma                                  | 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-23d    | 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, and miR-146a, miR-150, miR-214-3p and miR-584 were increased by iron in ovarian cancer and neuroblasta. 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. Inhibition of NRF2 has been confirmed to enhance ferroptosis. 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. 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, and increased the sensitivity of lung cancer cells to cisplatin, 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. Moreover, miRNAs regulate NRF2 via targeting KEAP1. In hepatocellular carcinoma, ovarian cancer, leukemia, and neuroblastosoma, KEAP1 was targeted by miR-141, miR-23a, miR-432, miR-7, and miR-200a. 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. 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. 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. 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-dependent manner, 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. Conversely, miR-181c, miR-378, miR-122, miR-17-5p, miR-1, and miR-206 were repressed by NRF2 in various cancer types. Hereinto, 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 miRNAs. 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. Mechanically, miR-21 targeted STAT3, proline oxidase (POX), and programmed cell death 4 (PDCD4) to induce oxidative stress. 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. In lung cancer, suppression of miR-146a restored catalase and inhibited ROS induction, and protected cancer cells from cisplatin-induced cytotoxicity. In addition, overexpression of miR-124, miR-526b, and miR-655 led to excess ROS via thioredoxin reductase 1 in breast cancer. Furthermore, the antioxidant enzyme SOD1 was downregulated by stable expression of miR-143 or miR-145 in colorectal cancer. 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. 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. 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, 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. Moreover, miR-125, miR-145-5p, miR-17-5p, miR-199, and miR-17-92, were decreased by excess intracellular ROS. 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
| 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 | 86,105,218        |
| 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      | 86,87,200,231     |
| 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      | 223               |
| miR-28  | Breast cancer, esophageal cancer                                                        | NRF2         | Down              | Cell culture, animal models | 81,224            |
| miR-340 | Hepatocellular carcinoma, esophageal cancer                                             | NRF2         | Down              | Cell culture      | 85,86,92          |
| 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 | 80,83,84          |
methylation in ovarian cancer. 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. 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, 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. Linc00336 was promoted by lymphoid-specific helicase in lung cancer and inhibited ferroptosis via sponging miR-6852. 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 down-regulation of SLC7A11. In addition, ferroptosis inducer erastin upregulated lncRNA 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. 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. 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. Similarly, in colorectal cancer, knockdown of lncRNA Xist inhibited doxorubicin resistance via suppressing GST and increasing GSH. In addition, in hepatocellular carcinoma cells, silencing lncRNA Neat1 inhibited IL-6-induced STAT3 phosphorylation which contributed to the increase of GST. 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. Moreover, knockdown of lncRNA H19 resulted in recovery of cisplatin sensitivity via reduction of GCL and GST. In total, regulation of GSH by lncRNAs mainly depends on GST and GCL. Moreover, in hepatocellular carcinoma, silencing of lncRNA Pvit1 inhibited...
| 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      | 252       |
| 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 | 237 |
| 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      | 233       |
| miR-25-5p  | Colorectal cancer                             | SQX10                               | Up               | Cell culture      | 243       |
| miR-26a-5p | Acute myeloid leukemia                         | PrxIII                              | Up               | Cell culture      | 244       |
| 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      | 247       |
| miR-34c    | Non-small 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  | 236       |
| miR-128    | Glioma, hepatocellular carcinoma              | PRK2                                | Up/Down           | Cell culture      | 237       |
| 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, TGF-β                                                        | Up/Down          | Cell culture      | 259,260   |
| miR-222    | Hepatocellular carcinoma, breast cancer                                                | NF-κ8, TGF-β                                                         | Up/Down          | Cell culture      | 251,262   |
| miR-23a/b  | Myeloma, renal cancer                                                                  | C-MYC, POX                                                           | Up/Down          | Cell culture      | 263,264   |
| miR-29     | Ovarian cancer, lung cancer, and lymphoma                                              | C-MYC, SIRT1                                                        | Up/Down          | Cell culture      | 265,266   |
| Let-7      | Hepatocellular carcinoma, prostate cancer, and pancreatic cancer                       | Heme oxygenase-1, P53                                               | Up/Down          | Cell culture      | 267       |
| miR-33a    | Glioma, hepatocellular carcinoma                                                       | SIRT6                                                                | Up/Down          | Cell culture      | 269       |
| miR-221    | Hepatocellular carcinoma, breast cancer                                                | NF-κ8, TGF-β, and DICER                                             | Up/Down/Induced by ROS | Cell culture, animal models | 261,26,270 |
| miR-21     | Lung cancer, colorectal cancer, gastric cancer, hepatocellular carcinoma, ovarian cancer, and prostate cancer | SOD, MAPK, SOD2, Glucose, NFκ8, STAT3, POX, and PDCD4 | Up/Down/Induced by ROS | Cell culture, animal models | 108,11,21,14,271 |
| miR-17-92  | Gastrointestinal cancer, uterine leiomyoma                                            | C-MYC, P53, and NFκ8                                               | Up/Down/Inhibited by ROS | Cell culture | 17,27,27,278 |
| miR-181    | Hepatocellular carcinoma, uterine leiomyoma                                            | Unknown                                                              | Up/Down          | Cell culture      | 182       |
| miR-200    | Breast cancer, cancer stem cells, hepatocellular carcinoma, and lung cancer            | P53, PRDX2, GAPB/NRF2, SESN1                                        | Up/Down          | Cell culture      | 222,275-277 |
| miR-34     | Cancer stem cells, bladder cancer, lung cancer                                         | C-MYC, P53                                                          | Up/Down          | Cell culture      | 278,279   |
| miR-182    | Uterine leiomyoma, lung cancer                                                         | PDK4                                                                 | Up/Down          | Cell culture      | 283       |
| miR-199    | Gastrointestinal cancer, ovarian cancer                                                | DNMT1                                                                | Up/Inhibited by ROS | Cell culture | 282       |
| miR-20a    | Breast cancer, pancreatic cancer                                                       | BECN1, ATG16L1, and SQSTM1                                          | Up/Inhibited by ROS | Cell culture, animal models | 284       |
| miR-125b   | Hepatocellular carcinoma, ovarian cancer, and breast cancer                            | Hexokinase 2, DNMT1, and HAX-1                                       | Up/Inhibited by ROS | Cell culture, animal models | 285       |
| miR-1246   | Breast cancer                                                                          | NF-κ8, TGF-β                                                        | Down             | Cell culture      | 286       |
| miR-137    | Ovarian cancer                                                                         | C-MYC                                                                | Down             | Cell culture      | 287       |
| miR-193b   | Liposarcoma                                                                            | Antioxidant methionine sulfide reductase A                           | Down             | Cell culture      | 288       |
| miR-199a-3p| Testicular cancer                                                                      | Transcription factor specificity protein 1                           | Down             | Cell culture      | 289       |
| miR-26a    | Hepatocellular carcinoma                                                                | Triglyceride, total cholesterol, malondialdehyde                     | Down             | Cell culture      | 290       |
| miR-30c-2-3p| Breast cancer                                                                          | NF-κ8, TGF-β                                                        | Down             | Cell culture      | 291       |
| miR-346    | Ovarian cancer                                                                         | GSK3B                                                                | Down             | Cell culture      | 292       |
| miR-373    | Breast cancer                                                                          | NF-κ8, TGF-β                                                        | Down             | Cell culture      | 293       |
| miR-520    | Breast cancer                                                                          | NF-κ8, TGF-β                                                        | Down             | Cell culture      | 294       |
| miR-7      | Non-small cell lung cancer                                                              | MAFG                                                                  | Down             | Cell culture      | 295       |
| miR-885-5p | Hepatocellular carcinoma                                                                | TigAR                                                                 | Down             | Cell culture      | 296       |
| miR-99a    | Lung cancer                                                                            | NOX4                                                                  | Down             | Cell culture      | 297       |
| miR-133a   | Rhabdomyosarcoma                                                                       | 9                                                                     | Induced by ROS   | Cell culture      | 298       |
| miR-150-3p | Hepatocellular carcinoma                                                                | –                                                                    | Induced by ROS   | Cell culture      | 299       |
| miR-1915-3p| Hepatocellular Carcinoma                                                                | –                                                                    | Induced by ROS   | Cell culture      | 300       |
| miR-206    | Rhabdomyosarcoma                                                                       | –                                                                    | Induced by ROS   | Cell culture      | 301       |
| miR-34a-3p | Hepatocellular carcinoma                                                                | –                                                                    | Induced by ROS   | Cell culture      | 302       |
| miR-638    | Hepatocellular carcinoma                                                                | –                                                                    | Induced by ROS   | Cell culture      | 303       |
| miR-125    | Gastric cancer                                                                         | –                                                                    | Inhibited by ROS | Cell culture      | 304       |
TFR expression and obstructed iron uptake via miR-150 

