Role of noncoding RNAs and untranslated regions in cancer
A review

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Abstract
Cancer is one of the most prevalent diseases worldwide, and poses a threat to human health. Noncoding RNAs (ncRNAs) constitute most transcripts, but they cannot be translated into proteins. Studies have shown that ncRNAs can act as tumor suppressors or oncogenes. This review describes the role of several ncRNAs in various cancers, including microRNAs (miRNAs) such as the miR-34 family, let-7, miR-17-92 cluster, miR-210, and long noncoding RNAs (lncRNAs) such as HOX transcript antisense intergenic RNA (HOTAIR), Metastasis associated lung adenocarcinoma transcript 1 (MALAT1), H19, NF-κB-interacting IncRNA (NKILA), as well as circular RNAs (circRNAs) and untranslated regions (UTRs), highlighting their effects on cancer growth, invasion, metastasis, angiogenesis, and apoptosis. They function as tumor suppressors or oncogenes that interfere with different axes and pathways, including p53 and IL-6, which are involved in the progression of cancer. The characteristic expression of some ncRNAs in cancer also allows them to be used as biomarkers for early diagnosis and therapeutic candidates. There is a complex network of interactions between ncRNAs, with some IncRNAs and circRNAs acting as competitive endogenous RNAs (ceRNAs) to decoy miRNAs and repress their expression. The ceRNA network is a part of the ncRNA network and numerous ncRNAs work as nodes or hubs in the network, and disruption of their interactions can cause cancer development. Therefore, the balance and stabilization of this network are important for cancer diagnosis and treatment.

Abbreviations: ceRNAs = competitive endogenous RNAs, circRNAs = circular RNAs, HOTAIR = HOX transcript antisense intergenic RNA, IncRNAs = long ncRNAs, MALAT1 = Metastasis associated lung adenocarcinoma transcript 1, miRNAs = microRNAs, ncRNAs = non-coding RNAs, NKILA = NF-κB-interacting IncRNA, UTRs = untranslated regions.

Keywords: cancer, long non-coding RNAs, microRNAs, non-coding RNAs, untranslated regions

1. Introduction
Cancer is a constant threat to human health and a common health and safety issue facing humanity worldwide. In a statistical survey in the United States, cancer was considered the second leading cause of death after heart disease.\textsuperscript{[1]} They pose a serious threat to human health, and their diagnosis and treatment have therefore become a major issue to be addressed. Studies have found that noncoding RNAs (ncRNAs) play an important role in the development of cancer. ncRNAs account for approximately 98% of all RNAs and cannot be encoded into proteins.\textsuperscript{[2]} There are 15 classes of ncRNAs that are classified into different groups, depending on the classification criteria. In terms of their functions, ncRNAs can be divided into two families: housekeeping ncRNAs and regulatory ncRNAs. Housekeeping ncRNAs, such as ribosomal RNAs (rRNAs), messenger RNAs (mRNAs) and transfer RNAs (tRNAs) involved in cellular genetic activities such as protein synthesis, RNA splicing, and RNA modification.\textsuperscript{[3]} Housekeeping ncRNAs act steadily in the production of proteins, and their roles have been extensively studied; therefore, they are not the subject of this review.

Regulatory ncRNAs act as regulators that participate in gene expression at the chromatin remodeling, transcriptional, and posttranscriptional levels, and function in signal transduction.\textsuperscript{[4]} Based on length, regulatory ncRNAs can be subclassified into two main groups: small ncRNAs (<200 nt) and long ncRNAs (>200 nt).\textsuperscript{[5]} Small ncRNAs include microRNAs (miRNAs), small interfering RNAs (siRNAs) and piwi-interacting RNAs (piRNAs). Among these, miRNAs are the most abundant and studied. Besides, some ncRNAs are variable in length, such as circular RNAs (circRNAs) and enhancer RNAs (eRNAs).\textsuperscript{[6]}

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MicroRNAs (miRNAs) are small regulatory ncRNAs that contain approximately 18-25 nucleotides. There exists a conserved miRNA region on nucleotides 2-7, which is considered the “seed” and guides miRNA target recognition. The seed sequence at the 5’ end of functional miRNA can form Watson-Crick pairing with the 3’-UTR of the target mRNA to promote targeted mRNA degradation or induce translational silencing. miRNAs act as powerful regulators that target numerous transcripts and their aberrations may disrupt signaling pathways and physiological activities, leading to cancer progression. They function as oncogenes or tumor suppressors in various cancers and affect the hallmarks of malignant tumors, including programmed cell death, limitless replication potential, sustained angiogenesis, self-sufficiency in growth signals, insensitivity to growth-inhibitory signals, invasion and metastasis. However, the initiation of a tumor or malignancy is not the only result of the action of one type of miRNA. Alterations that lead to cancer characteristics result from many miRNAs acting together.

3.1. Mir-34 family. The miR-34 family contains 3 types, miR-34a, miR-34b, and miR-34c, of which miR-34a and miR-34c are located on one chromosomal locus. The methylation of these genes leads to silencing. miR-34b/c is more strongly associated with cancer metastasis than miR-34a is. It inhibits anchorage-independent growth and epithelial-to-mesenchymal transition (EMT) in cancer cells, suppressing cancer growth, invasion, and metastasis. However, higher levels of miR-34a/b methylation have been found in nonsmall cell lung cancer (NSCLC) and its low expression level tends to correlate with age, gender, smoking status, tumor progression, poor prognosis and cancer metastasis. Hence, their methylation could be associated with NSCLC development and could be used as a prognostic marker.

The loss of miR-34a can be noted in many cancer types, including lung, prostate, and breast cancers, and its reduction mainly abrogates apoptosis. It can target cell cycle-related and anti-apoptotic genes to exert antitumor effects. As seen in Figure 1A, as an miRNA family directly regulated by p53, miR-34a involves in the regulation of many oncogenes, the most prominent of which is the regulation of apoptosis. In non-small cell lung cancer (NSCLC) exhibits multiple somatic mutations in several genes, among which mutations in the RAS and p53 pathways are important. miR-34a can slow cancer progression and increase survival in human KRAS-positive and p53-negative lung cancer patients by repressing Met and BCL-2 expression. This may be assisted by the involvement of sirtuin-associated factor 3 (SIRT3), a putative pre-miR-34a RNA binding protein (RBP), which is also involved in the miR-34a-CDK4/6 axis for G1 arrest.

In addition, a study on triple-negative breast cancer (TNBC) found that knockdown of multiple copies of T-cell malignancy 1 (MCT-1) can restore the level of miR-34a, which represses IL-6 expression and activates pro-inflammatory M1 macrophage polarization. There exists an IL-6R/signal transducer and activator of transcription 3 (STAT3)/miR-34a loop, in which upregulation of miR-34a can inhibit IL-6-induced EMT, reducing cancer invasiveness and metastasis (Figure 1B). This pathway also functioned in colorectal cancer that miR-34a represses IL-6R expression through a highly conserved miR-34a seed-matching sequence in the IL-6R 3’-UTR. The expression of IL-6 and miR-34a is mutually inhibited, whereas p53 can disrupt this balance by upregulating miR-34a expression. Furthermore, miR-34a can modulate the Notch signaling pathway to accelerate senescence and reduce TNBC cell proliferation and migration.

In conclusion, the miR-34a family acts as a tumor suppressor, promotes apoptosis, inhibits metastasis, and is an important target for cancer treatment.

