Application of non-coding RNAs in tumors (Review)

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Received October 20, 2024; Accepted January 31, 2025

DOI: 10.3892/mmr.2025.13529

Abstract. Tumors are associated with the highest mortality rates worldwide. For more than a decade, research has focused on the genetic involvement of proteins in cancer; however, a complete class of molecular non-coding (nc)RNAs have been discovered in recent years, and these are considered to be associated with cancer. Notably, ncRNAs are highly conserved and multifunctional. These interact with multiple signaling pathways, influencing cell cycle progression and various physiological processes. Therefore, the present review aimed to investigate ncRNA, microRNA, transfer RNA-derived small RNA, PIWI-interacting RNA and long non-coding RNA to further understand the associated generation processes, functional mechanisms and therapeutic roles in tumors. The present review demonstrated the critical role of ncRNAs in tumors, and may provide a novel theoretical basis for the role of ncRNAs as biomarkers or therapeutic tools in the treatment of cancer.

Contents

1. Introduction

Cancer is associated with high mortality rates worldwide. Notably, DNA fragments produce non-coding (nc)RNA, which was previously referred to genetic detritus, as they were considered to be non-functioning (1). Following the discovery of nucleic acids by Friedrich Miescher in 1871 (2), DNA and RNA were recognized as the genetic code containing the information required for correct cellular functioning. The Encyclopedia of the Elements of DNA (ENCODE) Transcriptome Project determined that ncRNAs account for a large fraction of nucleic acids, with protein-coding genes accounting for ~1.2% of the genome. By contrast, >80% of the genome is actively translated into different types of ncRNAs (3). Results of previous studies demonstrate that ncRNAs are crucial in numerous diseases; for example, ncRNAs cause disruption of healthy tumor function and control the expression of genes involved in tumor growth. Therefore, ncRNAs may play an important role in tumors (4-7). ncRNAs exhibit a wide range of diversity, including micro(mi)RNAs, PIWI-interacting (pi)RNAs, transfer RNA-derived small RNA (tsRNAs), small nucleolar RNA, small interfering (si)RNA, long ncRNAs (lncRNAs) and circular (circ)RNAs. Different types of ncRNAs exhibit specific regulatory roles and processes in numerous malignancies, forming complex networks. For example, results of a previous study showed that miRNAs may affect protein expression through binding to mRNA; however, results of a more recent study demonstrate that mRNAs are also found in the nucleus, suggesting that miRNAs may directly affect DNA through miRNAs, which also interact with other ncRNAs (8). In addition, specific RNAs encode peptides or proteins, leading to the development of novel therapeutic strategies for the treatment of cancer (9). Numerous ncRNAs exhibit high levels of stability in the bloodstream, highlighting their suitability in clinical cancer detection. In addition, results of a previous study showed that ncRNAs may act as targets for tumor therapy (4).

Therefore, the present review aimed to examine the characteristics and functions of short ncRNAs, including miRNAs, siRNAs, tRFs and lncRNAs. It described the distinct pathways and various functions of these ncRNAs in different types of cancer and aimed to review the potential of liquid biopsy biomarkers for early diagnosis or late prognosis in clinical settings. In conclusion, the present review may provide a novel theoretical basis for the role of ncRNAs in advanced cancer therapies and diagnostics.

2. Function of ncRNAs in tumors

Research has focused on the specific role of ncRNAs in numerous cancers, and results have demonstrated that these

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Key words: cancer, long non-coding RNA, microRNA, PIWI-interacting RNAs, transfer RNA-derived small RNA, non-coding RNA

may promote or inhibit cancer through various modes of action (Table I). Therefore, ncRNAs may exhibit potential as therapeutic options for the treatment of cancer.

miRNAs. In 1993, miRNAs were initially discovered in the cryptic nematode *Hidradenitis elegans* (10). However, it was not until 2002 that genomic alterations were uncovered in the miR-15a/16 cluster in leukemia (11), providing evidence for the association between miRNAs and human cancers. miRNAs are a type of small molecule RNA that are ~22 nucleotides in length, and are transcribed into a primary miRNA (pri-miRNA) by polymerase II (Pol II). Notably, pre-miRNA is processed through a complex consisting of ribonucleic acid endonuclease III, termed Drosha, and the protein, DGCR8. During this process, the pre-miRNA stem-loop enzyme is created and this enters the cytoplasm via exportin-5. Following entry into the cytoplasm, pre-miRNA is further processed by Dicer and the associated auxiliary proteins for the generation of miRNA duplexes, where mature miRNA binds to a member of the Argonaute family of proteins to form the RNA-induced silencing complex. Notably, binding to the 3' untranslated region (3'UTR) of mRNA may lead to degradation and translational repression (12) (Fig. 1). The genetic silencing of miRNAs plays a role in various mechanisms (13).

miRNAs exhibit key roles in cancer, both as oncogenes that promote tumor development and as tumor suppressors that inhibit development. Results of a previous study demonstrated that the expression of miRNA-199 was decreased in non-small cell lung cancer, and this miRNA was associated with cancer stage, the presence of distant metastasis and a negative prognosis (14). Notably, miRNA-129-5p may reduce the growth and spread of non-small cell lung cancer cells, and inhibit the formation of blood vessels that support tumor growth through VEGF (15). Results of a further previous study showed that miRNA-192 and -215 were upregulated in gastric cancer, affecting cell proliferation and migration through APC-mediated activation of the Wnt/β-catenin signaling pathway and thus leading to gastric cancer progression and the discovery of potential targets (16). The exosome miR-519a-3p induces liver metastasis of gastric cancer through M2 macrophage polarization and previous results showed that miR-519a-3p expression is significantly increased in the absence of liver metastasis. Therefore, miR-519a-3p may exhibit potential in the treatment of gastric cancer with liver metastasis (17). The abnormal expression of miRNAs has also been observed in breast cancer (BC). Through regulation of the NAT1 enzyme, miR-6744-5p promotes the apoptosis of cancer cells, inhibiting BC development by mediating the regulation of anoikis (18). In colorectal cancer, miR-1538 expression is reduced, leading to the suppression of cell proliferation and cancer progression through reduced levels of DNA methylase transferase 3A (DNMT3A) (19). Xiao *et al* (20) demonstrate that exosome miR-10527-5p is reduced in the serum of patients with lymph node metastasis, leading to reduced esophageal squamous cell carcinoma (ESCC) cell migration and invasion, and inhibition of ESCC lymphatic translocation through Rab10-mediated Wnt/β-catenin signaling (20). Notably, miRNAs exhibit diverse functions across various types of cancer. For example, miR-200a may play a role in colorectal cancer progression, affecting the prognosis of patients with this disease. However, miR-200a may also contribute to cervical carcinogenesis through regulation of the HIF-1α/VEGF signaling pathway. Results of further previous studies show that miR-200a may inhibit gastric cancer cell growth by targeting KLF12 (21-23). Collectively, these results highlight the complexity and diversity of cancers and the differing roles of miRNAs in cancer regulation.

miRNAs and therapy. miRNAs demonstrate key roles in cancer progression and development, using a variety of mechanisms that may affect genesis. Therefore, research has focused on the use of miRNA-based tumor therapy in the treatment of cancer. In a previous study, mRNA-targeted therapy was examined through the design of oligonucleotides that bind to mRNAs, thereby altering protein formation to affect disease processes (24). In addition, miRNAs may play key roles as potent tumor suppressors and oncogenes, highlighting the potential of miRNAs as novel therapeutic agents in the treatment of disease. Notably, alterations in pathological miRNA expression may be modified or reversed using molecule penetration, siRNA silencing and miRNA sponging (25). A previous clinical trial (trial no. NCT01829971) investigated the use of MRX34, a mimic of miR-34a, in the treatment of patients with hepatocellular carcinoma (26). However, this trial was ended prematurely, as four patients developed liver cancer as a result of drug dosage and severe immune adverse reactions (27,28). At present, a clinical trial involving the treatment of patients with gastric cancer is ongoing, in which miRNA measurements are obtained in response to treatment with capecitabine + cisplatin or capecitabine + oxaliplatin +/- trastuzumab (trial no. NCT03253107). Notably, miRNA-138 demonstrates potential as a therapeutic target in ovarian cancer and regulates pancreatic cancer cell growth by targeting FOXCI (29,30). Results of a previous study show the potential role of miRNA-138 as a target in the treatment of colorectal cancer, which interacts with the 3'UTR of PD-1 (31).

tsRNA. At present, research is focused on a novel form of ncRNA, tsRNA, due to advances in high-throughput sequencing. tsRNAs are tRNA-derived small RNAs that are widely distributed in the transcriptomes of eukaryotic and prokaryotic organisms. tRNAs primarily function as carriers of amino acids, facilitating the synthesis of proteins. They are transcribed into pre-tRNAs by Pol III, and undergo a series of modifications to generate mature tRNA. Notably, tRNAs are highly folded into a structure consisting of four arms and three loops (32) as shown in Fig. 2. tRNAs produce different tsRNAs depending on the cleavage site at which they are generated. There are two main categories of tsRNAs; tRNA-derived fragments (tRFs) and tRNA-derived stress-inducible RNAs (tiRNAs). As shown in Fig. 2, tRFs are generated following Dicer-mediated cleavage of mature tRNA, a process that occurs in the cytoplasm. By contrast, tiRNAs are generated following the accumulation of angiotensin (ANG) in the cytoplasm (33). Notably, some tsRNAs may also be located in the mitochondria, referred to as mt-tRNAs, and further investigations into the association between tsRNA and mt-tRNA may lead to further understanding of the mechanisms underlying tsRNA (33). Results of a previous study show that tsRNA performs various functions, including epigenetic regulation,

Table I. Mechanisms of non-coding RNAs in different types of cancer.