Furthermore, silencing of FHC in leukemia cells induced production of ROS and altered downstream genes via increasing H19 and miR-657 expression. 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. 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. 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. 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.

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. 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. Furthermore, in hepatocellular carcinoma, downregulation of H19 increased ROS via MAPK/ERK signaling pathway and reversed chemotherapy resistance. 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. 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. 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. However, studies on the relations between these ncRNAs and ferroptosis are few. The interactions have
| 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 |
|               | Rar | 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 | PS3 | 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. 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. 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. 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 down-regulation of circ-PVT1 in paclitaxel-resistant gastric cancer cells. Moreover, high-throughput 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. 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. Second, tRNAs have multiple interaction partners including aminoacyl-tRNA-synthetases, mRNAs, ribosomes and translation factors. 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. 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. 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. Additionally, Queuine-modified tRNAs promoted cellular antioxidant defense via catalase, SOD, GPX, and GSH reductase and inhibited lymphoma. 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. 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. In another study, hepatoma cells treated with ethidium bromide exhibited a 70% decrease in the 16S/18S rRNA ratio and enhanced NRF2 expression. 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. Furthermore, in leukemia HL-60 cells treated with iron chelator deferoxamine, rRNA synthesis in nucleoli was inhibited. 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. PiRNAs are involved in tumorigenesis of variety cancers. 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. 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\(^\text{174}\). There are currently no reports on ferroptosis and snoRNAs 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\(^\text{175}\). Future studies should focus on the possible regulation of snoRNAs 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\(^\text{176}\). In addition, GSH regulates iron trafficking, and inhibition of GSH synthesis leads to diminished iron efflux following nitric oxide exposure\(^\text{177}\). Moreover, iron is exported via multidrug resistant protein 1 (MRP1), a known transporter of GSH conjugates \(^\text{178}\). GSH depletion, MRP1 inhibition or MRP1 knock-out leads to decreased iron release upon nitric oxide treatment\(^\text{179}\). Conversely, the secondary increase in ROS induced by iron stimulates GSH production, indicating that iron and GSH are interconnected\(^\text{180}\). 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\(^\text{180,181}\). 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\(^\text{182–184}\). In total, regulation of ferroptosis is 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\(^\text{185–188}\). In addition, miR-146a could regulate ROS modulator catalase and SOD2 which repressed mitochondrial function\(^\text{189,190}\). 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\(^\text{191–194}\). In addition, some pathways such as the KEAP1-NRF2 axis, is inhibited by multiple miRNAs and IncRNAs 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\(^\text{195,196}\). 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. 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. 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. 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.

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Conflict of interest
The authors declare that they have no conflict of interest.

