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Review paper

# Non-coding RNAs as therapeutic targets in cancer and its clinical application

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ABSTRACT

Cancer genomics has led to the discovery of numerous oncogenes and tumor suppressor genes that play critical roles in cancer development and progression. Oncogenes promote cell growth and proliferation, whereas tumor suppressor genes inhibit cell growth and division. The dysregulation of these genes can lead to the development of cancer. Recent studies have focused on non-coding RNAs (ncRNAs), including circular RNA (circRNA), long non-coding RNA (lncRNA), and microRNA (miRNA), as therapeutic targets for cancer. In this article, we discuss the oncogenes and tumor suppressor genes of ncRNAs associated with different types of cancer and their potential as therapeutic targets. Here, we highlight the mechanisms of action of these genes and their clinical applications in cancer treatment. Understanding the molecular mechanisms underlying cancer development and identifying specific therapeutic targets are essential steps towards the development of effective cancer treatments.


## 1. Introduction

Cancer is a disease resulting from genetic mutations [1]. The discovery of genetic codon mutations in proteins was a breakthrough in understanding the tumorigenesis driven by these mutations, leading to the establishment of scientific treatments for malignant tumors [2]. The Human Genome Project (HGP) discovered that less than 2% of human genes encode proteins, and non-coding genes play a greater role in tumors. Moreover, changes in non-coding regions can affect gene expression and regulation, leading to tumor formation and development [3]. Recent studies have found that mutations in non-coding genes and changes in epigenetic and genomic structures can lead to tumor formation [4]. The gene expression and regulation of tumor cells differ from those of normal cells, with infinite proliferation, invasion, and even metastasis [5]. non-coding RNAs (ncRNAs), particularly circular RNA (circRNA), long non-coding RNA (lncRNA), and microRNA (miRNA), associated with human health and cancer have been the focus of numerous studies [6]. In this review, we provide a comprehensive overview of various ncRNAs, investigating the regulatory mechanisms of circRNAs, lncRNAs, and miRNAs in different cancer therapies. We analyze the dual roles of ncRNAs, including circRNA, lncRNA, and miRNA, as both promoters and suppressors in cancer therapy.

## 2. Classification of ncRNA

According to a report on HGP, there are approximately 20,000 protein-coding genes, which account for less than 2% of the entire human genome [7]. Initially, scientists thought that the majority of the remainder of the human genome had no function and was considered "junk DNA." However, recent studies based on advanced technologies such as tiling arrays and RNA deep sequencing have identified thousands of RNA transcripts that are not derived from known genes and do not encode proteins [8]. ncRNAs, including circRNAs, lncRNAs, and miRNAs, have remained the focus of recent studies as potential therapeutic targets for cancer. ncRNAs can be

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classified into two categories: housekeeping ncRNAs and regulatory ncRNAs [9]. The former include transfer RNAs (tRNA), small nuclear RNAs (snRNAs), small nucleolar RNAs (snoRNAs), ribosomal RNAs (rRNA), tRNA-derived fragments (tRF), tRNA half (tiRNA), and telomerases (TERC). The latter can be further divided into circRNAs and linear RNAs. Based on their length, linear RNAs are further classified into small ncRNAs (sncRNAs), which are shorter than 200 nucleotides, and long ncRNAs (lncRNAs), which are longer than 200 nucleotides. The sncRNA group includes miRNAs, small interfering RNAs (siRNAs), Piwi-associated RNAs (piRNAs), RNA, and enhancer RNAs (eRNAs) [10]. Fig. 1 illustrates the biosynthesis of the nine ncRNAs, and Table 1 [10–26] summarizes their main functions.

### 2.1. tRNA

tRNAs are the most abundant small non-coding ribonucleic acids, constituting approximately 4%–10% of all cellular RNAs. tRNAs function as adaptor molecules in the protein translation machinery and are thus considered housekeeping products [11]. The mature form of tRNAs is composed of 70–90 nucleotides and folds into a “clover” secondary structure and an L-shaped tertiary structure [11]. tRNA biogenesis involves the synthesis of the initial transcript, followed by processing to remove the 5′ leader, trim the 3′ trailer, add CCA, splice introns that may be present, modify multiple nucleoside residues, and, for eukaryotes, export the tRNA to the cytoplasm before its use in translation [27]. Fragments generated from tRNA molecules play diverse roles in various cellular processes beyond their canonical functions in translation. Fragments generated from tRNA molecules play diverse roles in various cellular processes beyond their canonical functions in translation. tiRNAs, tRNA-derived small RNAs (tsRNAs), and tRFs have been shown to regulate gene expression, participate in stress responses, and play roles in disease development [28,29]. Researchers have suggested that tiRNAs play a role in translational regulation by binding to ribosomes and preventing their association with mRNA. They have also been shown to be involved in stress responses such as heat shock and oxidative stress [30]. tsRNAs are implicated in gene silencing and post-transcriptional regulation. They intefere with various RNA-binding proteins, leading to altered gene expression. tsRNAs have also been linked to stress responses and cancer development and progression [31]. tRFs, specifically tRF-3s, have been shown to have a role in the regulation of protein synthesis by binding to ribosomes and inhibiting their activity. tRF-5s have been implicated in the regulation of RNA stability and gene expression, whereas inter-tRFs have been suggested to play a role in the regulation of chromatin structure and gene expression [32]. Overall, the discovery of these tRNA-derived fragments has expanded our understanding of the complexity of cellular RNA networks and their roles in diverse cellular processes.

### 2.2. snRNA

snRNAs typically range from 60 to 220 nucleotides in length. They play crucial roles in pre-mRNA splicing, which is a crucial step in gene expression [12]. snRNAs are part of the spliceosome, which is a large RNA-protein complex responsible for removing introns

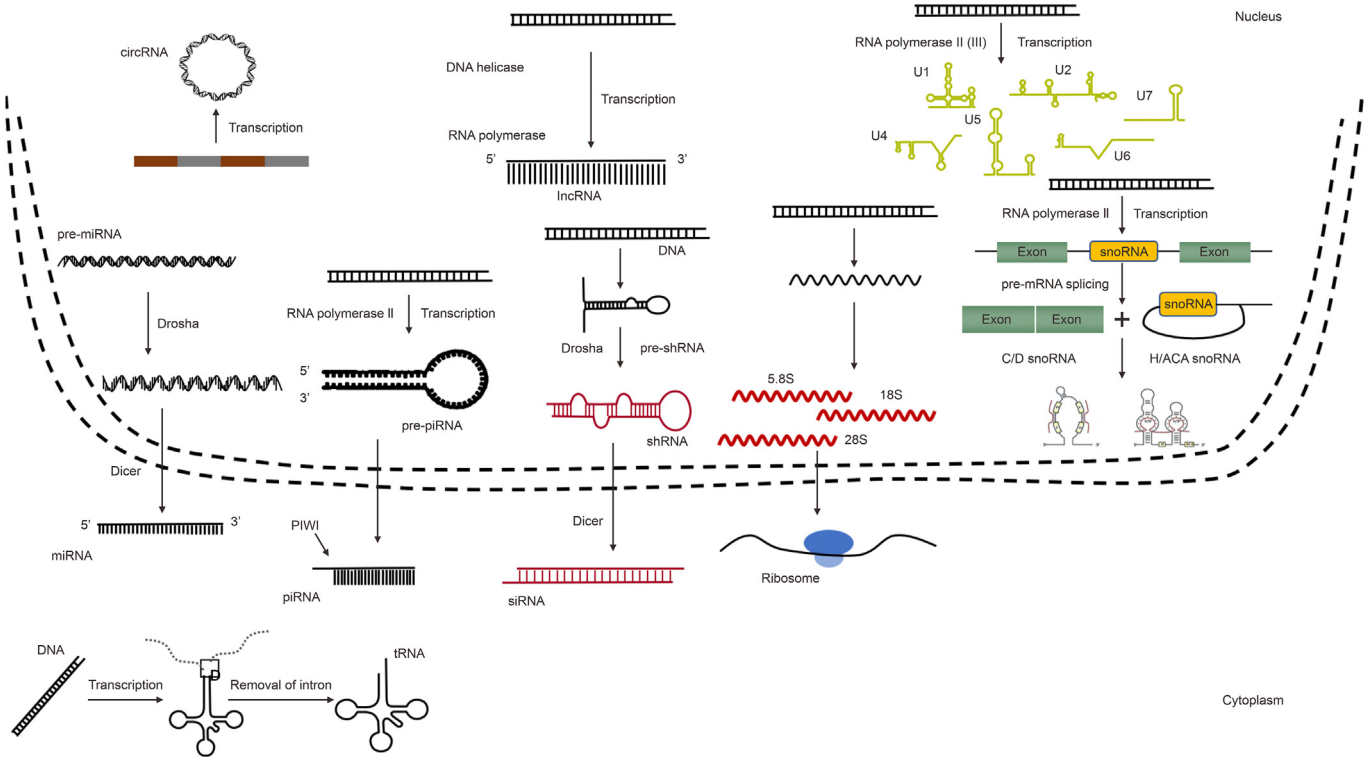


**Fig. 1.** Nine types of non-coding RNAs (ncRNAs) are synthesized in different ways. In the nucleus, RNA polymerase (Pol) II transcribes microRNAs (miRNA) primary transcripts, which is then cleaved into pre-miRNA. Esportin-5 transports pre-miRNA from the nucleus to the cytoplasm, where it is further processed by RNA Pol III into mature miRNA. PIWI-associated RNA (piRNA) genes are transcribed by RNA Pol II to generate small nucleotide sequences, which serve as the primary synthesis of piRNA. Circular RNA (circRNA) is generated through a unique alternative splicing process called backsplicing, which results in a closed-loop structure with a back-splicing junction site. Long non-coding RNAs (lncRNAs) are transcribed from various regions of mRNAs, including the anti-sense strand, promoter region, intron region, and intergenic region. Short hairpin RNA (shRNA) is produced in the nucleus from DNA, and the Dicer enzyme cleaves it into small interfering RNA (siRNA) in the cytoplasm. Transfer RNA (tRNA) genes on DNA molecules are transcribed into tRNA precursors, which are then processed into mature tRNA. rDNAs are transcribed by RNA Pol I to generate pre-rRNAs that undergo several modifications and processing steps, resulting in mature 18S, 5.8S and 28S rRNAs. Except for U6, which is transcribed by RNA Pol III, all other small nuclear RNAs (snRNAs) are transcribed by RNA Pol II. Most small nucleolar RNAs (snoRNAs) are mainly located in the intron region of genes transcribed by RNA Pol II.