First author/s, year	ncRNA	ncRNA type	Type of tumor	Function	Mechanism	(Refs.)
Su *et al*, 2019	miRNA-199	miRNA	LC	Tumor inhibitors	Inhibits cell proliferation and invasion	(14)
Cheng *et al*, 2019	miRNA-129-5p	miRNA	LC	Tumor inhibitors	Inhibits the proliferative ability and invasiveness of LCa cells and tumor angiogenesis by interacting with VEGF	(15)
Deng *et al*, 2020	miRNA192, -215 miRNA	miRNA	GC	Oncogenes	Activation of Wnt/β-catenin signaling pathway in gastric cancer by APC	(16)
Qiu *et al*, 2022	miR-519a-3p	miRNA	HCC	Oncogenes	Promotes liver metastasis by M2 macrophage polarization	(17)
Malagobadan *et al*, 2020	miR-6744-5p	miRNA	BC	Tumor inhibitors	Inhibition of cancer progression through NAT1 enzyme-mediated and regulated anaerobic responses	(18)
Xiao *et al*, 2023	miR-10527-5p	miRNA	ESCC	Tumor inhibitors	Lymphatic metastasis of ESCC is inhibited by Wnt/β-Catenin signaling of Rab10	(20)
Ying *et al*, 2024	3' tiRNA LysTTT	tsRNA	BCa	Oncogenes	Modified by m7G modifying enzyme mettl1, it is found to bind to Annexin A2 tumor protein and promote cancer progression	(40)
Xiong *et al*, 2024	tiRNA-Val-CAC-2	tsRNA	PC	Oncogenes	Binds to FUBP1 protein, promotes the transcription of c-MYC, and promotes cell proliferation	(41)
Xu *et al*, 2022	tRF-Val-CAC-016	tsRNA	GC	Tumor inhibitors	Binding to CACNA1d protein mediates the classical MAPK signaling pathway and inhibits the malignant progression of gastric cancer	(42)
Zhang *et al*, 2024	tRF-23-Q99P9P9NDD	tsRNA	GC	Oncogenes	Binding to the target protein ACADSB protein promotes the development of gastric cancer	(43)
Yang *et al*, 2022	AS-tDR-007333	tsRNA	NSCLC	Oncogenes	Through the HSPB1/MED29 and ELK4/MED29 axes, the MED29 promoter is activated to promote cancer	(46)
Tao *et al*, 2021	5'tiRNA-His-GTG	tsRNA	CRC	Oncogenes	In the hypoxic microenvironment, it binds to LATS2 protein through the HIF1α/angipoietin axis to promote cancer progression	(45)
Xie *et al*, 2022	piRNA-14633	piRNA	Cervical cancer	Oncogenes	Increase m6A RNA methylation level and METTL14 mRNA stability, promote cell proliferation and cancer progression	(51)
Liu *et al*, 2023	piRNA-18	piRNA	CRC	Tumor inhibitors	Promotes apoptosis, cessation of the G_1/S phase in the cell cycle, and thus inhibits cancer	(54)
Peng *et al*, 2024	piRNA-4447944	piRNA	PCA	Oncogenes	Inhibits tumor suppressor NEFH, prevents apoptosis and promotes cell proliferation and migration to ultimately achieve the promoting effect	(55)
Ben *et al*, 2024	PROPER	piRNA	PCA	Oncogenes	Promote the interaction of RNA-binding proteins between EIF2S3 and YTHDF2/YBX3, promote DUSP1 cyclization, and ultimately lead to the malignant occurrence of PCa	(56)

Table I. Continued.

First author/s, year	ncRNA	ncRNA type	Type of tumor	Function	Mechanism	(Refs.)
Hua *et al*, 2019	lncRN ALINC01123	lncRNA	NSCLC	Oncogenes	By interacting with miR-199a-5p sponge, it promotes cell proliferation and glycolysis	(65)
Zhang *et al*, 2023	SPRY4-IT1	lncRNA	BC	Oncogenes	Promoted by pyruvate dehydrogenase kinase 1, it promotes the expression and stability of SPRY4-IT1 and ultimately promotes cell proliferation	(66)
Zhou *et al*, 2022	STEAP3-AS1	lncRNA	CRC	Oncogenes	STEAP3-AS1 competes with YTHDF2 to protect against m6A-mediated degradation and further activatesWnt/β-catenin signaling to promote CRC cell proliferation and development	(67)
Wang *et al*, 2023	FTO-IT1	lncRNA	HCC	Oncogenes	FTO promotes HCC tumorigenesis by reducing the modification of m6A by glycolytic genes GLUT1, PKM2 and c-Myc	(68)
Huang *et al*, 2021	PSMA3-AS1	lncRNA	GBM	Oncogenes	Effects miR-411-3p is down-regulated in glioma cells and promotes the malignant progression of glioma by regulating HOXA10 protein	(70)
Yang *et al*, 2024	LINC01133	lncRNA	PDAC	Oncogenes	The expression of secretory phospho-protein 1 was up-regulated, resulting in epithelial-mesenchymal transition in pancreatic ductal adenocarcinoma and promoting malignant progression	(72)
Fang *et al*, 2022	TP53TG1	lncRNA	GC	Tumor inhibitors	M6A modification mediates interaction with cellular inhibitor phosphatase 2A	(74)
Kong *et al*, 2019	MORT	lncRNA	HCC	Tumor inhibitors	MORT overexpression inhibits the expression of NOTCH1, thereby reducing cell proliferation and invasion	(71)
Wang *et al*, 2024	PGM5-AS1	lncRNA	LC	Tumor inhibitors	Acts with miR-423-5p to promote apoptosis, resulting in G_0/G_1 cell cycle arrest	(75)
Hu *et al*, 2024	PRDM16-DT	lncRNA	CRC	Tumor inhibitors	PRDM16-DT reduces chemo-resistance by competing with HNRNPA2B1 and binds to FOXP3 to inhibit cell metastasis	(76)

GC, gastric cancer; HCC, hepatocellular carcinoma; LC, lung cancer; CRC, colorectal cancer; GBM, glioblastoma; PDAC, pancreatic adeno-carcinomas; BC, breast cancer; NSCLC, non-small cell lung cancer; PCA, prostatic cancer; ESCC, esophageal squamous cell cancer; miRNA, microRNA; lncRNA, long non-coding RNA; tsRNA, transfer RNA-derived small RNAs; piRNA, PIWI-interacting RNAs; VEGF, vascular endothelial growth factor; APC, protein phosphatase 1; NAT1, N-acetyltransferase 1; FUBP1, far upstream element binding protein 1; CACNA1d, calcium voltage-gated channel subunit α1 D; PKM2, pyruvate kinase 2; HOXA10, homeobox A10; MED29, mediator complex subunit 29; YTHDF2, YTH N6-methyladenosine RNA binding protein F2; HNRNPA2B1, heterogeneous nuclear ribonucleoprotein A2/B1; FOXP3, forkhead box P3; FTO, FTO α-ketoglutarate dependent dioxygenase; DUSP1, dual specificity phosphatase 1; NEFH, neurofilament heavy chain; SPRY4-IT1, SPRY4 intronic transcript 1; EIF2S3, eukaryotic translation initiation factor 2 subunit γ; LATS2, large tumor suppressor kinase 2; ACADSB, acyl-CoA dehydrogenase short/branched chain; HSPB1, heat shock protein family B (small) member 1; YTHDF2, YTH N6-methyladenosine RNA binding protein F2; YBX3, Y-box binding protein 3; STEAP3-AS1, STEAP3 antisense RNA 1; NOTCH1, notch receptor 1; GLUT1, glycolysis-associated genes; HSPB1, heat shock protein family B (small) member 1; Rab10, RAB10, member RAS oncogene family.

post-transcriptional modification (34) and participation in RNA interference. tsRNA was initially discovered in urine; therefore, tsRNA was considered a product of degradation. However, further previous studies demonstrated that tsRNAs