References
1. Su, Y. L. et al. Myeloid cell-targeted miR-146a mimic inhibits NF-kB-driven inflammation and leukemia progression in vivo. Blood https://doi.org/10.1182/blood.2019002045 (2019).
2. Kim, J. et al. Structure and drug resistance of the Plasmodium falciparum transporter PCRT. Nature https://doi.org/10.1038/s41586-019-1795-x (2019).
3. Ros-Lucì, C. et al. Adaptive resistance to trastuzumab impairs response to neratinib and lapatinib through deregulation of cell death mechanisms. Cancer Lett. https://doi.org/10.1016/j.canlet.2019.11.026 (2019).
4. Dixon, S. J. et al. Ferroptosis: an iron-dependent form of nonapoptotic cell death. Cell 149, 1060–1072 (2012).
5. Gagliardi, M. et al. Alko-keto reductases protect metastatic melanoma from ER-stress-independent ferroptosis. Cell Death Dis. 10, 902 (2019).
6. Bibli, S. I. et al. Shear stress regulates cystathionine gamma lyase expression to preserve endothelial redox balance and reduce membrane lipid peroxidation. Redox Biol. 28, 101379 (2019).
7. Wei, S. et al. Antisense induces pancreatic dysfunction and ferroptosis via mitochondrial ROS-antioxidase-horizontal pathway. J. Hazard. Mater. https://doi.org/10.1016/j.jhazmat.2019.121390 (2019).
8. Koppula, P., Zhang, Y., Zhuang, L. & Gan, B. Amino acid transporter SLC7A11/xCT at the crossroads of regulating redox homeostasis and nutrient dependency of cancer. Cancer Commun. 38, 12 (2018).
9. Lang, X. et al. Radiotherapy and immunotherapy promote tumoral lipid oxidation and ferroptosis via synergistic repression of SLC7A11. Cancer Discov. https://doi.org/10.1158/2326-7278.CD-19-0338 (2019).
10. Muri, J., Thut, H., Bornkamm, G. W. & Kopf, M. B1 and marginal zone B cells but not follicular B2 cells Require Gpx4 to prevent lipid peroxidation and ferroptosis. Cell Rep. 29, 2731–2744 e2734 (2019).
11. Xie, Y. et al. Ferroptosis process and function. Cell Death Differ. 23, 369–379 (2016).
12. Dujl, S. et al. FSP1 is a glutathione-independent ferroptosis suppressor. Nature 575, 693–698 (2019).
13. Kajarabille, N. & Latunde-Dada, G. O. Programmed cell-death by ferroptosis: antioxidants as mitigators. Int. J. Mol. Sci. https://doi.org/10.3390/ijms20194968 (2018).
14. Hassaniia, B., Vandenabeele, P. & Vanden Berghe, T. Targeting ferroptosis to iron out cancer. Cancer Cell 35, 830–849 (2019).
15. Sui, X. et al. RSL3 drives ferroptosis through GPX4 inactivation and ROS production in colorectal cancer. Front. Pharmacol. 9, 1371 (2018).
16. Tang, H. et al. Dual GSH-exhausting sorafenib loaded manganese-silica nanodrugs for inducing the ferroptosis of hepatocellular carcinoma cells. Int. J. Pharm. 572, 118782 (2019).
17. Yu, Y. et al. The ferroptosis inducer erastin enhances sensitivity of acute myeloid leukemia cells to chemotherapy agents. Mol. Cell. Oncol. 2, e1054549 (2015).
18. Roh, J. L., Kim, E. H., Jang, H. J., Park, J. Y. & Shin, D. Induction of ferroptotic cell death for overcoming cisplatin resistance of head and neck cancer. Cancer Lett. 381, 96–103 (2016).
19. Moreau, C. et al. Iron as a therapeutic target for Parkinson’s disease. Mov. Disord. 33, 568–574 (2018).
20. Su, L. et al. Pannexin 1 mediates ferroptosis that contributes to renal ischaemia/reperfusion injury. J. Biol. Chem. https://doi.org/10.1074/jbc.RA119.010949 (2019).
21. Di Bella, S. et al. A benchmarking of pipelines for detecting ncRNAs from RNA-Seq data. Brief. Bioinform. https://doi.org/10.1093/bib/bbz110 (2019).
22. Alizahri, R. et al. Improving the therapeutic efficiency of noncoding RNAs in cancers using targeted drug delivery systems. Drug Discov. Today https://doi.org/10.1016/j.drudis.2019.11.006 (2019).
23. Wang, J. et al. ncRNA-encoded peptides or proteins and cancer. Mol. Ther. 27, 1718–1725 (2019).
24. Justic, A., Devalos, Y. & Action, E. U.-C. C. Noncoding RNAs in Hypertension. Hypertension 74, 477–482 (2019).
25. Yao, R. W., Wang, Y. & Chen, L. L. Cellular functions of long noncoding RNAs. Nat. Cell Biol. 21, 542–551 (2019).
26. Costa, V. et al. MiR-675-5p supports hypoxia induced epithelial to mesenchymal transition in colon cancer cells. Oncotarget 8, 24292–24302 (2017).
27. Pawlowska, E., Szczepanska, J. & Blasko, J. The long noncoding RNA HOTAIR in breast cancer: does autophagy play a role? J. Int. Med. Sci. https://doi.org/10.3390/jms18112317 (2017).

28. Kong, Z. et al. Circular RNA circFOXO3 promotes prostate cancer progression through sponging miR-29a-3p. J. Cell. Med. https://doi.org/10.1111/jcm.14791 (2019).

29. Majdinia, M., Karimian, A., Alemi, F., Yousefi, B. & Safa, A. Targeting miRNAs by polyphenols: novel therapeutic strategy for aging. Biochem. Pharmacol. https://doi.org/10.1016/j.bcp.2019.113688 (2019).

30. Tomita, K. et al. MiR-7-5p is a key factor that controls radiosensitivity via intracellular Fe2+ content in clinically relevant radioresistant cancer cells. Biophys. Res. Commun. 518, 712–718 (2019).

31. Zhang, K. et al. miR-9 regulates ferroptosis by targeting glutamic-oxyacetic transaminase GOT1 in melanoma. Mol. Carcinogr. 57, 1566–1576 (2018).

32. Wang, M. et al. Long noncoding RNA LINCO0336 inhibits ferroptosis in lung cancer by functioning as a competing endogenous RNA. Cell Death Differ. 26, 2359–2363 (2019).

33. Hsu, J. L. et al. Glutathione peroxidase 8 negatively regulates caspase-4/11 to protect against cancer. J. Exp. Med. https://doi.org/10.15252/emmo.201908386 (2019).

34. Koeberle, S. C. et al. Distinct and overlapping functions of glutathione peroxidases 1 and 2 in limiting NF-kappaB-driven inflammation through redox-active mechanisms. Redox Biol. 28, 101388 (2019).

35. Desideri, E., Ciccarone, F. & Ciriolo, M. R. Targeting glutathione metabolism: partner in crime in anticancer therapy. Nutrients https://doi.org/10.3390/nu11081026 (2019).

36. Nunes, S. C. & Serpa, J. Glutathione in ovarian cancer-a double-edged sword. Int. J. Mol. Sci. https://doi.org/10.3390/ijms19072882 (2018).

37. Anderton, B. et al. MYC-driven inhibition of the glutamate-cysteine ligase cationic reciprocal microRNA-mRNA pairs asso- ciated with iron overload: therapeutic targets unravelled. J. Cell. Physiol. 236, 267 (2018).

38. Kong, Z. et al. Circular RNA circFOXO3 promotes prostate cancer progression through sponging miR-29a-3p. J. Cell. Med. https://doi.org/10.1111/jcm.14791 (2019).

39. Lu, P. et al. MicroRNA-218 increases the sensitivity of bladder cancer to cisplatin by targeting Glut1. Cell. Physiol. Biochem. 41, 921–932 (2017).

40. Huang, J., Wang, Y., Guo, Y. & Sun, S. Down-regulated microRNA-152 induces aberrant DNA methylation in hepatitis B virus-related hepatocellular carcinoma by targeting DNA methyltransferase 1. Hepatol. Pathol. 52, 60–70 (2010).

41. Lu, L., An, K., Li, H. & Ma, L. Effect of miR-155 knockdown on the reversal of doxorubicin resistance in human lung cancer A549/dox cells. Oncol. Lett. 11, 1161–1166 (2016).

42. Kefas, B. et al. Pyruvate kinase M2 is a target of the tumor-suppressive microRNA-133a in breast cancer. J. Exp. Clin. Cancer Res. 38, 406 (2019).

43. Harama, K. et al. Altered expression of miRNA-133 promotes prostate cancer stem cell self-renewal and stemness in non-small-cell lung cancer through upregulating GPX3 expression. Int. J. Biochem. Cell Biol. 115, 105571 (2019).