**Table 1**
The history and the main function of common non-coding RNAs (ncRNAs).

| ncRNAs | Discovery time | Discoverer | Length | Function | Refs. |
|---|---|---|---|---|---|
| tRNA | 1955 | Paul Zamecnick | 70–90 nt | As an adaptor molecule in protein translation machinery | [11] |
| snRNA | 1968 | Weinberg and Penman | 60–220 nt | RNA modification/processing. | [12,13] |
| snoRNA | 1982 | Bob Weinberg | 60–300 nt | Precursors of miRNA | [13,14] |
| rRNA | – | – | Variable | Integral structural component of ribosomes | [15] |
| circRNA | 1976 | Sanger et al. | 100–500 nt | Acting as a microRNA sponge, RNA binding protein sponge and translational regulator | [16–19] |
| lncRNA | 1984 | Pachnis et al. | ≥200 nt | Affecting transcriptional regulation, post-transcriptional regulation | [20–22] |
| miRNA | 1993 | Victor Ambros and Gary Ruvkun | 18–22 nt | Inhibiting translation of mRNA | [23,24] |
| siRNA | 1999 | Hamilton and Baulcombe | 20–25 nt | Promoting the degradation of mRNA. | [10] |
| piRNA | 2006 | Aravin | 20–35 nt | Silencing transposons in the germ line | [25,26] |

tRNA: transfer RNA; snRNA: small nuclear RNA; snoRNA: small nucleolar RNA; rRNA: ribosomal RNA; circRNA: circular RNA; lncRNA: long non-coding RNA; miRNA: microRNA; siRNA: small interfering RNA; piRNA: PIWI-associated RNA. –: no data.

and ligating exons in pre-mRNA molecules. Furthermore, some snRNAs are involved in other RNA processing events, such as the 3′-end formation of histone mRNAs and the processing of rRNA in the nucleolus. snRNAs are transcribed by RNA Pol II or III and are then extensively modified and processed to generate mature functional snRNAs. These modifications include the addition of a 5′-cap structure and a 3′-poly(A) tail, as well as chemical modifications to individual nucleotides [13]. There are several types of snRNAs, including U1, U2, U4, U5, U6, and U12, that differ in size, sequence, and function. The U1, U2, U4, U5, and U6 snRNAs are involved in the major spliceosome, which is responsible for splicing most pre-mRNA molecules. The U12 snRNA, on the other hand, is part of the minor spliceosome, which is responsible for the splicing of a small subset of pre-mRNA molecules [14,33–35]. Overall, snRNAs are essential components of the gene expression machinery, and their dysregulation has been implicated in various human diseases, including cancer and neurological disorders.

### 2.3. snoRNA

snoRNAs are a class of small ncRNAs (60–300 nt) that play a crucial role in the regulation of rRNA modification by guiding the chemical modification of rRNA [14]. There are two main types of snoRNAs: box C/D and box H/ACA snoRNAs. Box C/D snoRNAs guide rRNA methylation, whereas box H/ACA snoRNAs guide the pseudouridylation of rRNA. These snoRNAs are usually transcribed from the introns of protein-coding genes by RNA Pol II and are then processed and modified by various protein factors to generate mature snoRNAs [36]. Recent studies revealed that snoRNAs are involved in various biological processes beyond rRNA modification. These processes include alternative splicing, mRNA stabilization, and translational regulation. At least 2000 snoRNAs have been annotated within the human genome, indicating their widespread importance in gene regulation [37].

### 2.4. rRNA

Ribosomes are essential ribonucleoprotein machines that decode mRNA-encoded genetic information into polypeptide chains. Ribosome biogenesis is a tightly regulated and coordinated process that begins with the transcription of pre-rRNA by RNA Pol I, followed by a series of processing steps that remove the external and internal transcribed spacers (ETSs and ITSs) to produce mature 18S, 5.8S, and 28S rRNAs. Defects or disorders in rRNA production can result in a range of human ribosomopathy diseases. Humans have approximately 300–400 copies of rDNA genes per haploid genome, distributed over five chromosomes [38]. Pol I activity is a critical determinant of ribosomal abundance and essential for cell growth and proliferation [39]. Although rRNA accounts for more than 80% of total cellular RNA, little is known about the physiological functions of rRNA modifications [15]. Most rRNA molecules in a cell are ribosome-associated, and rRNA is an essential component of ribosomes in all known microorganisms [40].

### 2.5. circRNA

circRNAs are a novel type of RNA in which the 5′ and 3′ termini are covalently linked to form a continuous loop through back-splicing of exons from a single pre-mRNA [41]. They account for 1% of all cellular RNA [16] and were first observed in plant viruses in 1976, where they were formed by enzymatic connections rather than back-splicing [42]. In 1979, circRNAs were detected in the cytoplasm of eukaryotic cells by electron microscopy [43]. For decades, circRNAs have been considered by-products or missplicing products because of their low abundance [17]. Recent studies have indicated that circRNAs play an important role in regulating gene expression by acting as RNA-binding protein sponges, miRNA sponges, and translational regulators [18]. They are derived from many housekeeping genes and exist as circular molecules, mostly 100–500 nucleotides in length [19]. Based on the components of exons and introns from the parental genes, circRNAs can be divided into three categories: exonic circRNAs (ecircRNAs) that only contain back-spliced exons, exon-intron circRNAs (EIciRNAs) that are circularized with both exons and introns, and circular intronic RNAs (ciRNAs) that originate from introns [44].

### 2.6. lncRNA

lncRNAs are a diverse group of RNA molecules that are longer than 200 nucleotides in size [20]. They are transcribed by RNA Pol II from intergenic, exonic, or distal protein-coding regions of the genome. lncRNAs are capped on the 5′-end with methyl-guanosine and 3′-polyadenylated [21]. According to the Encyclopedia of DNA Elements, lncRNAs comprise 4%–9% of the total RNA in cells, with over 50,000 human lncRNAs identified to date [45,46]. Based on their genomic location, lncRNAs can be categorized into three groups: long intergenic non-coding RNAs (lincRNAs), natural antisense transcripts (NATs), and intronic lncRNAs [47]. They can also be divided into different length groups, including small lncRNAs (200–950 nt), medium lncRNAs (950–4800 nt) and large lncRNAs (4800 nt or more). While the majority of lncRNAs in humans are small (58%), the majority of lncRNAs in mice are medium-sized (78%) [22].

### 2.7. miRNA

As the most widely studied small ncRNAs, miRNAs are approximately 18–22 nucleotides long and regulate gene expression at the post-transcriptional level via translational repression or transcript degradation [23]. In 1993, Lee et al. [24] identified the first miRNA molecule, lin-4, using a classical positional cloning approach. In 2000, Reinhart et al. [48] identified another miRNA, let-7, and discovered that let-7 plays an important role in the post-transcriptional regulation of gene expression. The human genome encodes more than 1000 miRNA species that regulate 60% of all protein-coding genes [49]. Similar to transcription factors, miRNAs are widely believed to regulate most biological processes and diverse cellular pathways in both plants and animals, ranging from responses to environmental stress to housekeeping functions [50]. miRNA genes can be coding or non-coding genes based on their genomic locations [51]. Approximately 10% of miRNA loci are located in the exonic region of non-coding transcripts, 40% in the intronic region of non-coding transcripts, and 40% in the intronic region of protein-coding genes [52].

### 2.8. siRNA

As a regulatory mechanism in most eukaryotic cells for directly controlling gene activity, RNA interference (RNAi) has become a mechanism of action for the development of RNAi-based therapies [53]. Researchers have found that short strands of RNA, such as siRNAs, can cause targeted gene suppression [54]. siRNAs are double-stranded RNAs (dsRNAs) with lengths of 21–25 nucleotides that are responsible for RNAi events [10]. The molecular mechanisms underlying synthetic siRNAs' induction of gene silencing involve several key steps. Initially, the synthetic siRNA enters the cell through endocytosis and escapes from the endosome. Following this, the siRNA associates with the RNA-induced silencing complex (RISC). Within RISC, a member of the Argonaute (AGO) protein family identifies and chooses one strand of the duplex as the guide (anti-sense) strand. Simultaneously, the non-guide (sense) strand undergoes degradation [55]. This is initiated by the binding of siRNA with RISC, followed by RISC activation, resulting in the recognition of the target mRNA and degradation of the latter [56]. As gene knockdown tools used in laboratories, siRNAs can also be chemically synthesized and introduced into cells by direct transfection [57] or delivered into cells in the form of hairpin precursors through plasmids or viral vectors [58]. siRNA helps maintain genome stability through RNAi and is a potent tool for target-specific gene silencing [59].

### 2.9. piRNA

piRNAs interact with P-element Induced Wimpy (PIWI) proteins. They were first described in the germ cells of Mus musculus and Drosophila melanogaster in 2006 and are considered the “guardians of the genome” [25]. piRNAs range from 20 to 35 nucleotides in length and are longer than AGO-interacting small RNAs. They were abundantly expressed in the gonads. Unlike miRNAs, piRNA sequences are not well conserved across species and are highly heterogeneous [26]. Furthermore, piRNAs are processed from long single-stranded precursor transcripts, unlike miRNAs and siRNAs, which are derived from double-stranded RNA precursors [60]. Additionally, piRNAs are the least characterized class of sncRNAs, detected only in the germline cells of fish, Drosophila melanogaster, and mammals, in contrast to miRNAs and siRNAs, which are widely expressed in different tissues and cell types [61]. Based on the known functions of PIWI proteins, piRNAs are speculated to have three functions: transcriptional gene silencing, regulation of translation and mRNA stability [62], and maintenance of germline stem cell function. piRNAs can be classified based on their origin, including transposon-derived piRNAs, which have a well-understood function, lncRNA-derived piRNAs, and mRNA-derived piRNAs [63].

## 3. ncRNA as therapeutic targets of cancer

Cancer remains one of the most significant threats to human health and safety, despite the availability of various clinical treatments. Many cancers have unmet medical needs, and the development of anti-tumor drugs relies on the identification of target molecules. As a result, the development of new anti-tumor drugs based on novel targets is at the forefront of innovative drug research and development. In recent years, the targeting of RNAs for cancer treatment and the development of RNAs as drugs have expanded the scope of cancer therapy. Several preparations have been developed for ncRNAs, including anti-sense oligonucleotides, small interfering RNA, ribozymes, and aptamers [6]. Among these, circRNAs, lncRNAs, and miRNAs have been the subject of numerous studies as potential therapeutic targets for cancer treatment. In this review, we discuss their research progress and roles as potential targets for cancer therapy.