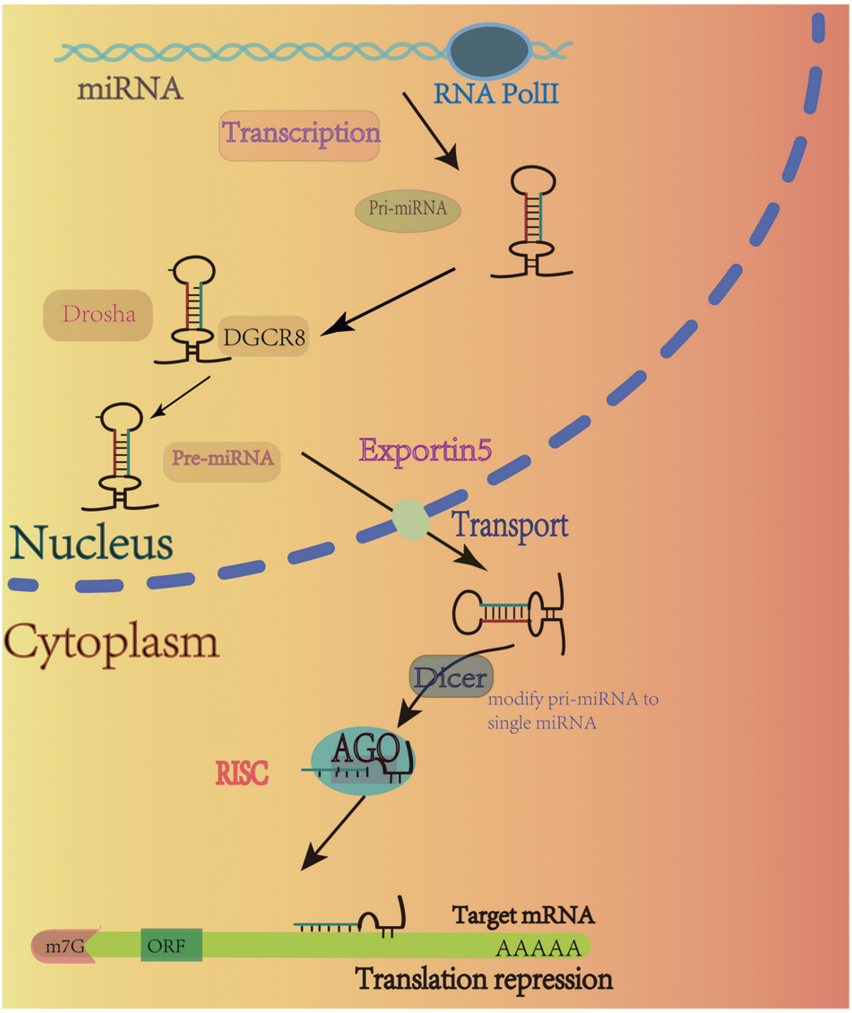

Figure 1. Canonical miRNA biosynthesis. Initially, primary miRNA transcripts (pri-miRNAs) are transcribed by RNA polymerase II from the miRNA gene. Then, pri-miRNAs are processed by DGCR8 and Drosha to generate precursor miRNAs (pre-miRNAs) that are exported into the cytoplasm by Exportin 5. Subsequently, Dicer recognizes and cleaves the pre-miRNA. Finally, the resulting miRNA duplex binds to the AGO protein and matures into a single-stranded miRNA. miRNA, microRNA; pri-mRNA, primary miRNA; AGO, Argonaute; RISC, RNA-induced silencing complex.

play essential roles in numerous biological activities, including cell proliferation, cell migration, cancer cell progression (35,36), DNA damage (37), sperm modification (38) and epigenetic modifications (39). Therefore, further investigations into the role of tsRNAs in tumors are required.

tsRNAs exhibit potential as oncogenes and are involved in gene regulation in a variety of types of cancer. Results of a previous study showed that m7G-3' tiRNA LysTTT interacts with tumor protein ANXA2 following methyltransferase-like protein (METTL)11-mediated modification. This interaction results in the phosphorylation of Tyr24 in the protein, facilitating cell proliferation and migration and the advance of bladder cancer (40). In addition, Xiong *et al* (41) demonstrated that tiRNA-Val-CAC-2, a stress tsRNA, is highly expressed in pancreatic cancer. Results of this study show that tiRNA-Val-CAC-2 binds to the Far upstream element-binding protein 1 (FUBP1) protein in pancreatic cancer cells, thereby promoting the transcription of c-MYC, which, in turn, increases the stability of FUBP1. Notably, metastasis is inhibited following FUBP1 knockdown, highlighting the potential of tiRNA-Val-CAC-2 as a biomarker for pancreatic cancer (41). In addition, results of a previous study show that tRF-Val-CAC-016 expression is reduced in gastric cancer and this tRF mediates the classical MAPK signaling pathway by binding to the downstream Calcium Voltage-Gated Channel Subunit Alpha1 D protein (42). This study demonstrates that increased tRF-Val-CAC-016 expression inhibits gastric cancer cell proliferation, migration and invasion, and cell proliferation is inhibited following knockdown. Therefore, tRF-Val-CAC-016 may inhibit gastric cancer development, highlighting the potential of this tRF as a therapeutic target in the treatment of gastric cancer (42). As an oncogene, tRF-23-Q99P9P9NDD is highly expressed in gastric cancer, promoting cancer development through binding to the Acyl-CoA dehydrogenase short/branched chain target protein (43). Moreover, tRF-17-79MP9PP expression is reduced in BC and tRF-17 reduces cell invasion and migration by binding to THBS1 (44). Results of a previous study show that stress tsRNA, 5'tiRNA-His-GTG, is differentially expressed in colorectal cancer. Notably, this tsRNA is regulated through the HIF1α/ANG axis in a hypoxic microenvironment and LATS2 acted as the target gene of 5'tiRNA-His-GTG. Following binding to the protein, cell apoptosis is suppressed, thereby promoting the progression of colorectal cancer (45).