44. Dong, Z. et al. Effect of microRNA-21 on multidrug resistance reversal in colorectal cancer cells, increasing ABCC1 level accompanies decreasing level of miR-302c-5p, miR-3664-5p and miR-129-5p. Biomed. Pharmacother. 108, 1070–1080 (2018).

45. Singh, S., Shulka, G. C. & Gupta, S. MicroRNA regulating glutathione S-transferase P1 in prostate cancer. Curr. Pharmacol. Rep. 1, 79–88 (2015).
80. Yamamoto, S. et al. The impact of miRNA-based molecular diagnostics and treatment of NRf2-stabilized tumors. Mol. Cancer Res. 12, 58–68 (2014).

81. Tian, Y. et al. Emerging roles of NRf2 signal in non-small cell lung cancer. J. Hematol. Oncol. 9, 14 (2016).

82. Wang, B., Teng, Y. & Lu, Q. MicroRNA-153 regulates NRf2 expression and is associated with breast carcinogenesis. Oncol. Lett. 62, 39–47 (2016).

83. Qaiyia, M., Coda Zabetta, C. D., Bellarosa, C. & Tribelli, C. Bilirubin mediated oxidative stress involves antioxidant response activation via NRf2 pathway. Cell. Signal. 26, 512–520 (2014).

84. Narasimhan, M. et al. Identification of novel microRNAs in post-transcriptional control of NRf2 expression and redox homeostasis in neuronal, SH-SY5Y cells. PLoS ONE 7, e51111 (2012).

85. Shi, L. et al. miR-340 reverses cisplatin resistance of hepatocellular carcinoma cell lines by targeting NRf2-dependent antioxidant pathway. Asian Pac. J. Cancer Prev. 15, 10439–10444 (2014).

86. Hämäläinen, M. et al. NRf1 and NRf2 mRNA and protein expression decrease early during melanoma carcinogenesis: an insight into survival and MicroRNAs. Cytokine. Cell. Therapeut. 2019, 2647068 (2019).

87. Yin, Y. et al. miR-144 regulates the resistance of lung cancer to cisplatin by targeting NRf2. Oncol. Rep. 40, 3479–3488 (2018).

88. Raghunath, A., Sundarraj, K., Arfuso, F., Sethi, G. & Perumal, E. Dysregulation of NRf2 in hepatocellular carcinoma: role in cancer progression and chemoresistance. Cancers. https://doi.org/10.3390/cancers10120481 (2018).

89. Zhou, S. et al. MicroRNA-144 modulates oxidative stress tolerance in SH-SY5Y cells by regulating nuclear factor erythroid 2-related factor 2-glutathione axis. Neurosci. Lett. 655, 21–27 (2017).

90. Zhou, S. et al. miR-144 reverses chemoresistance of hepatocellular carcinoma cell lines by targeting NRf2-dependent antioxidant pathway. Am. J. Transl. Res. 8, 3992–3002 (2016).

91. Wul, L. et al. IncRNA KRAL reverses S-fluorouracil resistance in hepatocellular carcinoma cells by acting as a ceRNA against miR-141. Cell. Commun. Signal. 16, 47 (2018).

92. Fabbrizio, F. P., Spanelo, A., Trombetta, D. & Muscarella, L. A. Epigenetic versus genetic deregulation of the KEAP1/NRF2 axis in solid tumors: focus on methylation and noncoding RNAs. Cytokine. Cell. Therapeut. 2018, 2492063 (2018).

93. Shi, L. et al. MR-141 activates NRf2-dependent antioxidant pathway via down-regulating the expression of Keap1 conferring the resistance of hepatocellular carcinoma cells to 5-fluorouracil. Cell. Physiol. Biochem. 35, 2333–2348 (2015).

94. Khan, A. U. H. et al. Human leukemic cells performing oxidative phosphorylation (OXPHOS) generate an antioxidant response independently of reactive oxygen species (ROS) production. BioloMedicine 3, 43–53 (2016).

95. Akedir, B., Nakajima, I., Inazawa, J. & Inoue, J. miR-342 induces NRf2 stabilization by directly targeting KEAP1. Mol. Cancer Res. 15, 1570–1578 (2017).

96. Liu, M. et al. Methyl-ethylenic acid activates Keap1/Nrf2 pathway via up-regulating miR-200a in human oesophageal squamous cell carcinoma cells. Biosci. Rep. https://doi.org/10.1042/BSR20150099 (2015).

97. Sun, J. et al. miR-137 mediates the functional link between c-Myc and EZH2 mechanism. J. Biol. Chem. 289, 5654–5663 (2014).

98. Shin, B. et al. miR-200a in human oesophageal squamous cell carcinoma cells. Biosci. Rep. https://doi.org/10.1042/BSR20150099 (2015).

99. Hao, C. et al. MicroRNA-124 regulate the radiosensitivity of non-small cell lung cancer cells. PLoS ONE 4, e3479 (2008).

100. Chen, Y. F. et al. miR-125b suppresses oral oncogenicity by targeting the antioxidant gene PRKLR.2A. Res. Biol. 22, 1011–1140 (2019).

101. Sun, W. et al. miR-21-129-3p/mTOR axis controls an miRNA regulatory network involved in HDAC-inhibited autophagy. Mol. Ther. 27, 1039–1050 (2019).

102. Gai, Z. et al. NRF2-regulated miR-380-3p blocks the translation of Sp1 protein and its mediation of paraperttin-induced toxicity in mouse neuroblastoma N2a cells. Toxicol. Sci. https://doi.org/10.1093/toxsci/kfz162 (2019).

103. Jung, K. A., Lee, S. & Kwak, M. K. NFE2L2/NRF2 activity is linked to mitochondrial and AMP-activated protein kinase signaling in cancers through miR-181c/Mitochondria-encoded cytochrome c oxidase regulation. Antioxid. Redox Signal. 27, 945–961 (2017).

104. Kallikogliou, I. et al. MicroRNA-520-3P regulates lung cancer cell growth by targeting the miR-20a/144-3p pathway. Cancers. https://doi.org/10.3390/cancers11101407 (2019).

105. Martinez, T. et al. The orally active pterocarpanquinone LQB-118 exhibits cytotoxicity in prostate cancer cell and tumor models through cellular redox status. Prostate 78, 140–151 (2018).

106. Shin, B. et al. miR526b and miR655 induce oxidative stress in breast cancer. Oncotarget 8, 53 (2016).

107. Su, Y. et al. Silencing miR-21 induces polarization of astrocytes to the A2 phenotype and improves the formation of synapses by targeting gliadin 6 via the signal transducer and activator of transcription-5 pathway after acute ischemic spinal cord injury. FASEB J. 33, 10859–10871 (2019).