### 3.1. circRNAs as therapeutic targets in cancer

Recent studies have revealed that circRNAs play critical roles in cancer progression and metastasis. They act as miRNA sponges, RNA-binding protein sponges, and translational regulators that affect gene expression and contribute to cancer development [31,34–36]. Consequently, targeting circRNAs has become a promising strategy for cancer treatment. circRNAs can function as either tumor suppressors or oncogenes. For example, circCDYL is downregulated in colon, bladder, and triple-negative breast cancers, and its expression is positively correlated with patient survival [64]. Additionally, further studies have shown that overexpression of circCDYL promotes apoptosis and inhibits the proliferation of breast cancer cells [65]. In contrast, some circRNAs have been identified as oncogenes. For instance, circRNAHIPK3, derived from exon 2 of the HIPK3 gene, is highly expressed in several types of cancer, including glioma [66], prostate cancer [67], breast cancer [68], colorectal cancer [69], and renal cancer [70]. circ-ITCH is a well-known circRNA generated from several exons of the itchy E3 ubiquitin protein ligase (ITCH) gene, which was first identified in a study by Memczak et al. [71]. It has been reported to be downregulated in several types of cancer, including colorectal cancer [72], esophageal squamous cell carcinoma [73], lung cancer [74], and hepatocellular carcinoma [75]. circ-ITCH functions as a powerful tumor suppressor via a classic pathway, in which it acts as a sponge for certain miRNAs that target the parental transcripts of ITCH [72–74]. hsa-circ-0000423 encodes a functional protein (circPPP1R12A-73aa) that promotes the proliferation, migration, and invasion of colon cancer cells [76]. Another example is the circRNA ciRS-7 (also known as CDR1AS), first identified by Hansen in 2011 [77]. Abnormal ciRS-7 expression has been reported in various types of cancers, including lung cancer, hepatocellular carcinoma, cholangiocarcinoma, osteosarcoma, melanoma, colorectal cancer, breast cancer, esophageal squamous cell carcinoma, nasopharyngeal carcinoma, gastric cancer, pancreatic ductal adenocarcinoma, laryngeal squamous cell carcinoma, and cholangiocarcinoma. Upregulation of ciRS-7 can act as an oncogene and promote tumor progression, particularly in lung cancer, hepatocellular carcinoma, colorectal cancer, and esophageal squamous cell carcinoma [78]. Finally, circFNDC3B functions as a tumor suppressor by sponging miR-1178 in human bladder cancer [79].

CircKIF4A (circ_0007255) increased the expression of phosphorylated protein kinase B (p-AKT)/phosphatidylinositol 3-kinase (PI3K), promoting bladder cancer growth and metastasis *in vitro* and *in vivo*. circKIF4A acted as a sponge for miR-375 and miR-1231 to enhance the expression of Notch2, which plays an oncogenic role in bladder cancer [80]. However, the function of circRNAs as "miRNA sponges" in bladder cancer has not been clearly elucidated [81]. For example, circ_0058063 promotes bladder cancer progression by sponging miR-145-5p and regulating CDK6 expression [82]. circRNA mitochondrial translation optimization 1 homolog (circMTO1) (hsa_circRNA_0007874/hsa_circRNA_104135) was significantly downregulated in hepatocellular carcinoma tissues. Upregulation of circMTO1 suppresses hepatocellular carcinoma by sponging oncogenic miR-9 [83]. While circPVT1 promoted gastric cancer proliferation by sponging members of the miR-125 family and has been proposed as an independent prognostic marker for overall survival [84], circABCB10 modulated the proliferation and progression of breast cancer by sponging miR-1271 [85], and circTP63 promoted lung squamous cell carcinoma progression by competitively binding to miR-873-3p and upregulating forkhead box protein M1 (FOXM1) [86]. Further, circPTPRA inhibits the proliferation of bladder cancer cells by inhibiting the miR-636/KLF9 interaction [87] and circZKSCAN1 inhibited hepatocellular carcinoma growth and migration [88]. According to an unbiased bioinformatics analysis, circ-VANGL1, which is derived from the back-splicing of exon three and exon four of VANGL1 mRNA, is significantly upregulated in bladder cancer tissues [89]. circRNAs, characterized by a covalently closed continuous loop structure [89], have been identified as endogenous ncRNAs in various cell lines and species using high-throughput sequencing technology. Recent reports have shown that circRNAs are involved in the initiation, development, and progression of several diseases, including cancer [90]. Numerous studies have demonstrated that circRNAs play crucial roles in various cancers, serving as potential biomarkers and therapeutic targets [91]. circ-ZKSCAN1 is downregulated in bladder cancer and is correlated with tumor metastasis status, recurrence, pathological T stage, and histological grade [92]. Moreover, circRNA-Cdr1as directly binds to miR-135a and inhibits its activity in bladder cancer [93]. Hsa_circ_001569, a circRNA of 1776 bp, is spliced from a linear RNA precursor. The official name of hsa_circ_001569 was hsa_circ_0000677 [94]. Xie et al. [95] found that hsa_circ_001569 was highly expressed in colorectal cancer tissues and correlated positively with the degree of clinical features such as TNM stage. circAGFG1 could promote triple negative breast cancer (TNBC) cell proliferation, mobility, invasion, tumorigenesis, and metastasis *in vivo* [96]. circRNA-MYLK promotes bladder carcinoma metastasis by inducing EMT via sponging miR-29a [97]. circSMARCA5 directly binds to miR-17-3p and miR-181b-5p to inhibit hepatocellular carcinoma (HCC) metastasis in hepatocellular carcinoma [98]. circDENND4C was validated as a sponge for miR-200b and miR-200c. Deficiency of miR-200b or miR-200c reverses the suppressive effect of circDENND4C knockdown on breast cancer progression [99]. circEPSTI1 binds miR-4753 and miR-6809 as

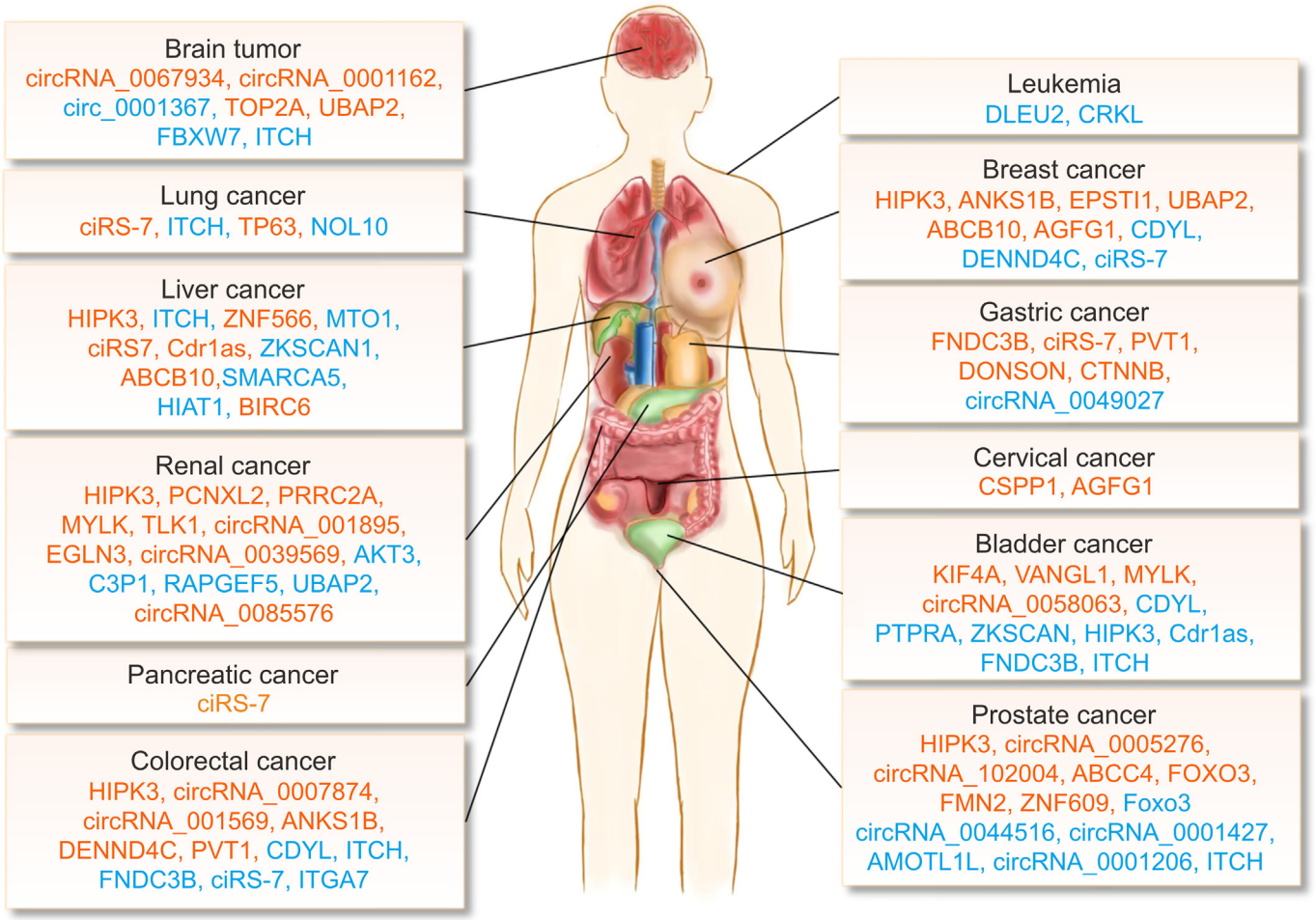


**Fig. 2.** Circular RNAs (circRNAs) associated with various types of cancer. Orange font represents oncogenes, and blue font represents tumor suppressor genes.