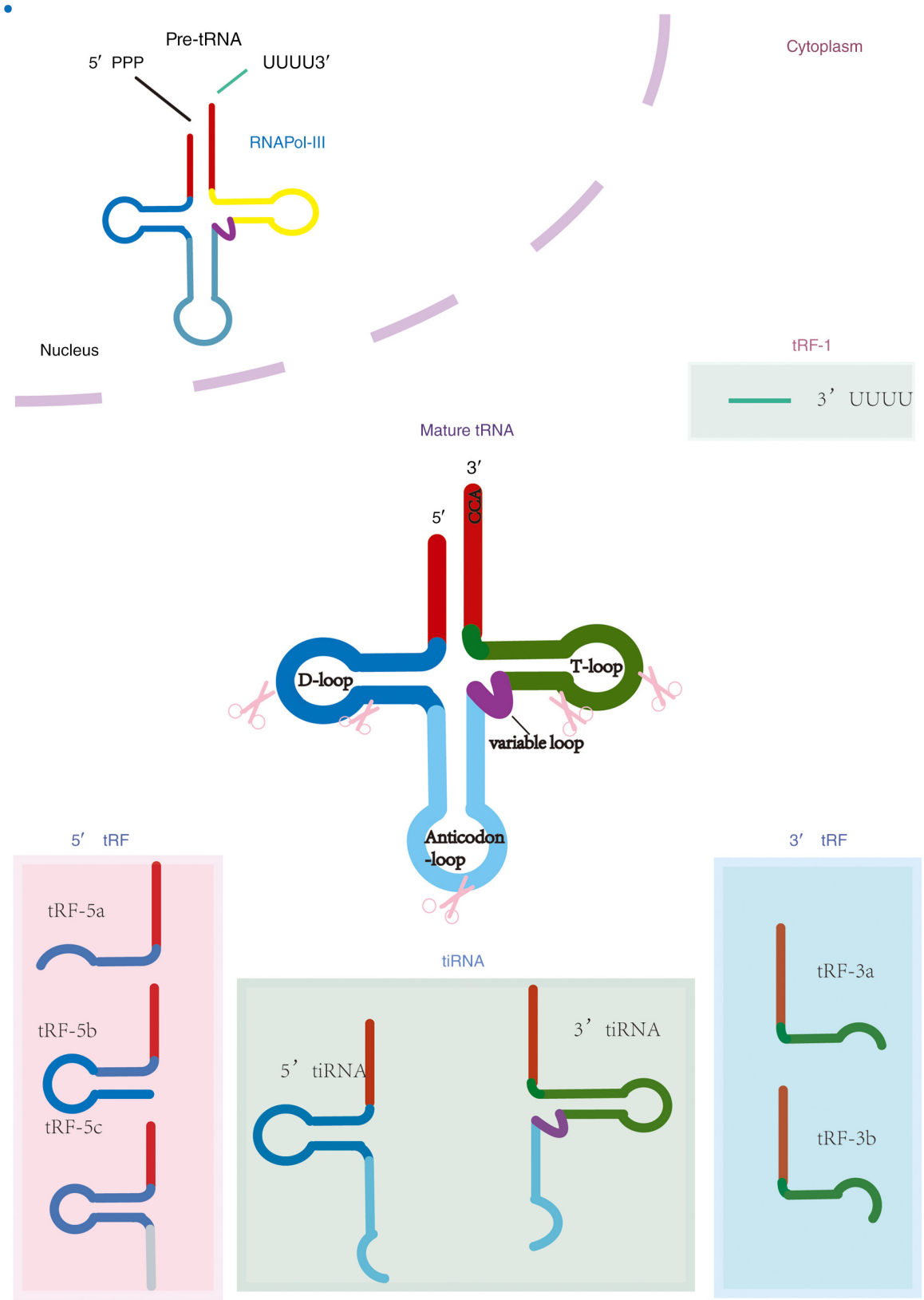

Figure 2. Canonical tsRNA biosynthesis. The tRNAs are divided into pre-tRNAs and mature tRNAs, which can be categorized into different types due to different splice sites and modification points. These six types, although cleaved from a single tRNA, have different functions and roles and the mechanism is not yet clear. tsRNA, tRNA-derived small RNA; tRNA, transfer RNA; tRF, telomeric repeat-binding factor; tiRNA, tRNA-derived stress-induced small RNAs.

In addition, AS-tDR-007333 is markedly upregulated in non-small cell lung cancer through two modes of action; the HSPB1/MED29 and the ELK4/MED29 axes. Notably, AS-tDR-007333 activates the MED29 promoter protein in both pathways to promote non-small cell lung cancer cell proliferation and migration (46).

piRNAs. Piwi interactors, known as piRNAs, are a group of ncRNAs that range from 24-31 nucleotides in length. With ~20,000 different combinations, piRNAs primarily bind to the piwi protein family, playing a crucial role in the regulation of various biological processes. Notably, piRNAs are expressed in eukaryotes and produced in the nucleus, where they are transcribed into precursor piRNA. With the assistance of cofactors, precursor piRNAs transform into piRNA intermediates containing 5' uracil (47). These intermediates bind the aforementioned cofactors to the Zuc-split-open piwi to generate complexes in the cytoplasm (47). piRNAs have been extensively studied in the field of reproductive biomedicine and directing the silencing of transcribed genes was considered the first functional role of these ncRNAs. Notably, this is categorized into the silencing of transposons and other repetitive sequences. piRNAs exhibit transcriptional and post-transcriptional silencing (48) and may act synergistically with other RNAs. For example, piRNAs and circRNAs play key roles in gene immunity due to their anti-degradation properties, regulating PD-L1 expression for immunization (49). In addition, piwil2 induces Argonaute protein, which mediates RNA cleavage in the presence of piwi and promotes gene silencing when expressed in miRNA precursors in human cells (50). Results of a previous study show that piRNA-14633 was expressed at high levels in cervical cancer and this piRNA may play a role in promoting cellular proliferation. In addition, METTL14 knockdown reverses piRNA-mediated proliferation and invasion (51). Previous studies show that piRNA-651 expression is increased in BC, leading to DNMT1-mediated phosphatase methylation of the PTEN promoter, ultimately promoting the progression of BC and dysregulation of non-small cell lung cancer through cyclin D1 and CDK4 (52,53). In addition, results of a previous study show that piRNA-18 suppresses the migration and invasion of colorectal cancer cells, both *in vivo* and *in vitro*. Notably, piRNA-18 may promote apoptosis and induce cell cycle arrest in the G_1/S phase. Collectively, these findings suggested that piRNA-18 may play a crucial role in inhibiting the progression of colorectal cancer (54).

Depopulation-resistant prostate cancer (CRPC) is associated with high mortality rates and piRNA-4447944 expression is increased in CRPC. piR-4447944/PIWIL2 binding inhibits the tumor suppressor NEFH, ultimately reducing apoptosis and promoting cell proliferation and migration to promote depopulation-resistant cancer cell growth (55). Moreover, a specific genetic variant, rs17201241, interacts with the piRNA PROPER to promote RNA-binding protein interactions between EIF2S3 at the 5'UTR and YTHDF2/YBX3 at the 3'UTR. This leads to the promotion of DUSP1 cyclization, ultimately leading to prostate cancer progression (56).

lncRNAs. lncRNAs are often produced following Pol II-mediated transcription and are >200 nucleotides in length. lncRNAs are capped and polyadenylated to ensure their stability (57). According to the ENCODE project report (3), the majority of the genome is transcribed into lncRNAs. There are different categories of lncRNAs based on their location in the genome, including intergenic long-chain ncRNAs, intronic long-chain ncRNAs, positive-strand ncRNAs and translational long-chain ncRNAs. lncRNAs also possess pairs of isoforms, such as circular (circ)RNA and competing endogenous (ce)RNA. Notably, lncRNAs are not highly evolutionarily conserved and therefore exhibit a high degree of specificity (58). lncRNAs are highly abundant in the nucleus, with localization dictating their function. Results of a previous study show that some lncRNAs may shuttle between the cytoplasm and the nucleus (59). Notably, lncRNAs were initially discovered as part of a group of genes that play a role in modifying chromosomes. These genes, known as xist, are only expressed in females and are responsible for silencing one of the X chromosomes to compensate for gene expression. Results of a previous study showed that xist contributes to a higher prevalence of autoimmune disease in females (60). Notably, lncRNAs demonstrate a higher level of stability in the cytoplasm, interacting with proteins to influence mRNA translation modification and the promotion of decay (61). In addition, lncRNAs also exhibit direct interactions with ribosomes, exporting them to the cytoplasm via organelles, including the Golgi apparatus and mitochondria (61,62). lncRNAs are complex with multiple transcription sites and these may affect gene expression both near to and at a distance from the transcription site (63). In addition, lncRNAs undergo splicing, leading to the development of multiple isoforms. However, investigations into these isoforms are limited. A previous study shows that certain lncRNAs encode peptides and proteins (64).

Oncogenes. lncRNAs may affect the regulation of oncogenes, such as miRNAs, and may also exhibit potential as oncogenes (57). The glycolytic pathway plays a crucial role in the association between lncRNAs and tumors. Newly-discovered lncRNAC01123 exhibits distinct gene expression patterns in both serum and tissues and is transcribed by c-Myc, a protein that enhances cell proliferation and glycolysis. A previous study shows that lncRNAC01123 functions through interacting with miR-199a-5p (65). This lncRNA also functions through enzymes involved in glycolysis, such as pyruvate dehydrogenase kinase 1 (PDK1). A previous study shows that increased SPRY4-IT1 expression is mediated by PDK1 in BC, leading to increased protein stability. This leads to the promotion of cell proliferation and inhibition of apoptosis, further contributing to BC progression (66). Some lncRNAs also function through RNA modification, such as m6A modification. A previous study shows that STEAP3-AS1 is expressed at high levels in colorectal cancer tissues, competing with YTHDF2 for binding to protect STEAP3 from m6A-mediated degradation. This results in the production of Fe^{2+} and the phosphorylation of glycogen synthase kinase 3β. This activation further promotes the Wnt/β-catenin signaling pathway, ultimately contributing to the proliferation and development of colorectal cancer (67). Moreover, lncRNA FTO-IT1 interacts with α-ketoglutarate-dependent dioxygenase FTO, a demethylase of m6A, in hepatocellular carcinoma. This interaction leads to the promotion of cell proliferation through glycolysis. In addition, FTO may contribute to hepatocellular carcinoma tumorigenesis by reducing the m6A-mediated modification of GLUT1, PKM2 and c-Myc (68).

Results of a previous study also show that lncRNAs play key roles as ceRNAs, where two RNAs act synergistically to promote cellular dysregulation. For example, PSMA3-AS1, an antisense lncRNA, is expressed at high levels in colorectal

Table II. Non-coding RNA as biomarkers.