108. Adam, O. et al. Role of miR-21 in the pathogenesis of atrial fibrillation. Basic Res. Cardioiol. 107, 278 (2012).

109. Galupipi, F. et al. Programmed cell death 4 (PDCD4) as a novel prognostic marker for papillary thyroid carcinoma. Cancer Manage. Res. 11, 7845–7855 (2019).

110. Cui, Y., Shen, K., Tian, D., Zhang, P. & Xin, X. miR-146a induces proliferation and enhances chemosensitivity in epithelial ovarian cancer via reduction of SOD2. Cancer Res. 43, 275–282 (2016).

111. Wang, Q. et al. Receptor-interacting protein 1 increases chemoresistance by maintaining inhibitor of apoptosis protein levels and reducing reactive oxygen species through a microRNA-146a-mediated catalase pathway. J. Biol. Chem. 289, 5654–5663 (2014).

112. Ning, J. et al. miR-200a-3p and miR555 induce oxidative stress in breast cancer. Int. J. Mol. Sci. https://doi.org/10.3390/ijms20164309 (2019).

113. Gomes, S. E. et al. Convergence of miR-143 overexpression, oxidative stress and cell death in HCC116 human colon cancer cells. PLoS ONE 13, e0196107 (2018).

114. Sun, M. et al. miR-99a regulates ROS-mediated invasion and migration of lung adenocarcinoma cells by targeting NOX4. Oncol. Rep. 35, 2755–2766 (2016).

115. Keelkrogliou, I. et al. MicroRNA-520-3P/73 family functions as a tumor suppressor in estrogen receptor negative breast cancer by targeting NF-kappaB and TGF-beta signaling pathways. Oncogene 31, 4150–4163 (2012).

116. Bott, A. et al. miR-1246 induces pro-inflammatory responses in mesenchymal stem/stromal cells by regulating PKA and PP2A. Oncotarget 8, 43897–43914 (2017).

117. Sun, J. et al. miR-137 mediates the functional link between c-Myc and EZH2 that regulates cisplatin resistance in ovarian cancer. Oncogene 38, 564–580 (2019).

118. Zhou, S. et al. miR199a-3p/Spi1/LDAH axis controls glycolytic metabolism in testicular tumor cells. Int. J. Mol. Med. 42, 2163–2174 (2018).

119. Maiso, Y. Z. et al. miR-193b-regulated signaling networks serve as tumor suppressors in liposarcoma and promote adipogenesis in adipose-derived stem cells. Cancer Res. 77, 5728–5740 (2017).

120. Aki, O., Darwish, H. A., Bidebi, K. M. & Abdel Azim, S. A. miR-26a potentially contributes to the regulation of fatty acid and sterol metabolism in vitro human HepG2 cell model of nonalcoholic fatty liver disease. Oxid. Med. Cell. Longev. 2018, 851343 (2018).
Beccafico, S. et al. Antisense induces ROS- and p38 MAPK-mediated apoptosis and counteracts tumor growth in vivo in embryonal rhabdomyosarcoma cells. *Carcinogenesis* **36**, 1071–1083 (2015).

Wan, Y. et al. Identification of four oxidative stress-responsive microRNAs, miR-34a-5p, miR-191-3p, miR-368, and miR-150-3p, in hepatocellular carcinoma. *Oncol. Rep.* **37**, 5189–5193 (2017).

Cesia, M. et al. Heme oxygenase-1 controls an HDAC4-miR-206 pathway of oxidative stress in rhabdomyosarcoma. *Cancer Res.* **76**, 5707–5718 (2016).

Xu, X. et al. Oxidative stress-induced miRNAs modulate AKT signaling and promote cellular senescence in uterine leiomyoma. *J. Mol. Med.* **96**, 1095–1106 (2018).

Lin, J., Huang, Z., Han, J., Shao, J. & Huang, C. Redox regulation of microRNAs in cancer. *Cancer Lett.* **418**, 250–259 (2018).

He, J. et al. Reactive oxygen species regulate ERBB2 and ERBB3 expression via miR-199a-1/25B and DNA methylation. *EMBO Rep.* **13**, 1116–1122 (2012).

Donzelli, S. et al. Epigenetic silencing of miR-145-5p contributes to brain metastasis. *OncoTarget* **6**, 35183–35201 (2015).

Juturu, I. et al. Mechanism of action of phenethylisothiocyanate and other related species-inducing antitumor agents. *Mol. Cell. Biol.* **34**, 2382–2395 (2014).

Hong, L. et al. The miR-17-92 cluster of microRNAs confers tumorigenicity by inhibiting oncogene-induced senescence. *Cancer Res.* **70**, 8547–8557 (2010).

Chen, L. et al. LncRNA GAS5 regulates redox balance and dysregulates the NF-κB pathways. *J. Cell. Physiol.* https://doi.org/10.1002/jcp.29296 (2019).

Wu, X. et al. The NmrA-like family domain containing 1 pseudogene of four oxidative stress-responsive microRNAs, miR-34a-5p, miR-191-3p, miR-638, and miR-150-3p, in hepatocellular carcinoma. *Oncol. Rep.* **37**, 5189–5193 (2017).

Xu, J. et al. Paclitaxel promotes lung cancer cell apoptosis via MEG3-PS3 pathway activation. *Biochem. Biophys. Res. Commun.* **504**, 123–128 (2018).

Zhang, H. Y., Zhang, B. W., Zhang, Z. B. & Deng, Q. J. Circular RNA TTBK2 regulates cell proliferation, invasion and ferroptosis via miR-761/ITGB8 axis in glioma. *Eur. Rev. Med. Pharmacol. Sci.* **24**, 2585–2600 (2020).

Li, C., Tian, Y., Li, X. & Li, Q. Circ_008035 contributes to cell proliferation and inhibits apoptosis and ferroptosis in gastric cancer via miR-599/EF4A1 axis. *Cancer Cell Int.* **20**, 84 (2020).

Liu, Y. Y., Zhang, L. Y. & Du, W. Z. Circular RNA circ-PVT1 contributes to paclitaxel resistance of gastric cancer cells through the regulation of ZEB1 expression by sponging miR-124-3p. *Biosci. Rep.* https://doi.org/10.1042/BSR20190045 (2019).

Zhang, S. et al. Human papillomavirus 16 E7 oncoprotein alters the expression profiles of circular RNAs in Caki cells. *J. Cancer* **9**, 3755–3764 (2018).

Lorenz, C., Lunse, C. E. & Mör, M. RNA modifications: impact on structure and thermal adaptation. *Biomolecules* https://doi.org/10.3390/biom7020035 (2017).

Hiramoto, K. et al. Myeloid lineage-specific deletion of antioxidant system enhances tumor metastasis. *Cancer Res.* **73**, 835–844 (2014).