3.1.2. Let-7. In addition to members of the miR-34 family, let-7 is a potent cancer suppressor. Its reduction can be observed in a variety of cancers and is associated with poor prognosis and stemness. The processes of let-7 biosynthesis and expression are interfered with by the Lin28 proteins, which are RBPs containing Lin28A and Lin28B. The expression of let-7 and Lin28 is reciprocally repressed, in that Lin28 represses the synthesis of Let-7, while Let-7 represses Lin28 translation. This feedback loop is critical for maintaining normal stem cell proliferation and self-renewal.

Figure 1. The mir-34a family function as tumor suppressors. (A) Schematic representation of p53/miR-34a loop. Abbreviations: EMT = epithelial-mesenchymal transition, IL-6 = Interleukin-6, IL-6R = Interleukin-6 receptor, SIRT1 = sirtuin 1, STAT3 = signal transducer and activator of transcription 3.
expression of let-7, whereas let-7 binds to the 3'-UTR of Lin28 for inhibition. Their expression forms a Lin28/let-7 axis and influences the development of diverse cancers, especially in the process of stemness (Fig. 2).

A study on breast cancer showed that carbonic anhydrase IX (CAIX) can adapt cancer cells to a hypoxic and acidic environment through the Lin28/let-7 pathway, promoting glycolysis and stemness. Silencing or suppressing CAIX can upregulate let-7 and inhibit Lin28. Meanwhile, the increase in let-7 causes a decrease in IL-6, which further suppresses nuclear factor-kB (NF-κB) and STAT3 expression, resulting in diminished proliferation and inflammation. A positive inflammatory feedback loop between IL-6 and let-7 has been identified. Inflammation can deliver growth signals, leading to the proliferation of malignant tumor cells. In addition, research has shown that M1 macrophages can induce self-renewal of cancer stem cells (CSCs). Increased expression of LIN-28 and high motility group box protein 2 (HMGA2), and decreased expression of let-7, the LIN-28B-let7-HMGA2 axis engages in the EMT process to accelerate metastasis and induce CSCs. HMGA2 is a target gene for let-7; attenuation of its expression can elevate E-cadherin and inhibit fibronectin induced by M1 macrophages, whereas this inhibition can be reverted by HMGA2 3'-UTR translocation.

In addition to IL-6 and HMGA2, let-7 can target many genes, including RAS, c-Myc, and Fas, which are engaged in self-renewal, differentiation, tumor cell growth, and apoptosis. By suppressing let-7 expression, cancer cells exhibit stemness and self-sufficiency in growth signaling. Thus, let-7 is a potent therapeutic target for inhibiting tumorigenesis.

3.1.3. Mir-17-92 cluster. However, studies have found that a proportion of miRNAs also behave as oncogenes that tend to be upregulated in cancer. They are known as “oncomirs” that often disrupt tumor suppressors or perturb normal cellular signaling pathways, leading to the development of cancer.

Hepatitis B virus infection led to a surge in mir-17-92, which further impaired the expression of DEAD-Box helicase 5 (DDX5) by targeting its mRNA 3'-UTR. The reduction of DDX5 facilitated the expression of c-Myc and hepatic cancer stem cell-like genes, aberrant AKT phosphorylation, and AMPK activity, as well as activated Wnt/β-catenin signaling, inducing stemness.

In addition, mir-17-92 has been shown to cooperate in cancers, including B-cell lymphoma, colorectal cancer, basal cell carcinoma, and lung cancer. Several mechanisms may be involved in the oncogenicity of this cluster, but they all collectively indicate a c-Myc/mir-17-92/PTEN axis that causes carcinogenesis and reduces apoptosis by repressing the PI3K/Akt signaling pathway. However, research has reported that miR-17-3p can tightly regulate c-Myc-induced cell proliferation and act as a tumor suppressor. miR-17-92 sensitively coordinates MYC oncogene activity and suppresses E2F by participating in the MYC feedforward loop, leading to cell cycle arrest and repression of tumor cell proliferation. It might be speculated that despite belonging to the same miRNAs, different isoforms might affect cell proliferation and tumorigenesis in a cell type-specific manner, while it might also depend on the function of different target mRNAs.

3.1.4. Mir-210. miR-210 is also an oncomir that is mainly involved in angiogenesis and metastasis. miR-210-3p consistently activates NF-κB to promote EMT, invasion, and induction of prostate cancer bone metastases. It takes its action through repressing TNF-α-induced protein 3 (TNIP1) and suppressor of cytokine signaling 1 (SOCS1), which act as negative regulators and inhibit the NF-κB signaling pathway. A surge in miR-210-3p was found in hypoxic environments, while its disorder could enhance HIF-1α expression and inhibit p53, causing aerobic glycolysis, which further enhances the role of hypoxia as a deleterious factor in carcinogenesis.

Furthermore, the overexpression of miR-210 has been shown to be related to angiogenesis. The JAK2/STAT3 and PI3K/Akt pathways may play a major role in cancer angiogenesis, especially the latter, which is also implicated in tumor metastasis and invasion.

Several miRNAs are involved in various processes of cancer, contributing to the complexity of cancer development and the diversity of its features. Therefore, numerous miRNAs have been investigated as tumor markers or therapeutic targets.

3.2. Role of lncRNAs in cancer

Long noncoding RNAs (lncRNAs) are a series of ncRNAs with transcripts longer than 200 nucleotides. Their expression exhibits more tissue-specific properties than that of miRNAs. According to their functions, lncRNAs can be classified as signaling, decoy, guide, or scaffold lncRNAs. Although the exact mechanisms are not yet clear, lncRNAs are involved in the regulation of gene expression and epigenetic modifications and are involved in genomic imprinting, cell differentiation, and

Figure 2. Schematic illustration of let-7/Lin28 axis involvement in inhibition of cancer. Abbreviations: CSCs = cancer stem cells, CAIX = carbonic anhydrase IX, HIF-1 = hypoxia-inducible factor-1, c-Myc = cellular-myelocytomatosis viral oncogene, IL-6 = Interleukin-6, HMGA2 = high mobility group AT-hook 2, NF-κB = nuclear factor kappa-light-chain-enhancer of activated B cells, STAT3 = signal transducer and activator of transcription 3.
inactivation of the X-chromosome.\textsuperscript{[49,51]} Additionally, numerous lncRNAs function as miRNA sponges to compete for expression. Their regulatory roles and their modulation functions in chromatin structures via recruiting chromatin-modifying enzymes, may indicate their importance in pluripotency and gene regulation.\textsuperscript{[52]} Therefore, misexpression of lncRNAs causes cancer development and plays a role in tumor progression. However, the differential expression of lncRNAs in various cancers may suggest potentially important values for diagnosis, treatment, and prognosis.

3.2.1. HOTAIR. HOX transcript antisense intergenic RNA (HOTAIR) is a scaffold lncRNA whose expression is related to metastasis and invasion in various cancers. HOTAIR can bind to polycomb repressive complex 2 (PRC2) and lysine-specific demethylase 1A (LSD1) for chromatin modulation.\textsuperscript{[53]} However, its high expression was observed in primary breast carcinomas and was evident in metastatic foci. By targeting PRC2 and mediating histone H3 lysine 27 (H3K27) trimethylation, HOTAIR induces PRC2 occupancy and alters many genes involved in cell-cell signaling and development pathways, leading to tumor metastasis, invasion, and angiogenesis.\textsuperscript{[54]} Its ability to induce breast cancer growth and metastasis was also demonstrated by Ren et al\textsuperscript{[55]} that elevated HOTAIR expression facilitated EMT and tumor metastasis.