First author/s, year	Name	ncRNA type	Cancer	Biomarkers	(Refs.)
Zhang *et al*, 2016	lncRNA H19	lncRNA	BC	Diagnosis	(80)
Han *et al*, 2023	lncRNA H19	lncRNA	THCA	Diagnosis, prognosis	(81)
Li *et al*, 2023	ENST00000503625	lncRNA	PCA	Prognosis	(89)
Wu *et al*, 2024	SNHG1	lncRNA	CRC	Prognosis	(88)
Li *et al*, 2024	tRF-33- RZYQHQ9M739P0J	tsRNA	GC	Diagnosis, prognosis	(84)
Jin *et al*, 2021	tRF-Pro-AGG-004, tRF-Leu-CAG-002	tsRNA	PC	Diagnosis, prognosis	(87)
Mai *et al*, 2020	piRNA-54265	piRNA	CRC	Diagnosis	(82)
Feng *et al*, 2020	piRNA-823	piRNA	CRC	Prognosis	(91)
Moya *et al*, 2019	miR-98-5p	miRNA	PCA	Diagnosis	(85)
Lian *et al*, 2024	hsa-miR-449a	miRNA	PCA	Prognosis	(90)

GC, gastric cancer; CRC, colorectal cancer; BC, breast cancer; PCA, prostatic cancer; THCA, thyroid; PC, pancreatic cancer; miRNA, microRNA; lncRNA, long non-coding RNA; tsRNA, transfer RNA-derived small RNAs; piRNA, PIWI-interacting RNAs.

cancer, leading to increased cell viability. Notably, miR-4429 expression is markedly reduced by PSMA3-AS1, leading to the progression of colorectal cancer (69). Moreover, PSMA3-AS1 expression is reduced in glioma cells through increased interactions with miR-411-3p and the regulation of HOXA10 (70). lncRNA-CDC6 may act as a miRNA-215 ceRNA, directly regulating CDC6 expression and promoting BC progression (71).

LINC01133 and secreted phosphoprotein 1 (SPP1) expression levels are increased in pancreatic ductal adenocarcinoma and these increases are associated with malignant progression and the induction of epithelial-mesenchymal transition (72). Moreover, lncRNAs may play key roles in promoting cancer progression by enhancing drug metastasis and resistance (73).

Tumor suppressors. Tumor suppressors inhibit cellular expression and promote disease progression by binding to RNAs, enzymes and proteins. lncRNAs may play a role in reducing the infiltration of cancer cells (63). Notably, m6A modification-mediated downregulation of the lncRNA TP53TG1 promotes apoptosis and inhibits the proliferation and migration of gastric cancer cells. In addition, cellular inhibitor of phosphatase 2A (CIP2A) degrades TP53TG1 to stabilize expression, suggesting that TP53TG1 may exhibit potential as a therapeutic target in the treatment of gastric cancer (74). A previous study shows that lncRNA MORT expression is decreased in hepatocellular carcinoma and MORT overexpression suppresses NOTCH1 expression, leading to enhanced cell proliferation and invasion (71). Moreover, Wang *et al* (75) show that PGM5-AS1 is overexpressed in non-small cell lung cancer, leading to reduced cell proliferation, increased apoptosis and G_0/G_1 cell cycle arrest. The results of this study show that PGM5-AS1 is negatively associated with miR-423-5p. In addition, miR-423-5p may interact with the SLIT2 gene to inhibit the activity of miRNA and promote the development of cancer (75).

Further studies show that lncRNAs may encode proteins that affect cancer progression. For example, PRDM16-DT, a protein encoded by LINC00982, inhibits metastasis and demonstrates levels of chemoresistance in metastatic colorectal cancer. Notably, CRISPR/Cas9 libraries were screened and the results show that reduced PRDM16-DT expression promotes colorectal cancer progression and PRDM16-DT secretes E-calmodulin to inhibit metastasis. This process is mediated by the decreased secretion of MMP9 through competitive interaction with HNRNPA2B1, a compound that acts through Cimicifugoside H-1 to reduce chemoresistance and bind to FOXP3 to inhibit cell metastasis (76).

Results of a previous study show that lncRNAs may exhibit potential as therapeutic tools (77). Certain RNAs, despite their potential therapeutic benefits in specific cancers, may not produce the desired effects in cells due to various physiological factors. This could be attributed to insufficient levels of RNAs within the cells. Su *et al* (78) show that PTENP1 may play a crucial role in enhancing PTEN expression in prostate cancer through the utilization of ceRNAs. Results of this study also show that ceRNAs may inhibit PTEN expression, which exhibits potential in the prevention of tumor formation. However, limited cellular uptake of PTEN1 may limit the effectiveness of this approach (78). Collectively, these results show that lncRNA may assist the uptake of therapeutic agents in the body.

3. ncRNAs as biomarkers

Molecular biomarkers are crucial for early diagnosis, providing patients with a postoperative prognosis, and in the development of individualized treatment plans (Table II) (79).

Diagnostic markers. The current lack of diagnostic markers in cancer is associated with high mortality rates; therefore, the development of novel diagnostic markers is required for early detection and the accurate prediction of prognosis. Notably, lncRNA H19 is expressed at high levels in the serum of patients with BC and this lncRNA is differentially expressed in the

plasma. Therefore, lncRNA H19 may exhibit potential as a diagnostic marker in BC (80). In addition, H19 is considered a biomarker for thyroid cancer (81).

Serum piRNA-54265 may also exhibit potential as a diagnostic marker for the early detection of colorectal cancer, with high levels of expression observed in the serum of patients. Notably, these expression levels were higher in colorectal cancer than in other cancers of the gastrointestinal tract, leading to improved diagnostic outcomes in patients with early-stage disease (82). In addition, serum exosome-derived piRNAs also exhibit potential as diagnostic markers for hepatocellular carcinoma (83). tRNA-ValTAC-3, tRNA-GlyTCC-5, tRNA-ValAAC-5 and tRNA-GluCTC-5 exhibit higher expression levels in patients with hepatocellular carcinoma, compared with healthy subjects. Therefore, measurement of these tsRNAs using liquid biopsy may exhibit potential in the diagnosis of hepatocellular carcinoma (35). Similarly, tRF-33-RZYQHQ9M739P0J was shown to serve as an exclusive novel biomarker for hepatocellular carcinoma (84).

Diagnostic markers in the prostate exhibit high levels of sensitivity; however, low levels of specificity may lead to inaccurate diagnoses. For example, results of a previous study showed that high miR-98-5p expression in the plasma of patients with prostate cancer may exhibit potential for disease diagnosis; however, miR-98-5p, miR-152-3p, miR-326 and miR-4289 expression was dysregulated. Notably, simultaneous testing of these miRNAs showed improved specificity and sensitivity in prostate cancer diagnosis (85).

Prognostic markers. Investigating the expression of ncRNAs following treatment may exhibit potential in predicting the prognosis of patients and examinations of both prognostic and diagnostic markers should be used in the clinic (86). Notably, tsRNAs are used as biomarkers of pancreatic cancer. For example, tRF-Pro-AGG-004 exhibits potential as a diagnostic marker when combined with tRF-Leu-CAG-002 examination and survival rates following surgery have been assessed using these tsRNAs (87). Notably, intraperitoneal-free carcinoma cells play a key role in prognosis during surgery and lncRNA SNHG1 acts as a tumor marker in colorectal cancer. Results of a previous study show that SNHG1 exhibits a higher potential than CEA in the detection of IFCC (88). Moreover, lncRNA ENST00000503625 may also exhibit potential as a prognostic marker for prostate cancer, as cell invasion is increased following lncRNA ENST00000503625 knockdown. By contrast, increased lncRNA ENST00000503625 expression is indicative of a more positive prognosis (89). ceRNAs may also play a role in determining prognosis. The TRHDE-AS1/hsa-miR-449a/ADAMTS5 axis acts as a ceRNA network, exhibiting potential as a novel prognostic marker for prostate cancer (90). A previous study also demonstrated that piRNA-823 may exhibit potential as a novel diagnostic and prognostic biomarker in colorectal cancer (91).

4. Conclusions

Gene editing technology, known as CRISPR/cas9, uses a combination of CRISPR RNA and cas9 protein to precisely identify and modify specific genetic sequences. Research has focused on the use of CRISPR/cas9 in cancer therapeutics (92,93) and the use of chimeric antigen receptor T-cell immunotherapy in the treatment of cancer, which involves modifying γδ T-cells using CRISPR/cas9 to inhibit autophagy, creating CAR-γδ TCD5-cells. These edited cells demonstrate high levels of functionality and notable anti-tumor effects when targeting malignant T-cell lines (94). Therefore, CRISPR/cas9 may exhibit potential in the treatment of cancer through modification of abnormal oncogenic ncRNAs, or as a tool for studying ncRNAs through targeting specific genes. These methods may aid in further understanding the functional roles of ncRNAs in cells, leading to the development of novel therapeutic strategies.

Research has also focused on the use of ncRNAs in the treatment of cancer (95). ncRNA expression is often disrupted in various types of cancer; however, the current understanding of specific underlying mechanisms is limited. Therefore, further investigations with improved experimental design are required to validate the function of ncRNAs in cancer. Multidisciplinary approaches may aid in further understanding the presence and secretion of ncRNAs in various body fluids, leading to the development of novel biomarkers. However, not all ncRNAs exhibit potential as biomarkers. Therefore, further research is required to determine the specific ncRNAs that exhibit potential as biomarkers and to understand the factors that contribute to the lack of biomarker function in other ncRNAs.