Pathak, C., Jaiswal, Y. K. & Vinyayk, M. Queueine promotes antioxidant defence system by activating cellular antioxidant enzyme activities in cancer. *Biosci. Rep.* **28**, 73–81 (2008).

Taniaka, M., Hart, S., Kupfer, P. A., Leumann, C. J. & Somatog, W. E. An assay for DNA oxidation induced albacis sites using the aldehyde reactive probe. *Free Radic. Res.* **45**, 237–247 (2011).

Li, W. et al. An internal ribosomal entry site mediates redox-sensitive translation of Nrf2. *Nucleic Acids Res.* **38**, 778–788 (2010).

Perez, M. J., Gonzalez-Sanchez, E., Gonzalez-Loyola, A., Gonzalez-Butrago, J. M. & Marin, J. J. Mitochondrial genome depletion dysregulates bile acid- and paracetamol-induced expression of the transporters Mdr1, Mtp1 and Mtp4 in liver cells. *Br. J. Pharmacol.* **162**, 1686–1699 (2011).

Jayaraman, S. et al. The nuclear mitotic apparatus protein NuMA controls ribosome biogenesis and thermal adaptation. *Biochem. Biophys. Res. Commun.* **502**, 49–56 (2018).

Watts, R. N. & Richardson, D. R. Nitrogen monoxide (NO) and glucose: unexpected links between energy metabolism and no-mediated iron mobilization from cells. *J. Biol. Chem.* **276**, 4742–4752 (2001).

Cole, S. P. & Deely, R. G. Transport of glutathione and glutathione conjugates by MRPs. *Trends Pharmacol. Sci.* **27**, 438–446 (2006).

Watts, R. N., Hawkins, C., Ponka, P. & Richardson, D. R. Nitrogen monoxide (NO)-mediated iron release from cells is linked to NO-induced glutathione

Official journal of the Cell Death Differentiation Association
efflux through multidrug resistance-associated protein 1. Proc Natl Acad Sci USA 103, 7670–7675 (2006).

180. Aygerman, A. S. et al. Transcriptomic and proteomic profiling of KEAP1 disrupted and sulfonamide-treated human breast epithelial cells reveals common expression profiles. Breast Cancer Res Treat 132, 175–187 (2012).

181. Harada, N. et al. Nrf2 regulates ferroportin 1-mediated iron efflux and counteracts lipopolysaccharide-induced ferroportin 1 mRNA suppression in macrophages. Arch Biochem Biophys. 508, 101–109 (2011).

182. Yang, H. et al. Nrf1 and Nrf2 regulate rat glutamate-cysteine ligase catalytic subunit transcription indirectly via NF-κappaB and AP-1. Mol Cell Biol. 25, 5933–5946 (2005).

183. Chan, J. Y. & Kwong, M. Impaired expression of glutathione synthetic enzymes in mice with targeted deletion of the Nrfl basic-leucine zipper protein. Biochem. et. Biophys. Acta. 1517, 19–36 (2000).

184. Ishii, T. et al. Transcription factorNrf2 coordinately regulates a group of oxidative stress-inducible genes in macrophages. J Biol. Chem. 275, 16023–16029 (2000).

185. Ju, S. et al. The effect and mechanism of miR-210 in down-regulating the autophagy of lung cancer cells. Pathol. Res. Pract. 215, 453–458 (2019).

186. Wang, Z., Deng, M., Liu, Z. & Wu, S. Hypoxia-induced miR-210 promoter demethylation enhances proliferation, autophagy and angiogenesis of schwannoma cells. Oncol Rep. 37, 3010–3018 (2017).

187. Wang, J. et al. The long noncoding RNA H19 promotes tamoxifen resistance in breast cancer via autophagy. J Hematol Oncol. 12, 61 (2019).

188. Wang, M. et al. Long non-coding RNA H19 confers 5-Fu resistance in colorectal cancer by promoting SIRT1-mediated autophagy. Cell Death Dis. 9, 1149 (2018).

189. Saenen, N. D. et al. Air pollution-induced placental alterations: an interplay of miR-133b through regulating expression of GSTP1. J Maternal-fetal Neonatal Med. 28, 101107 (2019).

190. Banerjee, N. et al. Plum polyphenols inhibit colorectal aberrant crypt foci formation and cancer cell proliferation. J Med Food 20, 227. (2017).

191. Saenz-de-Santa-Maria, I. et al. Clinically relevant HIF-1alpha-dependent metabolic reprogramming in oropharyngeal squamous cell carcinomas includes coordinated activation of CAIX and the miR-210/ISCU signaling axis, but not MCT1 and MCT4 upregulation. Oncotarget 8, 13790–13796 (2017).

192. Dong, M. T., Kim, H. G., Choi, J. H. & Jeong, H. G. Metformin induces microRNA-34a to downregulate the Sirt1/Pgc-1alpha/NRF2 pathway, leading to increased susceptibility of wild-type p53 cancer cells to oxidative stress and therapeutic agents. Free Radic Biol Med. 74, 21–34 (2014).

193. Tili, E. et al. The down-regulation of miR-125b in chronic lymphocytic leukemia leads to metabolic adaptation of cells to a transformed state. Blood 120, 2631–2638 (2012).

194. Sun, A. G., Meng, F. G. & Wang, M. G. GSD2 promotes the proliferation of glioma cells via suppressing bed1-mediated autophagy and is targeted by miRNA-449a. Mol. Med. Rep. 16, 1999–1994 (2017).

195. Zhang, L. et al. MicroRNA-related genetic variants in iron regulatory genes, dietary iron intake, microRNAs and lung cancer risk. Ann. Oncol. 28, 1124–1129 (2017).

196. McCormick, R. I. et al. miR-210 is a target of hypoxia-inducible factors 1 and 2 in renal cancer, regulates ISCU and correlates with good prognosis. Br. J. Cancer 108, 1133–1142 (2013).

197. Neal, C. S., Michael, M. Z., Rawlings, L. H., Van der Hoeck, M. B. & Gleedle, J. M. The VHL-dependent regulation of microRNAs in renal cancer. BMC Med. 8, 64 (2010).

198. Chou, S. H. & Toyokuni, S. Malignant mesothelioma as an oxidative stress-induced cancer: an update. Free Radic. Biol. Med. 56, 166–178 (2015).

199. Thakral, S. & Gill, V. A. MicroRNA/gene profiling unveils early molecular changes and nuclear factor erythroid related factor 2 (NRF2) activation in a rat model recapitulating human hepatocellular carcinoma (HCC). Hepatology 59, 228–241 (2014).

200. Eades, G., Yang, M., Yao, Y., Zhang, Y. & Zhou, Q. miR-200a regulates Nrf2 activation by targeting Keap1 mRNA in breast cancer cells. J Biol. Chem. 286, 40725–40733 (2011).