Furthermore, upregulation of HOTAIR attenuated cell apoptosis induced by TNF-related apoptosis-inducing ligand (TRAIL) in pancreatic cancer. Under the involvement of enhancer of zeste homolog 2 (EZH2), HOTAIR suppressed death receptor 5 (DR5) expression, which is a TRAIL receptor, resulting in resistance to TRAIL-induced apoptosis in pancreatic cancer.\textsuperscript{[56]} Overexpression of HOTAIR is accompanied by overexpression of hexokinase-2 (HK2), resulting in accelerated energy metabolism in pancreatic adenocarcinoma cells.\textsuperscript{[57,58]}

An increase in HOTAIR was also detected in NSCLC and paralleled by a decrease in miR-34a-5p, a tumor suppressor miRNA. Altering their interaction through the HOTAIR/miR-34a-5p axis could suppress Snail expression, thereby increasing E-cadherin levels and repressing EMT.\textsuperscript{[20]} Consistently, similar expression was found in esophageal cancer and PDAC, where HOTAIR acts as a competing endogenous lncRNA (ceRNA) to accelerate tumorigenesis by sponging miRNA.\textsuperscript{[19,59]}

Interfering with the interaction of HOTAIR with other molecules and the HOTAIR/miRNA axis has therapeutic implications and may be sensitive to target tumors overexpressing HOTAIR.

3.2.2. MALAT1. Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) can regulate the transcriptional processes of multiple genes and plays a role in a wide range of biological pathways, including glycolysis, adhesion, DNA repair, and vascularization, but it is chiefly involved in alternative splicing.\textsuperscript{[60]}

Notably, its expression is known to be a predictive marker for lung cancer, particularly metastasis.\textsuperscript{[60]} When MALAT1 is knocked down in A549 cells, dysregulation of metastasis-associated transcripts and growth control genes can be observed in lung cancer cells.\textsuperscript{[61]} In addition, silencing MALAT1 restored the expression level of E-cadherin and inhibited the EMT process, thereby reducing brain metastases in patients with lung cancer.\textsuperscript{[62]} While similar results were not observed in HeLa cells, implying that the role of MALAT1 may be cell type-specific.\textsuperscript{[63]}

Patients with osteosarcoma (OS) with high levels of MALAT1 expression exhibit a poor prognosis, a high rate of cancer metastasis, and an impact on tumor stage and size. The high metastasis rate induced by MALAT1 is associated with agonism of the PI3K/AKT pathway and reduced E-cadherin expression via the involvement of EZH2.\textsuperscript{[64]} Furthermore, MALAT1 can act as an miRNA sponge to regulate the miR-34a/cyclin D1 and miR-206/CDK9 axes, promoting OS tumor cell viability, proliferation, and activating tumor progression.\textsuperscript{[65,66]}

Similarly, its role as a ceRNA also occurs in colon cancer. By sponging miR-129-5p, MALAT1 enhances colon tumorigenesis and increases the expression of high mobility group box protein 1 (HMGB1), a target of miR-129-5p that ordinarily protects cells from injury.\textsuperscript{[67]} Analogous findings exist in the MALAT1/miR-429 axis in cervical cancer.\textsuperscript{[68]} MALAT1/miR-204/IGF2BP2/m6A-MYC axis in thyroid cancer.\textsuperscript{[69]} MALAT1/miR-23b-3p/ATG12 axis in gastric cancer (GC).\textsuperscript{[70]} and MALAT1/miR-140-3p/BRC6 axis in prostate cancer.\textsuperscript{[71]} Fortunately, knockdown and silencing can reverse the effects of MALAT1, inhibit the growth and metastasis of tumor cells, and promote apoptosis.

Although MALAT1 has been shown to be expressed in many cancers to promote cancer development and metastasis, Kim et al reported that its overexpression in breast cancer inhibits tumor metastasis. However, there is a lack of convincing evidence.\textsuperscript{[72]}

3.2.3. H19. H19 is thought to be an oncogenic lncRNA associated with several cancers. Its upregulation can be seen in the hypoxic stress response via the p53/HHI1-Q pathway and induces cell proliferation.\textsuperscript{[73]} Furthermore, H19 overexpression upregulates Lin28 by repressing let-7, leading to invasion and metastasis in breast cancer. It has been demonstrated that by modulating the H19/let-7/Lin28 network, autophagy can be enhanced by the inhibition of the EMT process.\textsuperscript{[74]}

In colorectal cancer (CRC), H19 promotes the EMT process and causes CRC lung metastasis by functioning as a sponge of miR-22-3p and miR-29b-3p, increasing the expression of matrix metalloprotease-14 (MMP14) and progranulin (PGRN), which further acts on the Wnt/β-catenin signaling pathway to enhance EMT.\textsuperscript{[75,76]} In addition, by inhibiting miR-141, H19 can activate the β-catenin signaling pathway, promoting CSC stemness and chemoresistance.\textsuperscript{[77]} H19 is also involved in steatosis through a positive feedback loop in thyroid carcinomas, where estradiol upregulates H19 expression via estrogen receptor β (ERβ) and H19 functions as an miRNA-3126-5p sponge to induce Erβ expression in turn.\textsuperscript{[78]}

3.2.4. NKILA. Surprisingly, some lncRNAs play a role in cancer suppression. NF-κB-interacting lncRNA (NKILA) has been identified as a tumor suppressor that regulates NF-κB activity, and its expression is decreased in various cancers.\textsuperscript{[79]}

A lncRNA-NKILA/NF-κB feedback loop exists in which NKILA can firmly combine with the NF-κB/IKκB complex to inhibit the phosphorylation of IKκB, leading to NF-κB inactivation and inflammation suppression, whereas NF-κB can bind to the NKILA promoter region and initiate its transcription.\textsuperscript{[79,80]} Herein, Wu et al also confirmed that TGF-β upregulated NKILA expression in an NF-κB-dependent manner, which in turn regulated NF-κB activity and EMT in breast cancer. In addition, there is a negative feedback mechanism whereby NKILA suppresses TGF-β-mediated EMT by inhibiting NF-κB.\textsuperscript{[81]} In addition, lower levels of NKILA lead to the activation of IkBα phosphorylation and the NF-κB pathway in rectal cancer, causing tumor proliferation and metastasis, ultimately resulting in exacerbating of the clinical stage of the tumor and poor prognosis.\textsuperscript{[82]}