Moreover, the intricate structure of ncRNAs may lead to limitations in the use of these agents in the treatment of cancer. At present, research is focused on enhancing the accuracy of ncRNA-mediated diagnosis. Notably, advances have been made in optimizing RNA therapies, leading to improved delivery of substances into specific cells. Reliable delivery systems are crucial for the safe and effective transportation of targeted drugs without impacting their intended targets. Expanding the current understanding of RNA therapies and delivery systems may aid in the use of ncRNAs in clinic. In conclusion, ncRNAs play key roles in tumors, and may exhibit potential in diagnosis, treatment and predicting the prognosis of patients with cancer. Further investigations are required to overcome the aforementioned challenges.

Acknowledgements

Not applicable.

Funding

The present review was supported by the Key Medical Research Projects of Jiangsu Provincial Health Commission (grant no. ZD2022008)

Availability of data and materials

Not applicable.

Authors' contributions

ZZ prepared the original manuscript draft. CM and ZZ participated in conceptualization. ZZ, YWa and YWu participated in guiding the preparation and design of this manuscript. HC reviewed and edited the paper. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. International Human Genome Sequencing Consortium: Finishing the euchromatic sequence of the human genome. Nature 431: 931-945, 2004.
2. Miescher F: On the chemical composition of pus cells. Medicinisch-chemische Untersuchungen 4: 441-460, 1871 (In German).
3. ENCODE Project Consortium; Moore JE, Purcaro MJ, Pratt HE, Epstein CB, Shoresh N, Adrian J, Kawli T, Davis CA, Dobin A, *et al*: Expanded encyclopaedias of DNA elements in the human and mouse genomes. Nature 583: 699-710, 2020.
4. Budakoti M, Panwar AS, Molpa D, Singh RK, Büsselberg D, Mishra AP, Coutinho HDM and Nigam M: Micro-RNA: The darkhorse of cancer. Cell Signal 83: 109995, 2021.
5. Chen H, Xu Z and Liu D: Small non-coding RNA and colorectal cancer. J Cell Mol Med 23: 3050-3057, 2019.
6. Fanale D, Taverna S, Russo A and Bazan V: Circular RNA in exosomes. Adv Exp Med Biol 1087: 109-117, 2018.
7. Li L, Wang Y, Zhang X, Huang Q, Diao Y, Yin H and Liu H: Long non-coding RNA HOXD-AS1 in cancer. Clin Chim Acta 487: 197-201, 2018.
8. Berindan-Neagoe I, Monroig P, Pasculli B and Calin GA: MicroRNAome genome: A treasure for cancer diagnosis and therapy. CA Cancer J Clin 64: 311-336, 2014.
9. Zhao H, Zhou Q and Li X: Protein bait hypothesis: circRNA-Encoded proteins competitively inhibit cognate functional isoforms. Trends Genet 37: 616-624, 2021.
10. Wightman B, Ha I and Ruvkun G: Posttranscriptional regulation of the heterochronic gene lin-14 by lin-4 mediates temporal pattern formation in C. elegans. Cell 75: 855-862, 1993.
11. Calin GA, Dumitru CD, Shimizu M, Bichi R, Zupo S, Noch E, Aldler H, Rattan S, Keating M, Rai K, *et al*: Frequent deletions and down-regulation of micro- RNA genes miR15 and miR16 at 13q14 in chronic lymphocytic leukemia. Proc Natl Acad Sci USA 99: 15524-15529, 2002.
12. He B, Zhao Z, Cai Q, Zhang Y, Zhang P, Shi S, Xie H, Peng X, Yin W, Tao Y and Wang X: miRNA-based biomarkers, therapies, and resistance in cancer. Int J Biol Sci 16: 2628-2647, 2020.
13. Gao Q, Lei F, Zeng Q, Gao Z, Niu P, Junnan, Ning, Li J and Zhang J: Functional passenger-Strand miRNAs in exosomes derived from human colon cancer cells and their heterogeneous paracrine effects. Int J Biol Sci 16: 1044-1058, 2020.
14. Su WZ and Ren LF: MiRNA-199 inhibits malignant progression of lung cancer through mediating RGS17. Eur Rev Med Pharmacol Sci 23: 3390-3400, 2019.
15. Cheng XK, Lin WR, Jiang H, Su ZH, Li L and Wang J: MicroRNA-129-5p inhibits invasiveness and metastasis of lung cancer cells and tumor angiogenesis via targeting VEGF. Eur Rev Med Pharmacol Sci 23: 2827-2837, 2019.
16. Deng S, Zhang X, Qin Y, Chen W, Fan H, Feng X, Wang J, Yan R, Zhao Y, Cheng Y, *et al*: miRNA-192 and -215 activate Wnt/β-catenin signaling pathway in gastric cancer via APC. J Cell Physiol 235: 6218-6229, 2020.
17. Qiu S, Xie L, Lu C, Gu C, Xia Y, Lv J, Xuan Z, Fang L, Yang J, Zhang L, *et al*: Gastric cancer-derived exosomal miR-519a-3p promotes liver metastasis by inducing intrahepatic M2-like macrophage-mediated angiogenesis. J Exp Clin Cancer Res 41: 296, 2022.
18. Malagobadan S, Ho CS and Nagoor NH: MicroRNA-6744-5p promotes anoikis in breast cancer and directly targets NAT1 enzyme. Cancer Biol Med 17: 101-111, 2020.
19. Zhang X, Yang Y, Zhang W, Huang K, Xu L, Shahid N, Pan Y, Xu C, Jiao X and Yang K: Downregulation of MiR-1538 promotes proliferation and metastasis of colorectal cancer by targeting DNMT3A. Biochem Biophys Res Commun 609: 119-126, 2022.
20. Xiao Z, Feng X, Zhou Y, Li P, Luo J, Zhang W, Zhou J, Zhao J, Wang D, Wang Y, *et al*: Exosomal miR-10527-5p inhibits migration, invasion, lymphangiogenesis and lymphatic metastasis by affecting Wnt/β-catenin signaling via Rab10 in esophageal squamous cell carcinoma. Int J Nanomedicine 18: 95-114, 2023.
21. Jia C, Zhang Y, Xie Y, Ren Y, Zhang H, Zhou Y, Gao N, Ding S and Han S: miR-200a-3p plays tumor suppressor roles in gastric cancer cells by targeting KLF12. Artif Cells Nanomed Biotechnol 47: 3697-3703, 2019.
22. Pichler M, Ress AL, Winter E, Stiegelbauer V, Karbiener M, Schwarzenbacher D, Scheideler M, Ivan C, Jahn SW, Kiesslich T, *et al*: MiR-200a regulates epithelial to mesenchymal transition-related gene expression and determines prognosis in colorectal cancer patients. Br J Cancer 110: 1614-1621, 2014.
23. Su X, Lang C, Luan A and Zhao P: MiR-200a promotes proliferation of cervical cancer cells by regulating HIF-1α/VEGF signaling pathway. J BUON 25: 1935-1940, 2020.
24. Matsui M and Corey DR: Non-coding RNAs as drug targets. Nat Rev Drug Discov 16: 167-179, 2017.
25. Diener C, Keller A and Meese E: Emerging concepts of miRNA therapeutics: From cells to clinic. Trends Genet 38: 613-626, 2022.
26. Bouchie A: First microRNA mimic enters clinic. Nat Biotechnol 31: 577, 2013.
27. Beg MS, Brenner AJ, Sachdev J, Borad M, Kang YK, Stoudemire J, Smith S, Bader AG, Kim S and Hong DS: Phase I study of MRX34, a liposomal miR-34a mimic, administered twice weekly in patients with advanced solid tumors. Invest New Drugs 35: 180-188, 2017.
28. Hong DS, Kang YK, Borad M, Sachdev J, Ejadi S, Lim HY, Brenner AJ, Park K, Lee JL, Kim TY, *et al*: Phase 1 study of MRX34, a liposomal miR-34a mimic, in patients with advanced solid tumours. Br J Cancer 122: 1630-1637, 2020.
29. Yeh YM, Chuang CM, Chao KC and Wang LH: MicroRNA-138 suppresses ovarian cancer cell invasion and metastasis by targeting SOX4 and HIF-1α. Int J Cancer 133: 867-878, 2013.
30. Yu C, Wang M, Li Z, Xiao J, Peng F, Guo X, Deng Y, Jiang J and Sun C: MicroRNA-138-5p regulates pancreatic cancer cell growth through targeting FOXC1. Cell Oncol (Dordr) 38: 173-181, 2015.
31. Zhao L, Yu H, Yi S, Peng X, Su P, Xiao Z, Liu R, Tang A, Li X, Liu F and Shen S: The tumor suppressor miR-138-5p targets PD-L1 in colorectal cancer. Oncotarget 7: 45370-45384, 2016.
32. Lee S, Kim J, Valdmanis PN and Kim HK: Emerging roles of tRNA-derived small RNAs in cancer biology. Exp Mol Med 55: 1293-1304, 2023.
33. Liu B, Cao J, Wang X, Guo C, Liu Y and Wang T: Deciphering the tRNA-derived small RNAs: Origin, development, and future. Cell Death Dis 13: 24, 2021.
34. Xu D, Qiao D, Lei Y, Zhang C, Bu Y and Zhang Y: Transfer RNA-derived small RNAs (tsRNAs): Versatile regulators in cancer. Cancer Lett 546: 215842, 2022.
35. Zhu L, Li J, Gong Y, Wu Q, Tan S, Sun D, Xu X, Zuo Y, Zhao Y, Wei YQ, *et al*: Exosomal tRNA-derived small RNA as a promising biomarker for cancer diagnosis. Mol Cancer 18: 74, 2019.
36. Du J, Huang T, Zheng Z, Fang S, Deng H and Liu K: Biological function and clinical application prospect of tsRNAs in digestive system biology and pathology. Cell Commun Signal 21: 302, 2023.
37. Burger K, Schlackow M and Gullerova M: Tyrosine kinase c-Abl couples RNA polymerase II transcription to DNA double-strand breaks. Nucleic Acids Res 47: 3467-3484, 2019.
38. Chen Q, Yan M, Cao Z, Li X, Zhang Y, Shi J, Feng GH, Peng H, Zhang X, Zhang Y, *et al*: Sperm tsRNAs contribute to intergenerational inheritance of an acquired metabolic disorder. Science 351: 397-400, 2016.
39. Park J, Ahn SH, Shin MG, Kim HK and Chang S: tRNA-derived small RNAs: Novel epigenetic regulators. Cancers (Basel) 12: 2773, 2020.
40. Ying X, Hu W, Huang Y, Lv Y, Ji D, Chen C, Yang B, Zhang C, Liang Y, Zhang H, *et al*: A Novel tsRNA, m7G-3' tiRNA LysTTT, promotes bladder cancer malignancy via regulating ANXA2 phosphorylation. Adv Sci (Weinh) 18: e2400115, 2024.
41. Xiong Q, Zhang Y, Xu Y, Yang Y, Zhang Z, Zhou Y, Zhang S, Zhou L, Wan X, Yang X, *et al*: tiRNA-Val-CAC-2 interacts with FUBP1 to promote pancreatic cancer metastasis by activating c-MYC transcription. Oncogene 43: 1274-1287, 2024.
42. Xu W, Zheng J, Wang X, Zhou B, Chen H, Li G and Yan F: tRF-Val-CAC-016 modulates the transduction of CACNA1d-mediated MAPK signaling pathways to suppress the proliferation of gastric carcinoma. Cell Commun Signal 20: 68, 2022.