**Table 2**
List of circular RNAs (circRNAs) and their role in cancer development.

| Cancer type | Oncogene | Mechanism of action | Tumor suppressor | Mechanism of action |
|---|---|---|---|---|
| Brain | 0067934 | Promotes cell proliferation [108]. | FBXW7 | Inhibits cell proliferation [109]. |
| | 0001162 | Promotes cell proliferation and invasion [110]. | ITCH | Inhibits cell proliferation and invasion [111]. |
| | TOP2A | Promotes cell proliferation and invasion [112]. | 0001367 | Inhibits cell migration, invasion and proliferation [113]. |
| | UBAP2 | Promotes cell proliferation [114]. | | |
| Lung | ciRS-7 | Promotes cells invsion and metastasis [115]. | ITCH | Inhibits cell proliferation [74]. |
| | TP63 | Promotes cell proliferation [86]. | NOL10 | Inhibits cell proliferation [116]. |
| Liver | HIPK3 | Regulates cell proliferation and migration [117]. | ITCH | Inhibits cell proliferation [75]. |
| | ZNF566 | Promotes cell migration, invasion and proliferation [118]. | MTO1 | Inhibits cell proliferation and invasion [83]. |
| | ciRS-7 | Promotes cells invsion and metastasis [119]. | ZKSCAN1 | Inhibits hepatocellular carcinoma growth and migration [88]. |
| | Cdr1as | Promotes cell migration and proliferation [120]. | SMARCA5 | Inhibits hepatocellular carcinoma growth and migration [98]. |
| | ABCB10 | Promotes cell migration and proliferation [121]. | HIAT1 | Inhibits cell proliferation [122]. |
| | BIRC6 | Promotes cell migration, invasion and proliferation [123]. | | |
| Renal | HIPK3 | Promotes cell proliferation and invasion [70]. | AKT3 | Inhibits cell metastasis [124]. |
| | PCNXL2 | Promotes the proliferation and invasion [125]. | C3P1 | Inhibits cell proliferation [126]. |
| | PRRC2A | Promotes cell migration and proliferation [127]. | RAPGEF5 | Inhibits cell proliferation and metastasis [128]. |
| | MYLK | Promotes cell migration and proliferation [129]. | UBAP2 | Inhibits cell proliferation and metastasis [130]. |
| | TLK1 | Promotes the proliferation and metastasis [131]. | | |
| | 001895 | Promotes the proliferation [132]. | | |
| | EGLN3 | Promotes cells invsion and proliferation [133]. | | |
| | 0039569 | Promotes the proliferation and metastasis [134]. | | |
| | 0085576 | Promotes the proliferation and metastasis [135]. | | |
| Pancreatic | ciRS-7 | Promotes cells invsion and metastasis [136]. | | |
| Colorectal | HIPK3 | Promotes cell proliferation and invasion [69]. | CDYL | Inhibits cell proliferation, migration and invasion [64]. |
| | 0000423 | Promotes the proliferation, migration and invasion of colon cancer cells [76]. | ITCH | Inhibits cell proliferation, migration and invasion [72]. |
| | 001569 | Promotes cell proliferation and invasion [95]. | FNDC3B | Inhibits cell proliferation, migration and invasion [137]. |
| | ANKS1B | Promotes migration and invasion [102]. | ciRS-7 | Inhibits cell proliferation and invasion [101]. |
| | DENND4C | Promotes cell proliferation [104]. | ITGA7 | Inhibits cell proliferation and migration [105]. |
| | PVT1 | Promotes metastasis [138]. | | |
| Leukemia | DLEU2 | Promotes cell proliferation [106]. | CRKL | Inhibits cell proliferation [107]. |
| Breast | HIPK3 | Promotes cell proliferation and invasion [68]. | CDYL | Inhibits cell proliferation, migration and invasion [64]. |
| | ANKS1B | Pro-metastasis [139]. | DENND4C | Inhibits cell migration and invasion [99]. |
| | EPSTI1 | Promotes cell proliferation [140]. | ciRS-7 | Inhibits cell migration and invasion [141]. |
| | UBAP2 | Promotes cell proliferation [142]. | | |
| | ABCB10 | Promotes cell proliferation [85]. | | |
| | AGFG1 | Promotes TNBC cell proliferation, mobility and invasion [96]. | | |
| Gastric | FNDC3B | Promotes the migration and invasion of gastric cancer [143]. | 0049027 | Suppresses the growth, invasion and metastasis of gastric cancer cells [144]. |
| | ciRS-7 | Promotes cell proliferation and invasion [145]. | | |
| | PVT1 | Promotes cell proliferation and invasion [84]. | | |
| | DONSON | Promotes cell proliferation and invasion [146]. | | |
| | CTNNB | Promotes cell proliferation and invasion [147]. | | |
| Ovarian | CSPP1 | Promotes cell migration and proliferation [103]. | | |
| | AGFG1 | Promotes cell proliferation [148]. | | |
| Bladder | KIF4A | Promotes cell proliferation [80]. | CDYL | Suppresses cell proliferation, migration and invasion [64]. |
| | VANGL1 | Promotes cell proliferation, migration and invasion [88]. | PTPRA | Suppresses cell proliferation [87]. |
| | MYLK | Promotes cell proliferation [97]. | ZKSCAN | Suppresses cell proliferation [92]. |
| | 0058063 | Promotes cell proliferation and invasion [82]. | HIPK3 | Inhibits migration, invasion and angiogenesis of bladder cancer [81]. |
| | | | Cdr1as | Suppresses cell proliferation [93]. |
| | | | FNDC3B | Suppresses cell proliferation, migration and invasion [79]. |
| | | | ITCH | Inhibits cell proliferation, migration, invasion and metastasis [149]. |
| Prostate | HIPK3 | Promotes cell proliferation and invasion [67]. | 0001427 | Inhibits cell proliferation [150]. |
| | 0005276 | Promotes cell proliferation and migration [151]. | AMOTL1L | Inhibits cell proliferation [152]. |
| | 102004 | Promotes cell proliferation [153]. | 0001206 | Inhibits cell proliferation, migration and invasion [154]. |
| | ABCC4 | Promotes cell proliferation [155]. | ITCH | Inhibits cell proliferation [156]. |
| | FOXO3 | Promotes cell proliferation [157]. | Foxo3 | Inhibits cell proliferation, migration and invasion [158]. |
| | FMN2 | Promotes cell proliferation [159]. | | |
| | ZNF609 | Promotes cell proliferation, migration and invasion [160]. | | |
| | 0044516 | Promotes cell proliferation, migration and invasion [161]. | | |

miRNA sponges to regulate BCL11A expression and affect TNBC proliferation and apoptosis [100].

By analyzing the Gene Expression Omnibus (GEO) database (GSE101123), Tang et al. [101] identified a novel circRNA, circ-UBAP2 (hsa_circ_0001846), which is significantly overexpressed in TNBC. Further, circANKS1B promoted colorectal cancer cell migration and invasion by acting as a molecular sponge for miR-149 to modulate FOXM1 and Slug protein levels [102] and circRNA hsa_circ_CSPP1 regulated cell migration and proliferation in cervical cancer through the miR-361-5p/ITGB1 pathway in PI3K-AKT signaling [103]. The expression of circDENND4C and GLUT1 was upregulated in colorectal cancer tissues and cells [104]. The knockdown of circITGA7 or ITGA7 promotes the proliferation and migration of colorectal cancer cells *in vitro* and enhances colorectal cancer growth *in vivo* [105]. Moreover, circRNA-DLEU2 accelerated acute myeloid leukemia (AML) by suppressing miR-496 and promoting PRKACB expression [106]. circCRKL inhibits the proliferation and colony-forming ability of AML cells when overexpressed, and its silencing has been found to promote these processes [107]. Fig. 2 and Table 2 ([64,67–70,72,74–88,92,93,95–99,101–161]) summarize the various circRNAs and their roles in cancer development.

### 3.2. lncRNAs as therapeutic targets in cancer

Reportedly, lncRNAs are involved in various processes of cancer development, such as tumor cell proliferation, metastasis, and drug resistance [38,43]. They play a critical role in gene regulation by interacting with DNA, RNA, and proteins. Given their myriad of roles, targeting them may support the development of novel cancer treatments. HOTTIP, lncTCF7, EPIC1, linc0624, and H19 play critical roles in cancer development and progression through various mechanisms, including epigenetic regulation, modulation of gene expression, and regulation of signaling pathways. Dysregulation of lncRNA expression has been associated with various cancers, and targeting these molecules has been proposed as a potential therapeutic strategy for cancer treatment.

HOTTIP, derived from the HOXA gene, has been shown to be highly expressed in multiple cancers. Recently, Luo et al. [162] demonstrated that HOTTIP acts as an oncogene in AML. They found that HOTTIP was aberrantly elevated in AML and functioned as an epigenetic regulator to modulate hematopoietic gene-associated chromatin signatures and transcription. lncTCF7 is another lncRNA transcribed from the TCF locus. Wang et al. [163] have shown that lncTCF7 is highly expressed in liver cancer stem cells (CSCs) and is important for liver CSC self-renewal. Mechanistically, lncTCF7 recruited the SWI/SNF complex to the TCF7 promoter and activated Wnt signaling to sustain the self-renewal of liver CSC. EPIC1 was first identified as an oncogene in luminal B breast cancer [164]. Recently, EPIC1 has been found to be highly expressed in glioma [165], cholangiocarcinoma [166], pancreatic [167], and lung cancers [168]. Elevated EPIC1 levels promote tumor growth by interacting with MYC to elevate its target genes, such as CDKN1A, CCNA2, and CDC20 [164]. Recently, Li et al. [169] demonstrated that linc0624, an anti-sense strand of CHD1L, functions as a molecular decoy to segregate HDAC6 and the TRIM28-ZNF354C transcriptional corepressor complex away from specific genomic loci, thus promoting the progression of hepatocellular carcinoma. The H19 lncRNA is located downstream of insulin growth factor 2 (IGF2) on chromosome 11p15 in humans and chromosome 7 in mice. Its expression is increased in various cancers, including gliomas, where it correlates with cell growth and invasion and plays an oncogenic role [170]. lncRNA H19 expression is increased in lung cancer tissues and cell lines, and H19 promotes cell proliferation and metastasis. H19 is upregulated in nearly all human cancers and involved in every stage of tumorigenesis [170]. It is significantly upregulated in hepatitis B virus (HBV)-related HCC tissues, which is associated with HCC progression; its expression correlates with tumor stage, distant metastasis, and poor prognosis of HBV-related HCC [171]. lncRNA H19 is significantly upregulated in pancreatic cancer cell lines and facilitates pancreatic cancer metastasis and EMT by directly targeting miR-675-3p [172]. H19 upregulates the expression of various cancer-related mRNA by serving as a ceRNA and participates in the PI3K-AKT signaling pathway, playing a key role in promoting cancer progression [173].

Furthermore, some lncRNAs suppress carcinogenesis. For instance, pvt1b, a p53-dependent isoform of an lncRNA, suppresses lung cancer growth by downregulating c-Myc expression [170]. DIRC3 is downregulated in melanomas, and its lower expression is associated with shorter survival [174]. Further studies revealed that DIRC3 inhibited the proliferation of melanoma cells by elevating the expression of the tumor suppressor IGFBP5. Recently, SATB2-AS1, an anti-sense transcript of the tumor suppressor SATB2, has been shown to be downregulated in colorectal cancer. SATB2-AS1 knockdown significantly increased cell proliferation, migration, and invasion [171]. Mechanistically, SATB2-AS1 functions as a scaffold to recruit p300 to the SATB2 promoter, up-regulating SATB2. Elevated SATB2 recruits HDAC1 to the snail promoter, thereby suppressing snail expression and epithelial-to-mesenchymal transition. MALAT1, a nuclear lncRNA, is also a tumor suppressor in breast cancer. Kim et al. demonstrated that MALAT1 knockout promotes breast cancer metastasis by disrupting the recruitment of the transcription factor TEAD and the co-activator YAP to target gene promoters [175]. MEG3 is an imprinted gene located at 14q32 that encodes ncRNAs with anti-proliferative functions [175]. MEG3 overexpression inhibits tumorigenesis in breast cancer cell lines by targeting miR-93-5p [176]. Additionally, ectopic overexpression of MEG3 effectively inhibits the growth of gallbladder cancer cells [177], reduces the proliferation and metastasis of gastric cancer cells [178], and inactivates the Wnt/β-catenin pathway, reducing podocyte injury in diabetic nephropathy [179]. A list of lncRNAs and their roles in cancer development is summarized in Fig. 3 and Table 3 [163,169,172,175,180–277].

Dysregulation of lncRNA expression is an emerging hallmark of cancer, and targeting lncRNAs has shown a great potential as a therapeutic approach. Recent advances in RNA-targeted therapies such as anti-sense oligonucleotides and siRNAs have made it possible to specifically target and modulate lncRNA expression. Clustered regularly interspaced short palindromic repeats (CRISPR)-CRISPR-associated protein (Cas)9-based gene editing technology provides a precise approach for regulating lncRNA expression. Several pre-clinical studies have demonstrated the effectiveness of targeting lncRNAs in cancer treatment, and clinical trials are underway. However, challenges remain in the development of safe and effective lncRNA-targeted therapies, including delivery and off-target effects. Further research is required to fully understand the molecular mechanisms of lncRNA regulation in cancer and identify suitable lncRNA targets for therapeutic interventions.