It can be speculated that the induction of NKILA expression could be a therapeutic approach for cancer. NKILA overexpression attenuates radiation resistance in laryngeal cancer cells.\textsuperscript{[83]} Nevertheless, it has been reported that NKILA assists tumor cells to avoid immunosurveillance. With the involvement of the NF-κB signaling pathway, high expression of NKILA can sensitize activated T cells to tumor-induced activation-induced cell death (AICD), resulting in cytotoxic T lymphocyte death and immunological disorders.\textsuperscript{[84]} From this perspective, inhibition of NKILA expression has a facilitating effect on the efficacy of these approaches for treating cancer by immunological means.
| IncRNA | Cancer type | Expression | Mechanism | Results | Ref. |
|--------|-------------|------------|-----------|---------|------|
| HOTAIR | Breast cancer | ↑ HOTAIR targeted PRC2 | Metastasis and invasion; Cancer aggression; Cell growth; Angiogenesis | [6] |
| HOTAIR | Breast cancer | ↑ TGF-β1/HOTAIR axis | Expression of E-cadherin; Expression of vimentin and β-catenin; EMT; Metastasis; Cell growth; Drug resistance | [4] |
| HOTAIR | Pancreatic cancer | ↑ HOTAIR regulated D95 expression via EZH2 | TRAIL resistance; Apoptosis; Cell invasion and proliferation | [4] |
| HOTAIR | Pancreatic cancer | ↑ HOTAIR promoted HK2 expression | Cell proliferation; Lactate production; Glucose uptake; ATP production; Cancer energy metabolism | [2] |
| HOTAIR | Lung cancer | ↑ HOTAIR/miR-34a-5p axis | miR-34a-5p expression; Migration and Invasion; Tumorigenesis; Cell proliferation and growth; Expression of E-cadherin; Expression of vimentin and snail; EMT; Poor prognosis | [3] |
| HOTAIR | Esophageal cancer | ↑ HOTAIR/miR-148a axis | miR-148a expression; Expression of Smad2/3; C proliferation, growth and differentiation | [5] |
| HOTAIR | Pancreatic cancer | ↑ HOTAIR and EZH2 inhibited miRNA-34a | MALAT1 regulates several metastasis-related genes expression | [1] |
| MALAT1 | Lung cancer | ↑ MALAT1 enhanced gene expression of cell motility and metastasis | MALAT1 Brain metastasis; EMT; Invasion and metastasis; Cancer cell motility and migration; E-cadherin expression; Patients’ survival rate | [1] |
| MALAT1 | Osteosarcoma | ↑ MALAT1/miR-34a/cyclin D1 axis | miR-34a expression; Cyclin D1 expression; OS cell viability and growth; Tumor invasion and migration; Tumor size, clinical stage and distant metastasis in patients | [5] |
| MALAT1 | Osteosarcoma | ↑ MALAT1/miR-206/CDK9 axis | miR-206 expression; CDK9 expression; OS cell proliferation; OS progression; Apoptosis | [5] |
| MALAT1 | Colon cancer (colorectal cancer) | ↑ MALAT1/miR-129-5p/HMGB1 axis | miR-129-5p expression; HMGB1 expression; Cell proliferation; Cancer progression | [1] |
| MALAT1 | Cervical cancer | ↑ MALAT1/miR-429 axis | miR-429 expression; Cervical cell viability and proliferation; Apoptosis; Cell invasion | [1] |
| MALAT1 | Thyroid cancer | ↑ MALAT1/miR-204/IGF2BP2/m6A/myc axis | miR-204 expression; Expression of IGF2BP2 and MYC; Cell proliferation; Migration and invasion; Apoptosis; LncRNA-NKILA/NF-κB -induced EMT by β-catenin axis miR-22-3p expression; PGRN, β-catenin and Wnt expression; Expression of let-7/Lin28 loop let-7 expression | [1] |
| MALAT1 | Gastric cancer | ↑ MALAT1/miR-23b-3p/ATG12 axis | miR-23b-3p expression; ATG12 expression; Chemoresistance; Autophagy | [1] |
| MALAT1 | Prostate cancer | ↑ MALAT1/miR-140/BIRC6 axis | miR-140 expression; BIRC6 expression; Cell proliferation; Migration and invasion; Tumor growth; Apoptosis | [1] |
| MALAT1 | Breast cancer | ↑ MALAT1 inactivated TEAD | MALAT1 Expression of apoptosis-associated molecules beclin-1 and LC3-II; Lung metastasis | [1] |
| H19 | Breast cancer | ↑ H19/let-7/Ln28 loop | let-7 expression; Ln28 expression; EMT; Invasion and metastasis; Expression of autophagy-associated molecules | [1] |
| H19 | Colon cancer (colorectal cancer) | ↑ H19/miR-22-3p/MMP14 axis | miR-22-3p expression; MMP14 expression; Metastasis; EMT; Expression of E-cadherin; Expression of fibronectin and ITGA5; miR-29b-3p expression; PGRN, β-catenin and Wnt expression; Expression of E-cadherin; Expression of vimentin, snail, c-Myc and cyclin D1; Cell proliferation; Metastasis | [1] |
| H19 | Colon cancer (colorectal cancer) | ↑ H19/miR-141-3p/β-catenin axis | miR-141 expression; β-catenin expression; Tumor stemness and chemoresistance; Tumor development | [1] |
| H19 | Thyroid cancer | ↑ ERβ-H19 positive feedback loop | miRNA-3126-5p expression; Expression of ERβ; Expression of NF-κB signaling activation; Cell proliferation, viability; EMT; Cell migration; Invasion; Radio resistance; MET; LncRNA-NKILA/NF-κB feedback loop NF-κB signaling pathway; activation of NF-κB signaling pathway | [1] |
| NKILA | Laryngeal cancer | ↑ IncRNA-NKILA/NF-κB feedback loop | IncRNA-NKILA/NF-κB feedback loop | NF-κB phosphorylation; Metastasis; Cancer progression; Poor prognosis | [1] |
| NKILA | Breast cancer | ↓ NKILA inhibits TGF-β-induced EMT by suppressing NF-κB | Expression of NF-κB and TGF-β; EMT; Invasion and metastasis; Expression of snail and vimentin; E-cadherin expression | [1] |
| NKILA | Rectal cancer | ↓ IncRNA-NKILA/NF-κB feedback loop | NF-κB pathway activation; Cell proliferation; Apoptosis and metastasis; Poor prognosis | [1] |

**Table 1**

Expression and mechanisms of some long noncoding RNAs in cancers.

**Gene symbols:**
- ACD = activation-induced cell death
- ATG12 = autophagy-related 12
- BIRC6 = baculoviral IAP repeat-containing 6
- CDK = cyclin-dependent kinase
- CTLs = cytotoxic T lymphocytes
- DR5 = death receptor 5
- EMT = epithelial-mesenchymal transition
- ERβ = estrogen receptor β
- EZH2 = enhancer of zeste homolog 2
- HK2 = hexokinase-2
- HMGB1 = high mobility group box protein 1
- HOTAIR = HOX transcript antisense intergenic RNA
- IGF2BP2 = insulin-like growth factor 2 mRNA binding protein 2
- ITGA5 = integrin subunit alpha 5
- LncRNA = long noncoding RNA
- MALAT1 = metastasis associated lung adenocarcinoma transcript 1
- MMP14 = matrix metalloproteinase-14
- MYC = myelocytomatosis
- NKILA = NF-κB-interacting IncRNA
- NF-κB = nuclear factor kappa-light-chain-enhancer of activated B cells
- OS = osteosarcoma
- PGRN = progranulin
- PRC2 = polycomb repressive complex 2
- PTEFb = transcription elongation factor b
- TEAD = TATA box binding protein
- TRAIL = TNF-related apoptosis-inducing ligand
- TGF-β = transforming growth factor β
- VEGF = vascular endothelial growth factor

**Abbreviations:**
- AICD = activation-induced cell death
- ACD = activation-induced cell death
- AGO = Argonaute
- ATG = autophagy
- CDK = cyclin-dependent kinase
- EMT = epithelial-mesenchymal transition
- ER = estrogen receptor
- EZH2 = enhancer of zeste homolog 2
- FAD = flavin adenine dinucleotide
- IGF = insulin-like growth factor
- KLF = Krüppel-like factor
- LncRNA = long noncoding RNA
- MEF2 = myocyte enhancer factor 2
- NF-κB = nuclear factor kappa-light-chain-enhancer of activated B cells
- OS = osteosarcoma
- PGRN = progranulin
- PRC2 = polycomb repressive complex 2
- PTEFb = transcription elongation factor b
- TRAIL = TNF-related apoptosis-inducing ligand
- TGF-β = transforming growth factor β
- TUNEL = terminal deoxynucleotidyl transferase dUTP nick-end labeling
- VEGF = vascular endothelial growth factor

**Notes:**
- Angle brackets are used to signify that the statement is inferred from the provided data.
- Square brackets are used to signify that the statement is not directly supported by the data but is inferred to be related.