43. Zhang Y, Gu X, Li Y, Li X, Huang Y and Ju S: Transfer RNA-derived fragment tRF-23-Q99P9P9NDD promotes progression of gastric cancer by targeting *ACADSB*. J Zhejiang Univ Sci B 25: 438-450, 2024 (In English, Chinese).
44. Mo D, He F, Zheng J, Chen H, Tang L and Yan F: tRNA-derived fragment tRF-17-79MP9PP attenuates cell invasion and migration *via* THBS1/TGF-β1/Smad3 axis in breast cancer. Front Oncol 11: 656078, 2021.
45. Tao EW, Wang HL, Cheng WY, Liu QQ, Chen YX and Gao QY: A specific tRNA half, 5'tiRNA-His-GTG, responds to hypoxia via the HIF1α/ANG axis and promotes colorectal cancer progression by regulating LATS2. J Exp Clin Cancer Res 40: 67, 2021.
46. Yang W, Gao K, Qian Y, Huang Y, Xiang Q, Chen C, Chen Q, Wang Y, Fang F, He Q, *et al*: A novel tRNA-derived fragment AS-tDR-007333 promotes the malignancy of NSCLC via the HSPB1/MED29 and ELK4/MED29 axes. J Hematol Oncol 15: 53, 2022.
47. Czech B, Munafò M, Ciabrelli F, Eastwood EL, Fabry MH, Kneuss E and Hannon GJ: piRNA-Guided genome defense: From biogenesis to silencing. Annu Rev Genet 52: 131-157, 2018.
48. Liu Y, Dou M, Song X, Dong Y, Liu S, Liu H, Tao J, Li W, Yin X and Xu W: The emerging role of the piRNA/piwi complex in cancer. Mol Cancer 18: 123, 2019.
49. Han R, Rao X, Zhou H and Lu L: Synergistic immunoregulation: Harnessing CircRNAs and PiRNAs to amplify PD-1/PD-L1 inhibition therapy. Int J Nanomedicine 19: 4803-4834, 2024.
50. Bastiaanssen C, Ugarte PB, Kim K, Finocchio G, Feng Y, Anzelon TA, Köstlbacher S, Tamarit D, Ettema TJG, Jinek M, *et al*: RNA-guided RNA silencing by an Asgard archaeal Argonaute. Nat Commun 15: 5499, 2024.
51. Xie Q, Li Z, Luo X, Wang D, Zhou Y, Zhao J, Gao S, Yang Y, Fu W, Kong L and Sun T: piRNA-14633 promotes cervical cancer cell malignancy in a METTL14-dependent m6A RNA methylation manner. J Transl Med 20: 51, 2022.
52. Li D, Luo Y, Gao Y, Yang Y, Wang Y, Xu Y, Tan S, Zhang Y, Duan J and Yang Y: piR-651 promotes tumor formation in non-small cell lung carcinoma through the upregulation of cyclin D1 and CDK4. Int J Mol Med 38: 927-936, 2016.
53. Liu T, Wang J, Sun L, Li M, He X, Jiang J and Zhou Q: Piwi-interacting RNA-651 promotes cell proliferation and migration and inhibits apoptosis in breast cancer by facilitating DNMT1-mediated PTEN promoter methylation. Cell Cycle 20: 1603-1616, 2021.
54. Liu Q, Chen Q, Zhou Z, Tian Z, Zheng X and Wang K: piRNA-18 inhibition cell proliferation, migration and invasion in colorectal cancer. Biochem Genet 61: 1881-1897, 2023.
55. Peng Q, Chen Y, Xie T, Pu D, Ho VW, Sun J, Liu K, Chan RC, Ding X, Teoh JY, *et al*: PiRNA-4447944 promotes castration-resistant growth and metastasis of prostate cancer by inhibiting NEFH expression through forming the piRNA-4447944-PIWIL2-NEFH complex. Int J Biol Sci 20: 3638-3655, 2024.
56. Ben S, Ding Z, Xin J, Li F, Cheng Y, Chen S, Fan L, Zhang Q, Li S, Du M, *et al*: piRNA PROPER suppresses DUSP1 translation by targeting N6-methyladenosine-mediated RNA circularization to promote oncogenesis of prostate cancer. Adv Sci (Weinh) 4: e2402954, 2024.
57. Tan YT, Lin JF, Li T, Li JJ, Xu RH and Ju HQ: LncRNA-mediated posttranslational modifications and reprogramming of energy metabolism in cancer. Cancer Commun (Lond) 41: 109-120, 2021.
58. Bridges MC, Daulagala AC and Kourtidis A: LNCcation: lncRNA localization and function. J Cell Biol 220: e202009045, 2021.
59. Bhan A, Soleimani M and Mandal SS: Long noncoding RNA and cancer: A new paradigm. Cancer Res 77: 3965-3981, 2017.
60. Dou DR, Zhao Y, Belk JA, Zhao Y, Casey KM, Chen DC, Li R, Yu B, Srinivasan S, Abe BT, *et al*: Xist ribonucleoproteins promote female sex-biased autoimmunity. Cell 187: 733-749.e16, 2024.
61. van Heesch S, Witte F, Schneider-Lunitz V, Schulz JF, Adami E, Faber AB, Kirchner M, Maatz H, Blachut S, Sandmann CL, *et al*: The translational landscape of the human heart. Cell 178: 242-260.e29, 2019.
62. Klinge CM: Estrogenic control of mitochondrial function. Redox Biol 31: 101435, 2020.
63. Kopp F and Mendell JT: Functional classification and experimental dissection of long noncoding RNAs. Cell 172: 393-407, 2018.
64. Matsumoto A, Pasut A, Matsumoto M, Yamashita R, Fung J, Monteleone E, Saghatelian A, Nakayama KI, Clohessy JG and Pandolfi PP: mTORC1 and muscle regeneration are regulated by the LINC00961-encoded SPAR polypeptide. Nature 541: 228-232, 2017.
65. Hua Q, Jin M, Mi B, Xu F, Li T, Zhao L, Liu J and Huang G: LINC01123, a c-Myc-activated long non-coding RNA, promotes proliferation and aerobic glycolysis of non-small cell lung cancer through miR-199a-5p/c-Myc axis. J Hematol Oncol 12: 91, 2019.
66. Zhang Y, Chen H, Yuan R, Wang Y, Zhang D, Zeng Q, Jiang W, Zhang R, Chen T, Chai C and Guo B: PDK1-stabilized LncRNA SPRY4-IT1 promotes breast cancer progression via activating NF-κB signaling pathway. Mol Carcinog 62: 1009-1024, 2023.
67. Zhou L, Jiang J, Huang Z, Jin P, Peng L, Luo M, Zhang Z, Chen Y, Xie N, Gao W, *et al*: Hypoxia-induced lncRNA STEAP3-AS1 activates Wnt/β-catenin signaling to promote colorectal cancer progression by preventing m6A-mediated degradation of STEAP3 mRNA. Mol Cancer 21: 168, 2022.
68. Wang F, Hu Y, Wang H, Hu P, Xiong H, Zeng Z, Han S, Wang D, Wang J, Zhao Y, *et al*: LncRNA FTO-IT1 promotes glycolysis and progression of hepatocellular carcinoma through modulating FTO-mediated N6-methyladenosine modification on GLUT1 and PKM2. J Exp Clin Cancer Res 42: 267, 2023.
69. Peng P, Wang Y, Wang BL, Song YH, Fang Y, Ji H, Huangfu CN, Wang KM and Zheng Q: LncRNA PSMA3-AS1 promotes colorectal cancer cell migration and invasion via regulating miR-4429. Eur Rev Med Pharmacol Sci 24: 11594-11601, 2020.
70. Huang T, Chen Y, Zeng Y, Xu C, Huang J, Hu W, Chen X and Fu H: Long non-coding RNA PSMA3-AS1 promotes glioma progression through modulating the miR-411-3p/HOXA10 pathway. BMC Cancer 21: 844, 2021.
71. Kong X, Duan Y, Sang Y, Li Y, Zhang H, Liang Y, Liu Y, Zhang N and Yang Q: LncRNA-CDC6 promotes breast cancer progression and function as ceRNA to target CDC6 by sponging microRNA-215. J Cell Physiol 234: 9105-9117, 2019.
72. Yang Y, Gong Y, Ding Y, Sun S, Bai R, Zhuo S and Zhang Z: LINC01133 promotes pancreatic ductal adenocarcinoma epithelial-mesenchymal transition mediated by SPP1 through binding to Arp3. Cell Death Dis 15: 492, 2024.
73. Liu C, Lu C, Yixi L, Hong J, Dong F, Ruan S, Hu T and Zhao X: Exosomal Linc00969 induces trastuzumab resistance in breast cancer by increasing HER-2 protein expression and mRNA stability by binding to HUR. Breast Cancer Res 25: 124, 2023.
74. Fang D, Ou X, Sun K, Zhou X, Li Y, Shi P, Zhao Z, He Y, Peng J and Xu J: m6A modification-mediated lncRNA TP53TG1 inhibits gastric cancer progression by regulating CIP2A stability. Cancer Sci 113: 4135-4150, 2022.
75. Wang J, Ye J, Dang Y and Xu S: LncRNA PGM5-AS1 inhibits non-small cell lung cancer progression by targeting miRNA-423-5p/SLIT2 axis. Cancer Cell Int 24: 216, 2024.
76. Hu HF, Han L, Fu JY, He X, Tan JF, Chen QP, Han JR and He QY: LINC00982-encoded protein PRDM16-DT regulates *CHEK2* splicing to suppress colorectal cancer metastasis and chemoresistance. Theranostics 14: 3317-3338, 2024.
77. Hashemi M, Moosavi MS, Abed HM, Dehghani M, Aalipour M, Heydari EA, Behroozaghdam M, Entezari M, Salimimoghadam S, Gunduz ES, *et al*: Long non-coding RNA (lncRNA) H19 in human cancer: From proliferation and metastasis to therapy. Pharmacol Res 184: 106418, 2022.
78. Su S, Liu L, Fu Q, Ma M, Yang N, Pan T, Geng S, Yu XF and Zhu J: A black phosphorus nanosheet-based RNA delivery system for prostate cancer therapy by increasing the expression level of tumor suppressor gene PTEN via CeRNA mechanism. J Nanobiotechnology 22: 391, 2024.
79. Biomarkers Definitions Working Group: Biomarkers and surrogate endpoints: Preferred definitions and conceptual framework. Clin Pharmacol Ther 69: 89-95, 2001.
80. Zhang K, Luo Z, Zhang Y, Zhang L, Wu L, Liu L, Yang J, Song X and Liu J: Circulating lncRNA H19 in plasma as a novel biomarker for breast cancer. Cancer Biomark 17: 187-194, 2016.
81. Han B, Li S, Huang S, Huang J, Wu T and Chen X: Cuproptosis-related lncRNA SNHG16 as a biomarker for the diagnosis and prognosis of head and neck squamous cell carcinoma. PeerJ 11: e16197, 2023.
82. Mai D, Zheng Y, Guo H, Ding P, Bai R, Li M, Ye Y, Zhang J, Huang X, Liu D, *et al*: Serum piRNA-54265 is a New Biomarker for early detection and clinical surveillance of human colorectal cancer. Theranostics 10: 8468-8478, 2020.