### 3.3. miRNAs as therapeutic cancer targets

miRNAs are small ncRNAs that play critical roles in gene expression regulation by binding to the 3′ untranslated regions of target mRNAs, leading to mRNA degradation or translational inhibition [44,45]. Numerous studies have demonstrated the important roles of miRNAs in various cancers. Several miRNAs are highly expressed in cancer cells and promote their development. miRNAs regulate the progression of various cancers. miR-126 is highly expressed in breast [278] and colorectal cancers [279]. Recently,

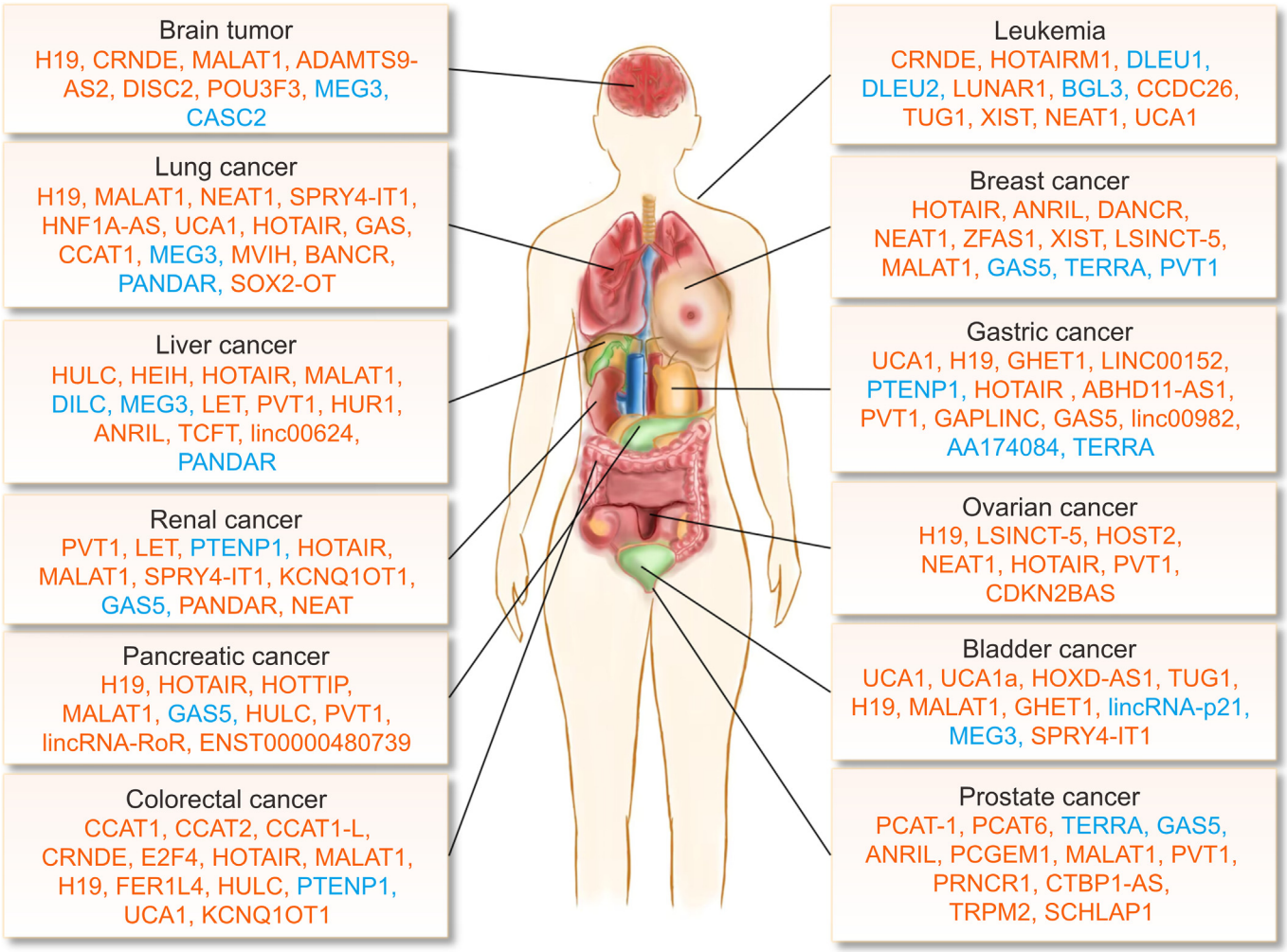


**Fig. 3.** Long non-coding RNAs (lncRNAs) associated with various types of cancer. Orange font represents oncogenes, and blue font represents tumor suppressor genes.

Lechman et al. showed that miR-126 is highly expressed in human B-ALL [280]. Forced expression of miR-126 in mouse hematopoietic stem progenitor cells results in B-cell leukemia. Further studies revealed that the overexpression of miR-126 downregulates the expression of p53 and its associated genes [281], whereas the suppression of miR-126 triggers apoptosis and inhibits B-ALL progression in xenograft mice. miR-155 has been identified as an oncogene in various types of cancer, including colon, breast, gastric, and liver cancer [282–286]. Consistent with its oncogenic role, miR-155 is regarded as a therapeutic target in different cancers. Recently, miR-155 has been shown to be upregulated in plexiform neurofibromas [287]. Upregulated miR-155 expression increases proliferation and sphere formation in plexiform neurofibroma-initiating cells. Conversely, anti-miR-155 nucleic acid decreased tumor number in a mouse spontaneous plexiform neurofibroma model. miR-215 is another oncogene that is upregulated in glioblastomas under hypoxia [288]. Hypoxia-elevated miR-215 targets the epigenetic regulator KDM1B to regulate related downstream signaling and thus maintains glioblastoma initiation of cell growth [288]. Some miRNAs, such as miR-105, which is highly expressed in metastatic breast cancer cells, are secreted by cancer cells via exosomes to modulate the tumor microenvironment [289]. After secretion, miR-105-containing exosomes enter endothelial monolayers and suppress the expression of the tight junction protein ZO-1, resulting in elevated vascular permeability and cancer metastasis [289].

Some miRNAs, such as let-7 and miR-34a, are regarded as tumor suppressors. The let-7 miRNA family contains various members. Most of these genes are downregulated in multiple types of cancer, including hepatocellular carcinoma [290], non-small cell lung cancer [291], prostate cancer [292], breast cancer [293], colon cancer [294], and pancreatic cancer [295]. let-7 miRNAs target and downregulate many oncogenic genes, including E2F1, ARID3B, KRAS, and c-Myc, resulting in the suppression of tumor progression [296]. Furthermore, higher levels of let-7 indicated a better prognosis in hepatocellular and thyroid carcinomas [297]. Recently, Tristán-Ramos et al. [298] showed that let-7 also targeted long interspersed element class 1 (LINE-1), the only autonomously active transposable element highly expressed in lung cancer, to impair its translation and reduce its mobilization. let-7 has been found to sustain somatic genome integrity by restricting LINE-1 retro-transposition. Another tumor suppressor that plays an important role in the suppression of cancer progression is miR-34a; Bu et al. found it to be critical for the asymmetric division of colon cancer stem cells (CCSCs) [299]. Silencing miR-34a inhibits asymmetric cell division, promotes CCSC self-renewal, and accelerates colon cancer progression. Kennerdell et al. [300] also demonstrated that miR-34a expression was decreased in most colon cancer cell lines and that low levels of miR-34a predicted a poor prognosis. Furthermore, the tumor suppressor miR-29 has been identified in the microenvironment of patients with chronic lymphocytic

**Table 3**
List of long non-coding RNAs (lncRNAs) and their role in cancer development.

| Cancer type | Oncogene | Mechanism of action | Tumor suppressor | Mechanism of action |
|---|---|---|---|---|
| Brain | H19 | Promotes angiogenesis [180]. | MEG3 | Inhibits proliferation [175]. |
| | CRNDE | Promotes proliferation and invasion [181]. | CASC2 | Inhibition of glioma cell apoptosis, migration and invasion [182]. |
| | MALAT1 | Promotes proliferation and inhibit apoptosis [183]. | | |
| | DISC | Genetic susceptibilitu factors [184]. | | |
| | ADAMTS9-AS2 | Promotes migration and invasion [185]. | | |
| | POU3F3 | Promotes melanoma cell proliferation [186]. | | |
| Lung | H19 | Promotes angiogenesis [187]. | PANDAR | Inhibits cell growth [188]. |
| | MALAT1 | Promotes proliferation invasion and metastasis [189]. | MEG3 | Inhibits proliferation [175]. |
| | NEAT1 | Promotes proliferation [190]. | GAS5 | Reduces cell proliferation and promotes apoptosis [191]. |
| | UCA1 | Promotes proliferation [192]. | | |
| | HOTAIR | Promotes proliferation and metastasis [193]. | | |
| | CCAT1 | Promotes cell cycle and cellproliferation [194]. | | |
| | BANCR | Promotes proliferation and invasion [195]. | | |
| | MVIH | Promote cell proliferation and the cell cycle [196]. | | |
| | HNF1A-AS1 | Promtes migration and invasion [197]. | | |
| | SOX2 | Increases proliferation, stemness, cell migration [198]. | | |
| | SPRY4-ITL | Promotes proliferation, apoptosis, migration and invasion [199]. | | |
| Liver | HOTAIR | Promotes proliferation and invasion [200]. | MEG3 | Inhibits proliferation [201]. |
| | HULC | Promotes metastasis [202]. | PANDAR | Inhibits cell growth [203]. |
| | PVT1 | Promotes proliferation invasion and metastasis [204]. | DILC | Promotes apoptosis [205]. |
| | HUR1 | Promotes proliferation [206]. | | |
| | TCFT | Self-renewal of liver CSCs and tumor propagation and acts as a tumor promoter [163]. | | |
| | MALAT1 | Promotes proliferation and inhibit apoptosis [207]. | | |
| | HEIH | Promotes cell proliferation, migration, invasion and drug resistance [208]. | | |
| | LINC00624 | Promotes tumor growth and metastasis [169]. | | |
| | LET | Promotes metastasis [209]. | | |
| | ANRIL | Inducing cell proliferation [210]. | | |
| Renal | PANDAR | Promotes proliferation [211]. | GAS5 | Inhibits cell growth [212]. |
| | HOTAIR | Promotes proliferation [213]. | PTENP1 | Tumor suppressor [210]. |
| | MALAT1 | Promotes proliferation [214]. | | |
| | LET | Promotes metastasis [209]. | | |
| | SPRY4-IT4 | Promotes proliferation [215]. | | |
| | KCNQ1OT1 | Promotes cell proliferation, cycle, migration and invasion, metastasis, glucose metabolism, and immune evasion [216]. | | |
| | NEAT1 | Promotes cell cycle and proliferation, anti-apoptosis [217]. | | |
| | PVT1 | Promotes proliferation invasion and metastasis [204]. | | |
| Pancreatic | H19 | Promotes proliferation invasion and metastasis [172]. | GAS5 | Inhibits cell growth [212]. |
| | HOTAIR | Promotes proliferation and metastasis anti-apoptosis [218]. | | |
| | HOTTIP | Promotes invasion and metastasis, anti-apoptosis [219]. | | |
| | MALAT1 | Promotes proliferation and metastasis [202]. | | |
| | HULC | Promotes metastasis [202]. | | |
| | PVT1 | Promotes proliferation [220]. | | |
| | LincRNA-ROR | Promotes proliferation invasion and metastasis [221]. | | |
| | ENST00000480739 | Promotes proliferation invasion and metastasis [219]. | | |
| Colorectal | CCAT1 | Tumorigenesis (cell cycle and cell proliferation), tumor progression (invasion) [222]. | PTENP1 | Tumor suppressor [210]. |
| | CCAT2 | Tumorigenesis (proliferation), tumorprogression (migration and invasion) [223]. | | |
| | CCAT1-L | Promotes metastasis [224]. | | |
| | H19 | Promotes proliferation invasion and metastasis [172]. | | |
| | CRNDE | Promotes proliferation [225]. | | |
| | KCNQ1OT1 | Upregulated in colorectal cancer [226]. | | |
| | FER1L4 | Promotes invasion [227]. | | |
| | MALAT1 | Promotes proliferation invasion and metastasis [228]. | | |
| | E2F4 | Promotes proliferation [229]. | | |
| | HOTAIR | Promotes proliferation and metastasis [230]. | | |
| | HULC | Promotes metastasis [202]. | | |
| | UCA1 | Promotes proliferation [231]. | | |
| Leukemia | CRNDE | Promotes proliferation [232]. | BGL3 | Inhibits proliferation [233]. |
| | XIST | Promotes proliferation and inhibit apoptosis [234]. | DLEU1 | Inhibits proliferation, apoptosis, migration and invasion [235]. |
| | HOTAIRM1 | Promotes proliferation and metastasis [236]. | DLEU2 | Inhibits proliferation, apoptosis, migration and invasion [237]. |
| | TUG1 | Promotes proliferation, migration, invasion [238]. | | |
| | LUNAR1 | Promotes proliferation, migration, invasion and tumour growth [239]. | | |
| | CCDC26 | Promotes proliferation [240]. | | |