**References:**
- [1] Zhang et al. (2022) Medicine 101:33 www.md-journal.com
In brief, most lncRNAs act primarily as oncogenic factors in tumor progression, whereas some have tumor-suppressive effects (Table 1). By sponging miRNAs with cancer-suppressive effects and promoting the expression of their downstream targets, they can disturb biological and cellular processes. There seems to be RNA crosstalk involving lncRNAs, miRNAs, mRNAs, or proteins to form a ceRNA network and functions in cancer development.[83]

### 3.3. Role of circRNAs in cancer

Circular RNAs (circRNAs) are unique compared to other ncRNAs in that their 5' and 3' ends are linked end-to-end to form a closed loop. They can directly target the UTRs of mRNAs for gene regulation.[84]

circRNAs tend to be highly expressed in terminally differentiated or proliferation-stable cells.[85] However, some circRNAs paradoxically show high expression in cancer, causing cancer progression. These circRNAs can function as miRNA sponges to inhibit their expression. In NSCLC, circ-ZKSCAN1 acts as a miR-330-5p sponge and influences downstream mRNA expression to inhibit the MAPK signaling pathway.[86] Furthermore, circ-CPA4 is highly expressed in NSCLC cells and represses let-7 expression. Through the circ-CPA4/let-7 axis, circ-CPA4 can further enhance programmed cell death ligand 1 (PD-L1), a target of let-7 that induces cell stemness and drug resistance.[87]

A similar mechanism of circRNAs as ceRNAs in promoting carcinogenesis has been found in other cancers, including breast,[88] colorectal,[89] endometrial cancer,[90] and esophageal squamous cell carcinomas.[91]

On top of serving as an miRNA sponge, it can also regulate downstream gene targets to promote cancer cell growth and invasion. In pancreatic cancer, circ0005276 can positively target X-linked inhibitor of apoptosis protein (XIAP), enhance EMT, and induce prostate cancer progression.[92]

In contrast, some circRNAs with reduced expression levels exhibited a suppressive effect on cancer cells. Once again, circ-ZKSCAN1 can inhibit the transcriptional actions of the Wnt/β-catenin signaling pathway by blocking another target, fragile X mental retardation protein (FMRP), suppressing the process of stemness.[93] Furthermore, hsa_circ_100395 can act as an miRNA sponge to inhibit miR-1228, which acts as an oncogene in lung cancer, and represses p53 expression to inhibit apoptosis.[94,95] We can infer that different circRNAs, or even for the same circRNA, their promotive or inhibitory effects on cancer are influenced by their targets and cell-specificity.

### 3.4. Role of UTRs in cancer

UTRs can impact proteins by managing the translation and location of mRNAs and causing mRNA degradation, thereby determining the fate of proteins by modulating protein-protein interactions (PPIs). The 3'-UTR acts as an intermediate regulator of mRNA to specific RNA-binding factors. Multiple factors can act collaboratively or competitively on the same mRNA 3'-UTR, eliciting final effects influenced by their respective expression levels, binding sites, and cellular activity.[96] Thus, disturbance of the UTR can result in tumorigenesis.

As it has briefly mentioned the presence of a MALAT1/miR-204/IGFB2BP2/m6A-MYC axis above, the insulin-like growth factor-2 mRNA-binding proteins 2 (IGFB2BP2, IMP-2) belongs to the IGF-2 mRNA-binding proteins 1,2 and 3 (IMPs) family, which is a tumor promoter can enhance tumor spread.[97] It targets the 3'-UTR region of cyclin D1, D3, and G1 mRNA, and with a surge in their expression, the cell cycle proceeds to cause cancer cell proliferation.[98] When IMP acts on the 3'-UTR of the 5.0kb CD44 mRNA, IMP contributes to CD44 stabilization, which further reduces cell adhesion, generates invadopodia, and ultimately promotes cancer cell metastasis.[99]

There is an AU-rich element (ARE) in the 3'-UTR, which is predominantly expressed in genes that require rigorous regulation and lead to rapid mRNA disassembly. ARE does not directly affect protein abundance, but can influence the gene expression levels of protooncogenes and cytokines by binding to RBPs or miRNAs. Therefore, alterations in AREs or disruption of ARE-containing miRNAs can lead to cancer development.[97,100] Precisely, this is supported by the finding that cancer cells typically express many mRNA isoforms with short 3'-UTRs lacking the ARE parts caused by alternative polyadenylation (APA).[101] The shorter 3'-UTR was observed in hematopoietic- and neurologic-expressed sequence 1 (HN1) in carcinomas. In contrast, when HN1 has a longer 3'-UTR, it is usually less stable and maintains a lower expression level, which can cause cellular senescence and improve patient survival.[102] Therefore, it is noteworthy that APA-induced shortening of 3'-UTRs is a mechanism that causes cancer development.

In addition, 5'-UTRs also participate in carcinogenesis. A study on hepatocellular carcinoma found that YTHDF2- OCT4 signaling is involved in cancer progression. By targeting m6A in the 5'UTR of OCT4 mRNA, YTHDF2 enhanced the methylation of m6A and upregulated OCT4 expression, a pluripotency factor whose enhanced expression increased the CSC phenotype and lung metastasis.[103]

Furthermore, some reports have suggested that the translation of p53 can be regulated through its 3' or 3'-UTR, especially the 5'-UTR of p53 mRNA, which can regulate the expression of p53 by binding to the 5'-UTR of its mRNA.[104,105] There are two internal ribosome entry sites (IRESes) in p53 mRNA, with one located in the 5'-UTR region, which regulates p53 translation when DNA is damaged. However, this abnormality was found in oncogene-induced senescence, leading to an increase in p53 translation.[106] p53 itself can negatively regulate its translation when DNA is damaged. However, this abnormality was found in oncogene-induced senescence, leading to an increase in p53 translation.[106] p53 itself can negatively regulate its translation by acting on the 3'-UTR of p53 mRNA.[107] Strikingly, lncRNAs also participate in the regulation of p53, and there is a complicated network between them.[108]

The combination of all these complexities and the binding and interaction of UTRs with proteins and ncRNAs literally complicates their role in cancers.

### 3.5. NcRNA network and therapy

It is difficult to identify ncRNA functions in isolation; many ncRNAs exhibit highly complex interactions in cancer progression and regulate the cellular growth cycle and properties. A vast network of intersecting ncRNAs passes different signals from one level to the next and many ncRNA interactions correspond to characteristic patterns and are part of network motifs.[109] Interactions between ncRNAs and ncRNAs, genes, other transcripts, or proteins are not only one-way regulation, but can also be feedback or feedforward regulation (Fig. 3). The aforementioned positive feedback loops between let-7 and IL-6 or the interaction between H19 and ERβ are both feedforward regulators. Compared to feedforward loops, negative feedback loops are more common in ncRNA networks and play an important role.
in maintaining inputs and outputs within a normal range. These simple and fragmented parts intertwine and intersect like rivers, forming complex networks. Among them, the most representative is the competitive endogenous RNA (ceRNA) networks.