83. Rui T, Wang K, Xiang A, Guo J, Tang N, Jin X, Lin Y, Liu J and Zhang X: Serum exosome-derived piRNAs could be promising biomarkers for HCC diagnosis. Int J Nanomedicine 18: 1989-2001, 2023.
84. Li X, Li Y, Yuan J, Zhang W, Xu T, Jing R and Ju S: Serum tRF-33-RZYQHQ9M739P0J as a novel biomarker for auxiliary diagnosis and disease course monitoring of hepatocellular carcinoma. Heliyon 10: e30084, 2024.
85. Moya L, Meijer J, Schubert S, Matin F and Batra J: Assessment of miR-98-5p, miR-152-3p, miR-326 and miR-4289 expression as biomarker for prostate cancer diagnosis. Int J Mol Sci 20: 1154, 2019.
86. Weng W, Liu N, Toiyama Y, Kusunoki M, Nagasaka T, Fujiwara T, Wei Q, Qin H, Lin H, Ma Y and Goel A: Novel evidence for a PIWI-interacting RNA (piRNA) as an oncogenic mediator of disease progression, and a potential prognostic biomarker in colorectal cancer. Mol Cancer 17: 16, 2018.
87. Jin F, Yang L, Wang W, Yuan N, Zhan S, Yang P, Chen X, Ma T and Wang Y: A novel class of tsRNA signatures as biomarkers for diagnosis and prognosis of pancreatic cancer. Mol Cancer 20: 95, 2021.
88. Wu Y, Liu L, He F, Zhang Y, Jiang W, Cao Z, Xu X and Gong J: Long noncoding RNA small nucleolar RNA host gene 1 as a potential novel biomarker for intraperitoneal free cancer cells in colorectal cancer. iScience 27: 110228, 2024.
89. Li Y, Fang Z, Ge S, Li J, Qu L, Shi X, Zhang W, Sun Y, Ren S and Wang L: Long non-coding RNA ENST00000503625 is a potential prognostic biomarker and metastasis suppressor gene in prostate cancer. J Cancer Res Clin Oncol 149: 7305-7317, 2023.
90. Lian X, Pang L, Zhou H and Liu S: Identification and validation of the TRHDE-AS1/hsa-miR-449a/ADAMTS5 axis as a novel prognostic biomarker in prostate cancer. Biofactors 50: 1251-1267, 2024.
91. Feng J, Yang M, Wei Q, Song F, Zhang Y, Wang X, Liu B and Li J: Novel evidence for oncogenic piRNA-823 as a promising prognostic biomarker and a potential therapeutic target in colorectal cancer. J Cell Mol Med 24: 9028-9040, 2020.
92. Woodward EA, Wang E, Wallis C, Sharma R, Tie AWJ, Murthy N and Blancafort P: Protocol for delivery of CRISPR/dCas9 systems for epigenetic editing into solid tumors using lipid nanoparticles encapsulating RNA. Methods Mol Biol 2842: 267-287, 2024.
93. Issa II, Due H, Brøndum RF, Veeravakaran V, Haraldsdóttir H, Sylvester C, Brogaard A, Dhanjal S, Schmierer B and Dybkær K: CRISPR-Cas9 knockout screens identify DNA damage response pathways and *BTK* as essential for cisplatin response in diffuse large B-Cell lymphoma. Cancers (Basel) 16: 2437, 2024.
94. Zhu Z, Li H, Lu Q, Zhang Z, Li J, Wang Z, Yang N, Yu Z, Yang C, Chen Y, *et al*: mRNA-engineered CD5-CAR-γδTCD5- cells for the immunotherapy of T-cell acute lymphoblastic leukemia. Adv Sci (Weinh) 16: e2400024, 2024.
95. Slack FJ and Chinnaiyan AM: The role of non-coding RNAs in oncology. Cell 179: 1033-1055, 2019.

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