(*continued on next page*)

**Table 3** (*continued*)

| Cancer type | Oncogene | Mechanism of action | Tumor suppressor | Mechanism of action |
|---|---|---|---|---|
| | NEAT1 | Promotes proliferation and migration [241]. | | |
| | UCA1 | Promotes proliferation [242]. | | |
| Breast | HOTAIR | Promotes proliferation and metastasis [243]. | TERRA | Affects the expression of its target gene [210]. |
| | ANRIL | Promotes proliferation invasion and metastasis, anti-apoptosis [244]. | PVT1 | Inhibits cell growth [215]. |
| | DANCR | Promotes proliferation invasion and metastasis [245]. | GAS5 | Inhibits cell growth [212]. |
| | NEAT1 | Promotes proliferation and anti-apoptosis [246]. | | |
| | XIST | Promotes proliferation and inhibit apoptosis [247]. | | |
| | LSINCT-5 | Promotes proliferation [248]. | | |
| | ZFAS1 | Tumorigenesis [249]. | | |
| | MALAT1 | Promotes metastasis [250]. | | |
| Gastric | UCA1 | Promotes proliferation and anti-apoptosis [251]. | PTENP1 | Tumor suppressor [210]. |
| | H19 | Promotes invasion [252]. | AA174084 | Tumor suppressor [253]. |
| | GHET1 | Promotes proliferation [254]. | TERRA | Affects the expression of its target gene [210]. |
| | ABHD11-AS1 | Promotes invasion [255]. | | |
| | GAPLINC | Associats with poor prognosis [256]. | | |
| | GAS5 | Inhibits cell apoptosis [210]. | | |
| | PVT1 | Promotes proliferation invasion and metastasis [204]. | | |
| | LINC00152 | Promotes migration and invasive [257]. | | |
| | LINC00982 | Promotes proliferation [258]. | | |
| | HOTAIR | Promotes invasion [252]. | | |
| Ovarian | H19 | Promotes proliferation invasion and metastasis [259]. | | |
| | LSINCT-5 | Promotes proliferation [260]. | | |
| | HOST2 | Promotes proliferation invasion and metastasis [261]. | | |
| | HOTAIR | Promotes proliferation and metastasis [262]. | | |
| | NEAT1 | Promotes proliferation [190]. | | |
| | PVT1 | Promotes proliferation [263]. | | |
| | CDKN2BAS | Promotes proliferation and metastasis [264]. | | |
| Bladder | UCA1, UCA1a | Promote proliferation [263]. | MEG3 | Inhibits proliferation [175]. |
| | H19 | Promotes proliferation invasion and metastasis [259]. | LincRNA-P21 | Tumor suppressor [265]. |
| | HOXD-AS1 | Promotes proliferation invasion and metastasis [266]. | | |
| | MALAT1 | Promotes metastasis [250]. | | |
| | TUG1 | Promotes invasion [267]. | | |
| | GHET1 | Promotes proliferation [254]. | | |
| | SPRY4-IT1 | Promotes proliferation [268]. | | |
| Prostate | PCAT-1 | Promotes proliferation and anti-apoptosis [269]. | TERRA | Affects the expression of its target gene [210]. |
| | PCAT6 | Promotes proliferation [270]. | GAS5 | Promotes apoptosis [271]. |
| | CTBP1-AS | Promotes proliferation [272]. | | |
| | PVT1 | Promotes proliferation [273]. | | |
| | TRPM2 | Promotes proliferation [274]. | | |
| | MALAT1 | Promotes metastasis [250]. | | |
| | SCHLAP1 | Promotes metastasis [275]. | | |
| | PRNCR1 | Involved in cell viability and transactivation activity [276]. | | |
| | PCGEM1 | Promotes proliferation [277]. | | |
| | ANRIL | Promotes proliferation invasion and metastasis anti-apoptosis [244]. | | |

leukemia (CLL). In CLL, miR-29 targets the tumor necrosis factor 4 (TRAF4), a factor associated with CD40 activation and B cell receptor signaling [301]. Downregulation of miR-29 increases TRAF4 expression and activates CD40 signaling in CLL. Conversely, activated CD40 represses the expression of miR-29. The miR-29-TRAF4-CD40 signaling axis acts as a negative feedback regulatory loop in CLL. The list of miRNAs and their roles in cancer development are summarized in Fig. 4 and Table 4 ([279,282,290,301–424]).

In summary, certain miRNAs, including let-7, miR-34a, and miR-29, function as tumor suppressors by targeting and downregulating oncogenic genes. This activity leads to the suppression of tumor progression and is associated with a more favorable prognosis. In contrast, some miRNAs, such as miR-21, miR-155, and miR-221/222, act as oncogenes. This activity results in the inhibition of tumor suppressor genes and the promotion of the proliferation, invasion, and metastasis of cancer cells, commonly leading to a poor prognosis. The effects of miRNAs on cancer development vary depending on the specific miRNA and the cancer type.

## 4. Impact of ncRNA on tumor immunity

ncRNAs play a crucial role in tumorigenesis, where DNA methylation, covalent modifications of histones, and the interplay of various ncRNAs contribute to the cellular manifestation of epigenetic changes in the genome [425]. Among the diverse factors influencing the epigenetic programming of the host, new-generation non-coding molecules, such as miRNAs, lncRNAs, and circRNAs, play a pivotal role. These ncRNAs influence a spectrum of cellular processes, including immunity, cellular differentiation, and tumor development [426]. The role of the immune system in tumor development is intricate, with the ability to impede and foster conditions conducive to tumor growth. The following paragraph summarizes typical cases illustrating the impact of the three major

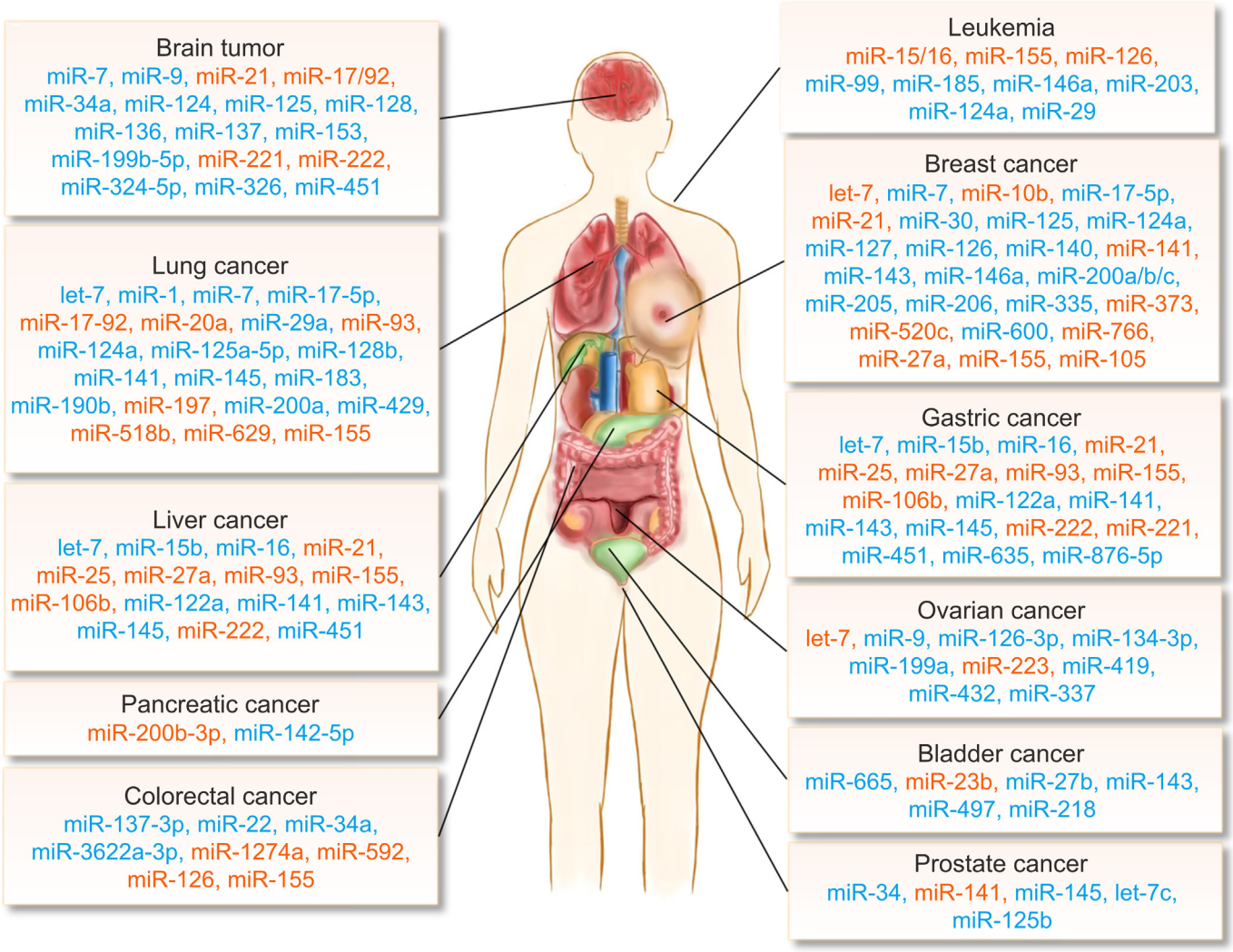


**Fig. 4.** microRNAs (miRNAs) associated with various types of cancer. Orange font represents oncogenes, and blue font represents tumor suppressor genes.

types of ncRNAs (miRNAs, lncRNAs, and circRNAs) on tumor immunity (Fig. 5).