As we have already mentioned that some ceRNAs, which means that these ncRNAs are in competitive regulatory interactions, and generally function as miRNA sponges to suppress their functions. For example, in the case of the H19/let-7/Lin28 axis, H19 inhibits the expression of let-7, elevating Lin28 levels, which are normally inhibited by let-7, to promote EMT and inhibit cellular autophagy. ncRNAs include IncRNAs, pseudogenes, circRNAs, or even mRNAs, and 3'UTRs can act as ceRNAs in cancers and have the potential to initiate tumorigenesis. They can decoy miRNAs, attenuate their regulation of genes, transcripts, or proteins, and serve as post-transcriptional regulators. Precisely because of their interaction with each other, once one of the components has changed, the impact can be far-reaching and perturbation can contribute to disease pathogenesis, including carcinogenesis.

Therefore, it has become a major research topic in diagnosis and prognosis. Studies have focused on ceRNA interactions to identify disordered RNA expression in specific cancer types as biomarkers and treatment targets. Tang et al. found that circ-KIAA1244 can be used as a biomarker for the early diagnosis of GC and assist in cancer staging. In addition, with C1632, an inhibitor of Lin28, let-7 expression is elevated, leading to PD-L1 inhibition and enhanced immunity to cancer. LIN28/let-7 therefore also serves as a candidate site for PD-L1-mediated immunotherapy.

Presumably, in the absence of a direct action on the target, it may be possible to use their interactions to hold them together for therapeutic purposes. Also, through gene knockdown or silencing, the expression of oncogenic ncRNAs can be inhibited to suppress cancer development.

4. Conclusions and Perspectives

As a momentous part of gene regulation, ncRNAs and UTRs can act as oncogenes or tumor suppressors to influence cancer development and affect cancer invasion, metastasis, proliferation, apoptosis, and angiogenesis. They constitute an ncRNA network that plays an important role in cellular life activities and disease development, of which ceRNAs, as competing miRNA decoys, account for a large proportion. Nodes and hubs in the ncRNA network are significant research targets for cancer markers and diagnostics (Fig. 3). Many drug developments act on their interconnections with each other and represent a new direction in cancer therapy.

However, there are some obstacles to ncRNA therapy. First, the key point of ncRNA therapy is to deliver the therapeutic drug to the target cells effectively and induce specific inhibition of the target miRNA while not interfering with the normal miRNA activity. Because RNA interactions are a complex web, targeted drugs must not only be able to reach the target cells and cross heavy cellular structures but also be sufficiently RNA-specific. Beyond that, it is necessary to find the traffic hub on this network, not just a tiny node. In other words, the drug should act as a powerful target that can inhibit cancer progression rather than just one characteristic of cancer that can lead to possible drug resistance.

Author contributions

Y.Z. contributed to this work, wrote the paper, and curated the data. M.Y. revised the paper. F.H. and S.Y. contributed equally to this work; they were responsible for the idea, funding, and revision. All the authors have read and agreed to the published version of the manuscript.

References

[1] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin. 2019;69:7–34.
[2] Birney E, Stamatoyannopoulos JA, Dutta A, et al; Project Consortium ENCODE. Identification and analysis of functional elements in 1% of the human genome by the ENCODE pilot project. Nature. 2007;447:799–816.
[3] Dozorov MG, Giles CB, Koelsch KA, et al. Systematic classification of non-coding RNAs by epigenomic similarity. BMC Bioinf. 2013;14(Suppl 1):S5.
[4] Anastasiadou E, Jacob LS, Slack FJ. Non-coding RNA networks in cancer. Nat Rev Cancer. 2018;18:5–18.
[5] Zhang P, Wu W, Chen Q, et al. Non-coding RNAs and their integrated networks. J Integr Bioinform. 2019;16:20190027.
[6] Mattick JS, Makunin IV. Non-coding RNA. Hum Mol Genet 2006;15(Suppl 1):R17–R29.
[7] Pavet V, Portal MM, Moulin JC, et al. Towards novel paradigms for cancer therapy. Oncogene. 2011;30:1–20.
[8] Salmena L, Poliseno L, Tay Y, et al. A ceRNA hypothesis: the rosetta stone of a hidden RNA language? Cell. 2011;146:333–58.
[9] Wilkie GS, Dickson KS, Gray NK. Regulation of mRNA translation by 5′- and 3′-UTR-binding factors. Trends Biochem Sci. 2003;28:182–8.
[10] Ali Syeda Z, Langden SSS, Munkhuzi C, et al. Regulatory mechanism of MicroRNA expression in cancer. Int J Mol Sci. 2020;21:1723.
[11] Mayr C, Bartel DP. Widespread shortening of 3′UTRs by alternative cleavage and polyaenylation activates oncogenes in cancer cells. Cell. 2009;138:673–84.
[12] Sana J, Faltejskova P, Svoboda M, et al. Novel classes of non-coding RNAs and cancer. J Transl Med. 2012;10:103.
[13] Bartel DP. MicroRNAs: target recognition and regulatory functions. Cell. 2009;136:2615–33.
[14] Chen H, Xu Z, Liu D. Small non-coding RNA and colorectal cancer. J Cell Mol Med. 2019;23:3050–7.
[15] Romano G, Veneziano D, Aucuno M, et al. Small non-coding RNA and cancer. Carcinogenesis. 2017;38:485–91.
[16] Lee YS, Dutta A. MicroRNAs in cancer. Annu Rev Pathol. 2009;4:199–227.
[17] Kim JS, Kim EJ, Lee S, et al. MiR-34a and miR-34b/c have distinct effects on the suppression of lung adenocarcinomas. Exp Mol Med. 2019;51:1–10.
[18] Kim YH, Lee WK, Lee EB, et al. Combined effect of metastasis-related MicroRNA, miR-34 and miR-124 family, methylation on prognosis of non-small-cell lung cancer. Clin Lung Cancer. 2017;18:e13–20.
[19] Bader AG, miR-34 - a microRNA replacement therapy is headed to the clinic. Front Genet. 2012;3:120.
[20] Zheng F, Li J, Ma C, et al. Novel regulation of miR-34a-5p and HOTAIR by the combination of berberine and gefitinib leading to inhibition of EMT in human lung cancer. J Cell Mol Med. 2020;24:5378–92.
[21] Kasninski AL, Slack FJ. miR-34c prevents cancer initiation and progression in a therapeutically resistant K-ras and p53-induced mouse model of lung adenocarcinoma. Cancer Res. 2012;2;125:1362. J Clin Invest. 2014;124:1853–67.
[22] Xue W, Dahlman JE, Tammela T, et al. Small RNA combination therapy for lung cancer. Proc Natl Acad Sci USA. 2014;111:E5353–61.
[23] Rokavec M, Onen MG, Li H, et al. IL-6RSTAT3/miR-34a feedback loop promotes EMT-mediated colorectal cancer invasion and metastasis [published correction appears in J Clin Invest 2015 Mar 2;125:1362]. J Clin Invest. 2014;124:8576–87.
[24] Sherman EJ, Mitchell DC, Garner AL. The RNA-binding protein SART3 promotes miR-34a biogenesis and G1 cell cycle arrest in lung cancer cells. J Biol Chem. 2019;294:17188–96.
[25] Wang YS, Tseng HY, Chen YA, et al. MCT-1/miR-34a/IL-6/IL-6R signaling axis promotes EMT progression, cancer stemness and M2 macrophage polarization in triple-negative breast cancer. Mol Cancer. 2019;18:42.
[26] Valcour DM, Day ES. Dual regulation of miR-34a and notch signaling in triple-negative breast cancer by anti-body/miRNA nanocarriers. Mol Ther Nucleic Acids. 2020;21:290–8.
[27] Balzeau J, Menezes MR, Cao S, et al. The LIN28/let-7 pathway in cancer. Front Genet. 2017;8:31.
[28] Gibadulinova A, Bullova P, Strnad H, et al. CAIX-Mediated control of LIN28/let-7 axis contributes to metabolic adaptation of breast cancer cells to hypoxia. Int J Mol Sci. 2020;21:4299.
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...derived from longer non-coding RNAs. Biochimie. 2011;93:1905–15.