201. Gu, S., Li, Y., Chen, H., Liu, Y. & Zhang, Z. miR-155 mediates androgen receptor expression by activating Nrf2 and repressing apoptosis in lung cancer cells. Sci. Rep. 7, 12155 (2017).

202. Gao, A. M., Zhang, X. Y. & Ke, Z. P. Apigenin sensitizes BEL-7402/AOM cells to doxorubicin through inhibiting miR-101/NRF2 pathway. Oncotarget 8, 82085–82091 (2017).

203. Gu, J., Zhang, L., Li, L. & Yu, M. miR-148b functions as a tumor suppressor by targeting endoplasmic reticulum metallo proteinase 1 in human endometrial cancer cells. Oncol. Res. 27, 81–88 (2018).

204. Chen, G. et al. Lico A causes ER stress and apoptosis via up-regulating miR-144-3p in human lung cancer cell line H522. Front. Pharmacol 9, 837 (2018).

205. Run, X., Liu, D., Yue, Y. & Hu, X. Enforced miR-144-3p expression as a non-invasive biomarker for the acute myeloid leukemia patients mainly by targeting NRF2. Clin. Lab. 63, 679–687 (2017).

206. Cortez, M. A. et al. Therapeutic delivery of miR-200c enhances radiosensitivity in lung cancer. Mol. Ther. 22, 1494–1503 (2014).

207. Singh, B., Ronghe, A. M., Chatterjee, A., Bhat, N. K. & Bhat, H. K. MicroRNA-93 regulates NRF2 expression and is associated with breast carcinogenesis. Carcinogenesis 34, 1165–1172 (2013).

208. Papp, D. et al. The NRF2-related integrator and regulator contain multiple functional proteins and fine-tuned autoregulatory loops. FEBS Lett. 586, 1795–1802 (2012).

209. Do, M. T., Kim, H. G., Choi, J. H. & Jeong, H. G. Metformin induces microRNA-34a to downregulate the Sirt1/Pgc-1alpha/NRF2 pathway, leading to increased susceptibility of wild-type p53 cancer cells to oxidative stress and therapeutic agents. Free Radic. Biol. Med. 74, 21–34 (2014).

210. Trivedi, M. et al. MicroRNA-34a encapululated in hyaluronic acid nanoparticles induces epigenetic changes with altered mitochondrial bioenergetics and apoptosis in non-small-cell lung cancer cells. Sci. Rep. 7, 3636 (2017).

211. Li, C. et al. Deregulation of UCA1 expression may be involved in the apoptosis in non-small-cell lung cancer cells. J. Cell. Biochem. 115, 2025–2029 (2017).

212. Chew, S. H. et al. MicroRNA-186 induces mitochondrial biogenesis in neurodegeneration. PLoS One 9, e105074 (2014).
252. Yin, M. et al. Selective killing of lung cancer cells by miRNA-506 molecule

253. Song, Y. H. et al. MicroRNA-509-5p functions as an anti-oncogene in breast cancer

241. Pant, K. et al. Butyrate induces ROS-mediated apoptosis by modulating miR-

251. Bublik, D. R. et al. Regulatory module involving FGF13, miR-504, and p53

236. Wu, L. et al. Polygonatum odoratum lectin induces apoptosis and autophagy

249. He, Z. et al. MiR-422a regulates cellular metabolism and malignancy by

232. Zhang, H. M. et al. miR-146b-5p within BCR-ABL1-positive microvesicles

230. Sosa, V. et al. Oxidative stress and cancer: an overview.

Zhang et al. through inhibiting NF-kappaB p65 to evoke reactive oxygen species generation and p53 activation. Onco Targets Ther. 12, 5729–5739 (2019).

245. Guo, X. et al. Immunosuppressive effects of hypoxia-induced glioma exosomes function in keratinocytes. Nat. Commun. 5, 5099 (2014).

258. Li, Q. et al. A signaling pathway consisting of miR-551b, catalase and MUC1 contributes to acquired apoptosis resistance and chemoresistance. Carcinogenesis 35, 2457–2466 (2014).

259. Cha, J. A. et al. miR-211 plays a critical role in Cnidium officinale Makino extract-induced, ROS/ER stress-mediated apoptosis in U937 and U266 cells. Int. J. Mol. Sci. https://doi.org/10.3390/ijms19020368 (2018).

257. Magenta, A. et al. miR-200c is upregulated by oxidative stress and induces endothelial cell apoptosis and senescence via ZEB1 inhibition. Aging Res. Rev. 17, 245–257 (2017).

254. Xu, X. et al. A signaling pathway consisting of miR-551b, catalase and MUC1 contributes to acquired apoptosis resistance and chemoresistance. Carcinogenesis 35, 2457–2466 (2014).

255. Gomez de Cedron, M. et al. MicroRNA-661 modulates redox and metabolic homeostasis in colon cancer. Mol. Oncol. 11, 1768–1787 (2017).

256. Carlin, R. et al. Oxidative DNA damage correlates with cell immortalization and miR-92 expression in hepatocellular carcinoma. BMC Cancer 12, 177 (2012).

257. Chen, P. H. et al. The inhibition of microRNA-128 on KEF1-activating mTOR signaling involves in temozolomide-induced glioma cell apoptotic death. PLoS ONE 11, e0167096 (2016).

258. Li, Q. et al. Insulin regulates glucose consumption and lactate production through reactive oxygen species and pyruvate kinase M2. Oncotarget 8, 30495 (2014).

259. Cha, J. A. et al. miR-211 plays a critical role in Cnidium officinale Makino extract-induced, ROS/ER stress-mediated apoptosis in U937 and U266 cells. Int. J. Mol. Sci. https://doi.org/10.3390/ijms19020368 (2018).

260. Chen, Y. F. et al. MicroRNA-211 enhances the oncogenicity of carcinogen-induced oral carcinoma by repression of TGFβ1 and increasing antioxidant activity. Cancer Res. 76, 4872–4886 (2016).

261. Bao, B. et al. Targeting CSCs in tumor microenvironment: the potential role of ROS-associated miRNAs in tumor aggressiveness. Curr. Stem Cell Res. Ther. 9, 22–35 (2014).

262. Li, B. et al. miR-221/222 promote cancer stem-like cell properties and tumor growth of breast cancer via targeting PTEN and sustained Akt/ NF-κB/p38 activation. Chem. Biol. Interact. 277, 33–42 (2017).

263. Fulciniti, M. et al. miR-23b/SIP1/c-myc forms a feed-forward loop supporting multiple myeloma cell growth. Blood Cancer J. 6, e380 (2016).

264. Liu, W. et al. miR-221 targets proline oxidase, a novel tumor suppressor protein in renal cancer. Oncogene 29, 4914–4924 (2010).

265. Kurinna, S. et al. A novel NF2-miR-29:desmocollin-2 axis regulates desmosome formation in keratinocytes. Nat. Commun. 5, 5099 (2014).