### 4.1. miRNA and tumor immunity

Macrophages, pivotal players in innate immunity, play dual roles as specialized antigen-presenting cells (APCs) and effectors in dissolving tumor cells, contributing to anti-tumor responses. However, during tumor development, macrophages undergo a phenotypic shift towards the M2 phenotype. M2-polarized cells mediate anti-inflammatory and pro-tumor responses, foster immunosuppression, and support tumor angiogenesis and metastasis. Tumor-associated macrophages (TAMs) predominantly display the M2 phenotype, which actively promotes tumor progression [427]. MiR-155 is a well-known regulator that hinders IFN-γ signal transduction, a crucial aspect in the context of precancerous lesions, thereby promoting the M2 polarization of M1 effector macrophages. The increased expression and stability of miR-155 in hematopoietic tumors strongly implicate its involvement in tumor development [428]. In contrast, miR-511-3p downregulates pro-tumor gene features in TAMs to halt M2 polarization, effectively inhibiting tumor growth [429]. This unique role of miR-511-3p makes it a promising target for cancer immunotherapy. Further studies, including miR-19a-3p [430] and miR-21 [431], exemplify this duality, promoting M2 polarization and contributing to cancer progression. These examples underscore the pivotal role of miRNAs as key regulators of host signaling pathways, emphasizing their importance in determining the fate of tumors within the host.

Natural killer (NK) cells are integral components of the innate immune system and contribute significantly to anti-tumor immunity. These lymphocytes exhibit cell-mediated cytotoxicity against tumor cells and play a regulatory role by secreting cytokines and chemokines that influence other immune cells [432]. Several miRNAs, such as miR-122, miR-21, miR-15b, and miR-155, have been identified in a mouse model and shown to activate immature NK cells, drive their differentiation, and inhibit tumor development [433]. The overexpression of miR-544 contributes to the suppression of NK cell cytotoxicity by downregulating interferon-γ (IFN-γ), leading to the promotion of immune escape in liver cancer cells. This effect is achieved by targeting RUNX3 and downregulating NCR1 [434]. Similarly, certain ncRNAs, such as miR-17/92 [435] and miR-20a [436], have been implicated in the inhibition of NK cell activation and antibody-dependent cytotoxicity (ADCC). Furthermore, miR-146a [437], miR-150 [438], and miR-30b [439] demonstrate inhibitory effects on NK/T cells, thereby promoting tumor development. Targeting these specific miRNAs is a critical strategy

**Table 4**
List of microRNAs (miRNAs) and their role in cancer development.

| Cancer type | Oncogene | Mechanism of action | Tumor suppressor | Mechanism of action |
|---|---|---|---|---|
| Brain | miR-21 | An antiapoptotic factor [302]. | miR-136 | Promotes apoptosis [303]. |
| | miR-221, miR-222 | Promotes cell proliferation [304]. | miR-128 | Inhibits proliferation and differentiation [305]. |
| | miR-17/92 | Promotes cell cycle progression [306]. | miR-7 | Decreases viability and invasiveness [307]. |
| | | | miR-153 | Inhibits proliferation and promotes apoptosis [308]. |
| | | | miR-451 | Inihibits cell growth [309]. |
| | | | miR-34a | Inihibits cell proliferation, cell cycle progression and invasion [310]. |
| | | | miR-124, miR-137 | Inhibits cell proliferation [311]. |
| | | | miR-9, miR-125a | Promotes cell growth arrest and apoptosis [312]. |
| | | | miR-199b-5p | Inhibits cell proliferation [313]. |
| | | | miR-125b, miR-324-5p, miR-326 | Inhibits cell growth [314]. |
| Lung | miR-518b | Promotes proliferation and metastasis [315]. | let-7 | Reduces cell proliferation [316]. |
| | miR-629 | Promotes proliferation and metastasis [317]. | miR-124a | Suppresses the expression of CDK6 [318]. |
| | miR-17-92 | Enhances cell proliferation [319]. | miR-200a, miR-141, miR-429 | Represses EMT [320]. |
| | miR-93, miR-98, miR-197 | Inhibits Fus1 protein expression [321]. | miR-190b | Suppresses cell growth [322]. |
| | miR-20a | Promotes cell growth, migration and invasion [323]. | miR-128b | The loss of heterozygosity (LOH) of MicroRNA-128b was found to be frequent in tumor samples and had a significant correlation with clinical response and survival after treatment with gefitinib. However, there was no correlation found between EGFR expression and mutation status and survival outcome [324]. |
| | | | miR-125a-5p | An epidermal growth factor-signaling-regulated miRNA, may function as a metastatic suppressor [325]. |
| | | | miR-29a | Anti-invasive and anti-proliferative [326]. |
| | | | miR-1 | The depletion of miR-1 resulted in the facilitation of N417 cell growth, along with an elevation of its targets. Moreover, ectopic miR-1 induced apoptosis in A549 cells when treated with the potent anticancer drug, doxorubicin. This was observed through the enhanced activation of caspases 3 and 7, cleavage of their substrate PARP-1, and depletion of the anti-apoptotic protein Mcl-1, which contributed to the sensitivity of miR-1-expressing cells to doxorubicin [327]. |
| | | | miR-183 | Inhibits migration and invasion of lung cancer cells [328]. |
| | | | miR-7 | Down-regulates both EGFR mRNA and protein expression leading to cell cycle arrest and cell death [329]. |
| | | | miR-145 | Inhibits cancer cell growth in EGFR mutant lung adenocarcinoma [330]. |
| | | | miR-17-5p | Suppresses cell growth [331]. |
| Liver | miR-21 | Promotes proliferation and migration [332]. | Let-7 | Inhibits cell growth [290]. |
| | miR-25 | Promotes growth, migration and invasion [333]. | miR-15b | Inhibits cell growth [334]. |
| | miR-27a | Promotes proliferation [335]. | miR-16 | Promotes the apoptosis of cancer cells [336]. |

**Table 4** (*continued*)

| Cancer type | Oncogene | Mechanism of action | Tumor suppressor | Mechanism of action |
|---|---|---|---|---|
| | miR-93 | Promotes cell proliferation, migration and invasion [337]. | miR-122a | Modulates cyclin G1 expression [338]. |
| | miR-106b | Promotes cancer development, proliferation and metastasis [339]. | miR-141 | Inhibits migration and invasion [340]. |
| | miR-143 | Promotes cell invasion/ migration and tumor metastasis [341]. | miR-145-5p | Inhibits migration, invasion and metastasis [342]. |
| | miR-222 | Promotes liver cancer cell proliferation, migration and invasion and inhibits apoptosis [343]. | miR-451 | Inhibits metastasis [344]. |
| | miR-155-5p | Overexpression of miR-155-5p could significantly activate pro-apoptotic proteins while inactivating anti-apoptotic proteins [345]. | | |
| Renal | miR-154-5p | Promotes cell proliferation, viability, migration as well as invasion [346]. | miR-384 | Inhibits the growth and invasion of renal cell [348]. |
| | miR-25-3p | Promotes cell migration [347]. | miR-106a-5p | Inhibits the cell migration and invasion of renal cell carcinoma [350]. |
| | miR-19 | Promotes cell proliferation [349]. | miR-199a | Inhibits proliferation and invasion [351]. |
| | miR-142-5p | Promotes cell growth and migration in renal cell carcinoma [352]. | miR-622 | Inhibits migration and invasion [353]. |
| | miR-543 | Promotes cell proliferation and metastasis of renal cell carcinoma [354]. | miR-363 | Inhibits proliferation, migration and invasion [355]. |
| | miR-21 | Promotes renal cell carcinoma cell invasiveness and angiogenesis [356]. | | |
| | miR-1274a | Promotes cell proliferation [357]. | | |
| Pancreatic | miR-200b-3p | Sustaining self-renewing [358]. | miR-142-5p | Inhibits proliferation [359]. |
| Colorectal | miR-1274a | Promotes proliferation and metastasis [360]. | miR-137-3p | Inhibits migration [361]. |
| | miR-592 | Promotes proliferation and clonogenicity [362]. | miR-22 | Represses invasion [363]. |
| | miR-155-5p | Promotes migration [282]. | miR-3622a-3p | Reduces stemness [364]. |
| | miR-126 | Promotes proliferation [279]. | miR-34a | Suppresses colorectal [365]. |
| Leukemia | miR-15/16 | Sustains stemness [366]. | miR-99 | Induces LSC differentiation [367]. |
| | miR155 | Initiates disease [368]. | miR-185 | Impairs survival of drug-resistant cells [369]. |
| | miR-126 | miR-126 overexpression activates genes that are highly expressed in leukemia stem cells/leukemia initiating cells and/or primitive hematopoietic stem/progenitor cells, likely through targeting ERRFI1 and SPRED1 [370]. | miR-146a | Induces cytotoxic effects [371]. |
| | | | miR-203 | Has therapeutic benefits in specific hematopoietic malignancies [372]. |
| | | | miR-124a | Contributes to the abnormal proliferation of ALL cells [373]. |
| | | | miR-29 | miR-29 down-modulation in an intraclonal chronic lymphocytic leukemia (CLL) subpopulation from immune niches allows for higher TRAF4 and increased CD40 responsiveness [301]. |
| Breast | let-7 | Sustains self-renewing [374]. | miR-30 | Promotes apoptosis [375]. |
| | miR-141 | Promotes metastasis [376]. | miR-140 | Inhibits proliferation [377]. |
| | miR-766 | Promotes proliferation, chemoresistance, migration and invasion [378]. | miR-143 | Inhibits proliferation [379]. |
| | miR-10b | Promotes cell migration and invasion [380]. | miR-600 | Inhibits stemness [381]. |
| | miR-21 | Promotes cell growth [382]. | miR-7 | Inhibits cell growth [383]. |