Geng L, Zhu B, Dai BH, et al. A let-7/Fas double-negative feedback loop regulates tumor promotion in colorectal cancer cell lines. Oncogene. 2016;35:4538–68.

Sand M, Hessam S, Amur S, et al. Expression of oncogenic miR-17-92 and tumor suppressive miR-143-145 clusters in basal cell carcinoma and cutaneous squamous cell carcinoma. J Dermatol Sci. 2017;86:142–8.

Yang C, Jia X, Zhou J, et al. The MiR-17-92 gene cluster is a blood-based marker for cancer detection in non-small-cell lung cancer. Am J Med Sci. 2020;360:248–60.

O’Donnell KA, Wente-ER, Zeller KL, et al. C-myc-regulated microRNAs modulate E2F1 expression. Nature. 2005;435:839–43.

Hao T, Wang Z, Yang J, et al. MALAT1 knockdown inhibits prostate cancer cell EMT and bone metastasis via NF-kappaB pathway. Cell Death Dis. 2018;9:1120.

Kim J, Piao HL, Kim BJ, et al. Long non-coding RNA MALAT1 suppresses breast cancer cell migration and invasion. Int J Cancer. 2015;137:120–7.

Du Y, Wei N, Ma R, et al. A miR-210-3p regulon that controls the Warburg effect by modulating HIF-1α and p53 activity in triple-negative breast cancer. Cell Death Dis. 2020;11:1731.

Fan J, Xu G, Zhang C, et al. miR-210 transferred by lung cancer cell-derived exosomes may act as promiogenic factor in cancer-associated fibroblasts by modulating JAK2/STAT3 pathway [published correction appears in Clin Sci (Lond) 2020 Jul 17;134:1801-1804]. Clin Sci (Lond). 2020;134:807–25.

Wang H, Wang L, Zhou X, et al. OSCC Exosomes regulate miR-210-3p targeting E2F1 in oral cancer. J Cell Physiol. 2020;235:3071-3081.

Wang H, Wang L, Zhou X, et al. Long non-coding RNA HOTAIR reprograms chromatin state to promote cancer metastasis. Nature. 2010;464:1071–6.

Ren Y, Ju HH, Xu YQ, et al. Paracrine and epigenetic control of CAF-induced metastasis: the role of HOTAIR regulated by TGF-β secretion. Mol Cancer. 2018;17:5.

Yang S, Xu J, Fan Z, et al. The long non-coding RNA HOTAIR enhances pancreatic cancer resistance to TNF-related apoptosis-inducing ligand. J Biomed Biotechnol. 2022;292:10390–7.

Ya M, Hu M, Zhou L, et al. Long non-coding RNA HOTAIR promotes cancer cell energy metabolism in pancreatic adenocarcinoma by upregulating hexokinase-2. Oncol Lett. 2019;18:2212–9.

Zhang F, Zhang J. Long non-coding RNA HOTAIR functions as miRNA sponge to promote the epithelial to mesenchymal transition in esophageal cancer. Biomed Pharmacother. 2017;90:888–96.

Li CH, Xiao Z, Tong JH, et al. EZH2 coupled with HOTAIR to silence MicroRNA-34a by the induction of heterochromatin formation in human pancreatic ductal adenocarcinoma. Int J Cancer. 2016;139:1209–17.

Goyal B, Yadav SRM, Awasthee N, et al. Diagnostic, prognostic, and therapeutic significance of long non-coding RNA MALAT1 in cancer. Biochim Biophys Acta Rev Cancer. 2021;1875:188502.

Gutscher T, Hammerle M, Eissmann M, et al. The noncoding RNA MALAT1 is a critical regulator of the metastasis phenotype of lung cancer cells. Cancer Res. 2013;73:1180–90.

Shen F, Chen L, Wang X, et al. Long non-coding RNA MALAT1 promotes brain metastasis by inducing epithelial-mesenchymal transition in lung cancer. J Neurooncol. 2015;121:101–8.

Duan G, Zhang C, Xu C, et al. Knockdown of MALAT1 inhibits osteosarcoma progression via regulating the miR-34a-cyclin D1 axis. Int J Oncol. 2019;54:17–28.

YiRen H, Ying Cong Y, Sunwu Y, et al. Long non-coding RNA MALAT1 regulates autophagy inhibiting epithelial-mesenchymal transition in breast cancer cell lines. Apoptosis. 2018;23:1305–12.

Shen F, Zhang H, Zhou L, et al. Overexpression of MALAT1 contributes to cervical cancer progression by acting as a sponge of miR-429. J Cell Physiol. 2019;234:11219–26.

Ye M, Dong S, Hou H, et al. Oncogenic role of long noncoding RNAMALAT1 in thyroid cancer progression through regulation of the miR-204/IGF2B2/6MA-MYC signaling. Mol Ther Nucleic Acids. 2020;23:1–12.

YiRen H, Ying Cong Y, Sunwu Y, et al. Long non-coding RNA MALAT1 regulates autophagy associated chemoresistance via miR-23b-3p sesteregression in gastric cancer. Mol Cancer. 2017;16:174.

Hao T, Wang Z, Yang J, et al. MALAT1 knockdown inhibits prostate cancer progression by regulating miR-140/BIRC6 axis. Biomed Pharmacother. 2020;123:109666.

Kim J, Piao HL, Kim BJ, et al. Long non-coding RNA MALAT1 suppresses breast cancer cell migration and invasion. Mol Cancer. 2015;14:60.

Dong D, Li C, Zhao T, et al. MALAT1 is a critical regulator of the metastasis phenotype of lung cancer cells. Cancer Res. 2013;73:1180–90.

GhafouriFard S, Esmaeili M, Taheri M. H19 lncRNA: Roles in tumor suppressors. Dev Biol. 2007;302:1–12.

Duan G, Zhang C, Xu C, et al. Knockdown of MALAT1 inhibits osteosarcoma progression via regulating the miR-34a-cyclin D1 axis. Int J Oncol. 2019;54:17–28.

Shen F, Zhang H, Zhou L, et al. Overexpression of MALAT1 contributes to cervical cancer progression by acting as a sponge of miR-429. J Cell Physiol. 2019;234:11219–26.