266. Hou, M., Zuo, X., Li, C., Zhang, Y. & Teng, Y. Mir-29b regulates oxidative stress by targeting SIRT1 in ovarian cancer cells. Cell Physiol. Biochem. 43, 1767–1776 (2017).

267. Kim, S. M., Hur, Y. D., Hong, S. W. & Kim, J. H. EBV-encoded EBNA1 regulates cell viability by modulating miR22-NOX2-ROS signaling in gastric cancer cells. Biochem. Biophys. Res. Commun. 494, 550–555 (2017).

268. Hou, W., Tian, Q., Steuwer, N. M., Schrum, L. W. & Bonkovsky, H. L. The let-7 microRNA enhances heme oxygenase-1 by suppressing Bach1 and attenuates oxidant injury in human hepatocytes. Biochem. et Biophys. Acta 1819, 1113–1122 (2012).

269. Chang, M. et al. Suppression of SIRT6 by miR-33a facilitates tumor growth of glioma through apoptosis and oxidative stress resistance. Oncol. Rep. 38, 1251–1258 (2017).

270. Pradhan, A. K. et al. MDA-MB-231 regulates the miRNA processing enzyme DICER through downregulation of MIF. Proc. Natl Acad. Sci. USA 116, 5687–5692 (2019).

271. Zhang, H. et al. Electrochemiluminescence-microscopy for microRNA imaging in single cancer cell combined with chemotherapy-photothermal therapy. Anal. Chem. 91, 12581–12586 (2019).

272. Smickertsson, J. A., Rasmussen, L. J. & Friis-Hansen, L. Enterococcus faecalis contributes to acquired apoptosis resistance and chemoresistance. Cancer Res. 73, 3371–3379 (2009).

273. Ebi, H. et al. Counterbalance between RB inactivation and miR-17-92 overexpression in cervical cancer by repression of TCF12 and increased antioxidant activity. Cancer Res. 76, 4872–4886 (2016).

274. Li, Q. et al. Insulin regulates glucose consumption and lactate production through reactive oxygen species and pyruvate kinase M2. Oncotarget 8, 30495 (2014).

275. Magenta, A. et al. miR-200c is upregulated by oxidative stress and induces endothelial cell apoptosis and senescence via ZEB1 inhibition. Aging Res. Rev. 17, 245–257 (2017).

276. Carlin, R. et al. Oxidative DNA damage correlates with cell immortalization and miR-92 expression in hepatocellular carcinoma. BMC Cancer 12, 177 (2012).

277. Chen, P. H. et al. The inhibition of microRNA-128 on KEF1-activating mTOR signaling involves in temozolomide-induced glioma cell apoptotic death. PLoS ONE 11, e0167096 (2016).

278. Baker, J. E. et al. Oxidative stress dependent microRNA-34a activation via PI3K/Akt reduces the expression of sirtuin-1 and sirtuin-6 in epithelial cells. Sci. Rep. 6, 35871 (2016).
279. Chakraborty, S. et al. Restoration of p53/miR-34a regulatory axis decreases survival advantage and ensures Bax-dependent apoptosis of non-small cell lung carcinoma cells. FEBS Lett. 588, 549–559 (2014).

280. Liu, L. et al. MicroRNA-20a-mediated loss of autophagy contributes to breast tumorigenesis by promoting genomic damage and instability. Oncogene 36, 5874–5884 (2017).

281. Li, W. et al. Astragalrin reduces hexokinase 2 through increasing miR-125b to inhibit the proliferation of hepatocellular carcinoma cells in vitro and in vivo. J. Agric. Food Chem. 65, 5961–5972 (2017).

282. Shukla, K. et al. MicroRNA-30c-2-3p negatively regulates NF-kappaB signaling and cell cycle progression through downregulation of TRADD and CCNE1 in breast cancer. Mol. Oncol. 9, 1106–1119 (2015).

283. Guo, J. et al. miR-346 functions as a pro-survival factor under ER stress by activating mitophagy. Cancer Lett. 413, 69–81 (2018).

284. Vera-Puente, O. et al. MAFG is a potential therapeutic target to restore chemosensitivity in cisplatin-resistant cancer cells by increasing reactive oxygen species. Transl. Res. 200, 1–17 (2018).

285. Zou, S., Rao, Y. & Chen, W. miR-885-5p plays an accomplice role in liver cancer by instigating TIGAR expression via targeting its promoter. Biotechnol. Appl. Biochem. 66, 763–771 (2019).

286. Noratto, G. D., Jutooru, I., Safe, S., Angel-Morales, G. & Mertens-Talcott, S. U. The drug resistance suppression induced by curcuminoids in colon cancer SW-480 cells is mediated by reactive oxygen species-induced disruption of the microRNA-27a-ZBTB10-5p axis. Mol. Nutr. Food Res. 57, 1638–1648 (2013).

287. Ishimoto, T. et al. Macrophage-derived reactive oxygen species suppress miR-328 targeting CD44 in cancer cells and promote redox adaptation. Carcinogenesis 35, 1003–1011 (2014).

288. Kang, H. et al. Downregulation of microRNA-362-3p and microRNA-329 promotes tumor progression in human breast cancer. Cell Death Differ. 23, 484–495 (2016).

289. Bouatli, A., Tonge, D. P. & Mountada-Maaraoui, M. RNA sequencing reveals a key role for the long non-coding RNA MIAT in regulating neuroblastoma and glioblastoma cell fate. Int. J. Biol. macromol. 130, 878–891 (2019).

290. Tober, R. et al. High error rates in selenocysteine insertion in mammalian cells treated with the antibiotic doxycycline, chloramphenicol, or genetin. J. Biol. Chem. 288, 14709–14715 (2013).

291. Schonberg, S. A. et al. Evidence that changes in Se-glutathione peroxidase levels affect the sensitivity of human tumour cell lines to n-3 fatty acids. Carcinogenesis 18, 1897–1904 (1997).

292. Shimada, K. et al. A novel human ALKB homologue, ALKBH8, contributes to human bladder cancer progression. Cancer Res. 69, 3157–3164 (2009).

293. Zolla, L. & Timperio, A. M. Involvement of active oxygen species in protein and oligonucleotide degradation induced by nitrofurans. Biochem. Cell Biol. 83, 166–175 (2005).

294. Gunderson, S. I., Vagner, S., Polycarpou-Schwarz, M. & Mattaj, I. W. Involvement of the carboxyl terminus of vertebrate poly(A) polymerase in U1A autoregulation and in the coupling of splicing and polyadenylation. Genes Dev. 11, 761–773 (1997).

295. Wan, L., Ottinger, E., Cho, S. & Dreyfuss, G. Inactivation of the SMN complex by oxidative stress. Mol. Cell 31, 244–254 (2008).