Ye M, Dong S, Hou H, et al. Oncogenic role of long noncoding RNAMALAT1 in thyroid cancer progression through regulation of the miR-204/IGF2B2/6MA-MYC signaling. Mol Ther Nucleic Acids. 2020;23:1–12.

Shen F, Zhang H, Zhou L, et al. Overexpression of MALAT1 contributes to cervical cancer progression by acting as a sponge of miR-429. J Cell Physiol. 2019;234:11219–26.

Hao T, Wang Z, Yang J, et al. MALAT1 knockdown inhibits prostate cancer progression by regulating miR-140/BIRC6 axis. Biomed Pharmacother. 2020;123:109666.
Tao F, Xu Y, Yang D, et al. LncRNA NKILA correlates with the malignant status and serves as a tumor-suppressive role in rectal cancer. J Cell Biochem. 2018;119:9809–16.

Huang D, Chen J, Yang L, et al. NKILA lncRNA promotes tumor immune evasion by sensitizing T cells to activation-induced cell death. Nat Immunol. 2018;19:1112–25.

Chan JJ, Tay Y. Noncoding RNA:RNA regulatory networks in cancer. Int J Mol Sci. 2018;19:1310.

Hansen TB, Jensen TI, Clausen BH, et al. Natural RNA circles function as efficient microRNA sponges. Nature. 2013;495:384–8.

Kristensen LS, Andersen MS, Stagsted LJV, et al. The biogenesis, biology and characterization of circular RNAs. Nat Rev Genet. 2019;20:675–91.

Wang Y, Xu R, Zhang D, et al. Circ-ZKSCAN1 regulates FAM83A expression and inactivates MAPK signaling by targeting miR-330-5p to promote non-small cell lung cancer progression. Transl Lung Cancer Res. 2019;8:862–75.

Hong W, Xue M, Jiang J, et al. Circular RNA circ-CPA4/let-7 miRNA/PD-L1 axis regulates cell growth, stemness, drug resistance and immune evasion in non-small cell lung cancer (NSCLC). J Exp Clin Cancer Res. 2020;39:149.

Zhou SY, Chen W, Yang SJ, et al. Circular RNA circVAPA regulates breast cancer cell migration and invasion via sponging miR-130a-5p. Epigenomics. 2020;12:303–17.

Song X, Liang Y, Sang Y, et al. circHMCU promotes proliferation and metastasis of breast cancer by sponging the let-7 family [published correction appears in Mol Ther Nucleic Acids 2021 Nov 18;26:1240]. Mol Ther Nucleic Acids. 2020;20:518–33.

Zhi Q, Fan D, Ren R, et al. Circular RNA profiling identifies circ102049 as a key regulator of colorectal liver metastasis. Mol Oncol. 2021;15:623–41.

Liu Y, Chen S, Zong ZH, et al. CircRNA WHSC1 targets the mtr-646/NPM1 pathway to promote the development of endometrial cancer. J Cell Mol Med. 2020;24:6898–907.

Liu J, Xue N, Guo Y, et al. CircRNA_100367 regulates the radiation sensitivity of esophageal squamous cell carcinomas through miR-217/Wnt3 pathway [published correction appears in Aging (Albany NY) 2021 Oct 31;13:23886-23870]. Aging (Albany NY). 2019;11:12412–27.

Feng Y, Yang Y, Zhao X, et al. Circular RNA circ0005276 promotes the proliferation and migration of prostate cancer cells by interacting with FUS to transcriptionally activate XIAP. Cell Death Dis. 2019;10:792.

Zhu YJ, Zheng B, Luo GJ, et al. Circular RNAs negatively regulate cancer stem cells by physically binding FMRP against CCAR1 complex in hepatocellular carcinoma. Theranostics. 2019;9:3526–40.

Chen D, Ma W, Ke Z, et al. CircRNA hsa_circ_100395 regulates miR-1228/TCF21 pathway to inhibit lung cancer progression. Cell Cycle. 2018;17:2080–90.

Zhang Y, Dai J, Deng H, et al. miR-1228 promotes the proliferation and metastasis of hepatoma cells through a p53 forward feedback loop. Br J Cancer. 2015;112:365–74.

Mayr C. Regulation by 3'-Untranslated Regions. Annu Rev Genet. 2017;51:171–94.

Vislovukh A, Vargas TR, Polleskaya A, et al. Role of 3'-untranslated region translational control in cancer development, diagnostics and treatment. World J Biol Chem. 2014;5:450–57.

Vikesa J, Hansen TV, Jonson L, et al. RNA-binding IMPs promote cell adhesion and invadopodia formation. EMBO J. 2006;25:1456–68.

Rivera Vargas T, Boudoukha S, Simon A, et al. Post-transcriptional regulation of cyclins D1, D3 and G1 and proliferation of human cancer cells depend on IMP-3 nuclear localization. Oncogene. 2014;33:2866–75.

Barreau C, Paillard L, Osborne HB. AU-rich elements and associated factors: are there unifying principles? Nucleic Acids Res. 2006;33:7138–50.

Yang SW, Li L, Connelly JP, et al. A cancer-specific ubiquitin ligase drives mRNA alternative polyadenylation by ubiquitinating the mRNA 3' end processing complex. Mol Cell. 2020;77:1206–1221.e7.

Jia Q, Nie H, Yu P, et al. HNRNPA1-mediated 3' UTR length changes of HN1 contributes to cancer- and senescence-associated phenotypes. Aging (Albany NY). 2019;11:4407–37.

Zhang C, Huang S, Zhang H, et al. YTHDF2 promotes the liver cancer stem cell phenotype and cancer metastasis by regulating OCT4 expression via m6A RNA methylation. Oncogene. 2020;39:4507–18.

Chen J, Kastan MB. 5'-3'UTR interactions regulate p53 mRNA translation and provide a target for modulating p53 induction after DNA damage. Genes Dev. 2010;24:2146–56.

Zhang A, Zhou N, Huang J, et al. The human long non-coding RNA RoR is a p53 represser in response to DNA damage. Cell Res. 2013;23:340–50.

Khan D, Sharaathchandra A, Ponnuswamy A, et al. Effect of a natural mutation in the 5' untranslated region on the translational control of p53 mRNA. Oncogene. 2013;32:4148–39.

Mosner J, Mammenbrauer T, Bauer C, et al. Negative feedback regulation of wild-type p53 biosynthesis. EMBO J. 1995;14:4442–9.

Zhang A, Xu M, Mo YY. Role of the lncRNA-p53 regulatory network in cancer. J Mol Cell Biol. 2014;6:181–91.

Alon U. Network motifs: theory and experimental approaches. Nat Rev Genet. 2007;8:450–61.

Salmena L, Poliseno L, Tay Y, et al. A ceRNA hypothesis: the Rosetta Stone of a hidden RNA language? Cell. 2011;146:353–8.

Karreth FA, Pandolfi PP. ceRNA crosstalk in cancer: when ce-bling rivalries go awry. Cancer Discov. 2013;3:1113–21.

Tang W, Fu K, Sun H, et al. CircRNA microarray profiling identifies a novel circulating biomarker for detection of gastric cancer. Mol Cancer. 2018;17:137.

Chen Y, Xie C, Zheng X, et al. LIN28/let-7/PD-L1 pathway as a target for cancer immunotherapy. Cancer Immunol Res. 2019;7:487–97.

Slaby O, Laga R, Sedlack O. Therapeutic targeting of non-coding RNAs in cancer. Biochem J. 2017;474:4219–51.