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**Table 4** (*continued*)

| Cancer type | Oncogene | Mechanism of action | Tumor suppressor | Mechanism of action |
|---|---|---|---|---|
| | miR-27a | Promotes cell cycle progression [384]. | miR-125 | Impairs migration and invasiveness [385]. |
| | miR-373, miR-520c | Promotes tumor invasion and metastasis [386]. | miR-124a | Inhibits cell proliferation [318]. |
| | miR-155 | Promotes proliferation [387]. | miR-127 | Inhibits cell growth [388]. |
| | miR-105 | Promotes metastasis [389]. | miR-126, miR-335 | Reduces overall tumour growth and proliferation; inhibits metastatic cell invasion [390]. |
| | | | miR-146a | Reduces the activity of the pathway [391]. |
| | | | miR-17-5p | Inhibits cell proliferation [392]. |
| | | | miR-200a/b/c, miR-205 | Inhibits cell growth [393]. |
| | | | miR-206 | Inhibits cell genesis and metastasis [394]. |
| Gastric | miR-106b, miR-93, miR-25 | Impairs cell-cycle arrest and apoptosis [395]. | let-7 | Inhibits invasion [396]. |
| | miR-221, miR-222 | Promotes G0/S phase transition [397]. | miR-15b, miR-16 | Promotes apoptosis [398]. |
| | miR-27a | Promotes cell growth [399]. | miR-122a | Inhibits cell growth [400]. |
| | miR-21 | Enhances cell proliferation and invasion [401]. | miR-451 | Reduces cell proliferation [402]. |
| | miR-155 | Promotes invasion [403]. | miR-141 | Inhibits cell proliferation [404]. |
| | | | miR-143, miR-145 | Inhibits cell growth [405]. |
| | | | miR-635 | Inhibits proliferation and invasion [406]. |
| | | | miR-876-5p | Inhibits proliferation and invasion [407]. |
| Ovarian | let-7 | Elevates multiple drug resistance [408]. | miR-134-3p | Reduces multiple drug resistance [409]. |
| | miR-223 | Promotes growth of ovarian carcinoma cells [410]. | miR-126 | Inhibits proliferation [411]. |
| | | | miR-199a | Promotes a proinflammatory environment [412]. |
| | | | miR-419, miR-432 | Associated with higher tumor proliferation [413]. |
| | | | miR-9 | Downregulated in ovarian carcinoma cells [310]. |
| | | | miR-377 | Inhibits metastasis [414]. |
| Bladder | miR-23b | Promotes bladder cancer cell migration and invasion [415]. | miR-665 | Inhibits migration [416]. |
| | | | miR-27b | Inhibits proliferation, invasion and migration [417]. |
| | | | miR-143 | Inhibites cell proliferation [418]. |
| | | | miR-497 | Inhibits cell invasion and metastasis [419]. |
| | | | miR-218 | Inhibits bladder cancer cell proliferation, migration and invasion [420]. |
| Prostate | miR-141 | Promotes proliferation [421]. | miR-145 | Inhibits proliferation and invasion [422]. |
| | | | miR-34 | Reduces stemness [423]. |
| | | | let-7c, miR-125b | Promotes apoptosis [424]. |

for rescuing and enhancing NK cell activity to achieve effective anti-tumor responses.

T lymphocytes, pivotal components of the anti-tumor immune response, encompass $CD8^+$ T cells, which differentiate into cytotoxic T lymphocytes (CTL), and $CD4^+$ T cells, which differentiate into various subtypes, such as helper T cells (Ths) and regulatory T cells (Tregs). Notably, Tregs exert immunosuppressive effects, and their abundant infiltration often correlates with poor prognosis, facilitating tumor cell evasion from the immune system. miR-21 plays a crucial role in modulating the Phosphatase and tensin homolog (PTEN)/AKT pathway, thereby controlling the population of $CCR6^+$ Treg cells and contributing to anti-tumor immunity [440]. miR-23a exerts its influence by inhibiting B lymphocyte-induced maturation protein-1 (BLPM-1). This disrupts the tumor-induced immune polarization of infiltrating T cells, promoting an anti-tumor immune response [441]. The orchestrated actions of miR-21 and miR-23a underscore their importance by modulating T-lymphocyte function, thereby enhancing the body's tumor defense systems.

### 4.2. lncRNA and tumor immunity

Certain lncRNAs play pivotal roles in immune regulation, particularly in Toll-like receptor 4 (TLR4) signaling in macrophages. Notable examples include cyclooxygenase-2 (COX2), p50-associated cyclooxygenase-2 exogenous RNA (PACER), anti-sense ncRNA located in the IL-1a locus (AS-IL1a), IL1b-RBT46, and IL1b-eRNA, all of which contribute to TLR4 signaling [442–445]. Similarly, nuclear factor-kappa-B (NF-κB)-interacting lncRNA (NKILA) exhibits upregulation in interleukin (IL)-1β and tumour necrosis factor-alpha (TNF-α)-mediated pathways, enhancing the anti-cancer response of the adaptive immune system [446]. Moreover, Cao et al. [447] highlighted the lncRNA MM2P as a key regulator of

**Table 5**
Non-coding RNAs (ncRNAs) as a therapeutic target for cancer in clinical application.

| Conditions | ClinicalTrials.gov identifier | Study title | Responsible party | History of changes | Status |
|---|---|---|---|---|---|
| Hepatocellular carcinoma | NCT03227510 | microRNAs as diagnostic biomarkers in hepatocellular carcinoma among somali patients | Mohamed Abdulkadir Hassan, MD, People's Friendship University of Russia, Moscow, Russia | Estimated study start date: November 2017; Estimated study completion date: September 2019 | Unknown |
| | NCT04767750 | Role of lncRNA H19 in the regulation of IGF-1R expression | Mansoura University, Dakahliya, Egypt | Actual study start date: January 1, 2020; Actual study completion date: April 4, 2022 | Completed |
| | NCT05088811 | The role of lncRNAs WRAP53 and UCA-1 as potential biomarkers in diagnosis of hepatocellular carcinoma | Experimental and clinical internal medicine, medical research institute, Alexandria University, Alexander, Egypt | Actual study start date: August 21, 2021; Estimated study completion date: September 2022 | Recruiting |
| | NCT02448056 | miRNA as a diagnostic and prognostic biomarker of hepatocellular carcinoma | National Taiwan University Hospital Taipei, Taiwan, China | Study start date: June 2015; Estimated study completion date: May 2025 | Not yet recruiting |
| Breast cancer | NCT03000764 | RNA and heat shock protein biomarkers in radiation-induced fibrosis in breast cancer | Institut de Cancérologie de Lorraine, Vandœuvre-lès-Nancy, France | Actual study start date: May 10, 2017; Actual study completion date: April 25, 2018 | Completed |
| | NCT03779022 | miRNA and relevant biomarkers of BC patients undergoing neoadjuvant treatment | Peking University First Hospital, Beijing, China | Actual study start date: November 1, 2015; Estimated study completion date: December 31, 2019 | Unknown |
| | NCT02641847 | TA(E)C-GP versus A(E)C-T for the high risk TNBC patients and validation of the mRNA-lncRNA signature | Fudan University Shanghai Cancer Center, Shanghai, China | Study start date: July 2015; Estimated study completion date: June 2021 | Unknown |
| | NCT04671498 | Droplet-BC screening test for the detection of breast cancer, the DROPLET-BC study | Preferred Medicine, Inc, New York, USA | Actual study start date: November 3, 2020; Estimated study completion date: December 31, 2022 | Recruiting |
| Hematological malignancies | NCT01556828 | Analysis of cutaneous and hematologic disorders by high-throughput nucleic acid sequencing | Stanford University, Stanford, California, USA | Study start date: June 2011; Actual study completion date: June 2014 | Terminated |
| | NCT02791217 | Identification of hematological malignancies and therapy predication using microRNAs as a diagnostic tool | shpilberg ofer, Head of hematology department, Assuta Medical Center, Israel | Study start date: June 2016; Estimated study completion date: June 2019 | Unknown |
| | NCT04288739 | Immunophenotyping and Xist gene in AML | Faculty of medicine Assiut, Egypt | Estimated study start date: October 2, 2020 Estimated study completion date: December 31, 2022 | Not yet recruiting |
| | NCT05477667 | Study of Let-7a and miRNA-124 in cases of non-Hodgkin's lymphoma and acute leukemia | Sohag University Hospital, Sohag, Egypt | Estimated study start date: October 1, 2022; Estimated study completion date: April 30, 2023 | Not yet recruiting |
| Prostate cancer | NCT04835454 | Role of piwi-protein interacting RNA, miRNA-194 and amino acids in patients with prostate cancer | Assiut University Assiut, Egypt | Estimated study start date: May 15, 2021; Estimated study completion date: December 15, 2021 | Not yet recruiting |
| | NCT04100811 | Identification of clinically insignificant or significant prostate cancer with the miR Scientific Sentinel™ Platform | miR Scientific LLC, North Brunswick, USA | Actual study start date: December 1, 2019; Estimated study completion date: December 15, 2023 | Recruiting |
| | NCT05141383 | Comparative study of diagnostic and prognosis biomarkers of prostate cancer in liquid biopsy | Institut Curie, Paris, France | Actual study start date: May 4, 2022; Estimated study completion date: May 4, 2027 | Recruiting |
| Colorectal cancer | NCT04523389 | Contents of circulating extracellular vesicles: Biomarkers in colorectal cancer patients | Centre Hospitalier Universitaire Dijon, France | Actual study start date: July 1, 2020; Estimated study completion date: July 2021 | Unknown |
| | NCT04269746 | Assessment of long noncoding RNA CCAT1 in colorectal cancer patients | Assiut University, Esute, Egypt | Estimated study start date: December 2020; Estimated study completion date: September 2021 | Unknown |

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**Table 5** (*continued*)

| Conditions | ClinicalTrials.gov identifier | Study title | Responsible party | History of changes | Status |
|---|---|---|---|---|---|
| Thyroid cancer | NCT03469544 | Long non coding RNA HOTAIR and midkine as biomarkers in thyroid cancer | Assiut University, Esute, Egypt | Estimated study start date: March 29, 2018; Estimated study completion date: March 29, 2020 | Unknown |
| | NCT04594720 | Circulating biomarkers to identify thyroid cancer | Kaohsiung Chang Gung Memorial Hospital Kaohsiung, Taiwan, China | Actual study start date: October 1, 2018; Actual study completion date: September 30, 2020 | Completed |
| Ovarian cancer | NCT01187602 | Short non-coding RNA biomarkers of predisposition to ovarian cancer | University of Virginia, Charlottesville, Virginia, USA | Study start date: August 2010; Estimated study completion date: June 2015 | Unknown |
| | NCT03738319 | ncRNA in the exosome of the epithelia ovarian cancer | Peking Union Medical College Hospital, Beijing, China | Actual study start date: November 10, 2018; Estimated study completion date: November 23, 2019 | Unknown |
| Pancreatic adenocarcinoma | NCT04765410 | The impact of tissue miRNA profile from EUS-FNA in pancreatic adenocarcinoma | Carol Davila University of Medicine and Pharmacy, Romania | Actual study start date: March 21, 2019; Estimated study completion date: June 1, 2021 | Recruiting |
| | NCT04584996 | circRNAs as clinically useful biomarkers in pancreaticobiliary cancers | Royal Surrey County Hospital NHS Foundation Trust, Guildford, UK | Actual study start date: October 4, 2020; Estimated study completion date: November 5, 2023 | Recruiting |
| Oral cancer | NCT05400057 | The oncogenic potential of salivary miRNA-93 and miRNA-412-3P in oral lichen planus patients | Cairo University, Cairo, Egypt | Estimated study start date: July 15, 2022; Estimated study completion date: October 30, 2022 | Not yet recruiting |
| Cholangiocarcinoma | NCT03102268 | ncRNAs in exosomes of cholangiocarcinoma | The Second Hospital of Nanjing Medical University, Nanjing, China | Estimated study start date: May 1, 2017; Estimated study completion date: March 31, 2020 | Unknown |
| Lung cancer | NCT03830619 | Serum exosomal long noncoding RNAs as potential biomarkers for lung cancer diagnosis | Union Hospital, Tongji Medical College, Huazhong University of Science and Technology Wuhan, China | Actual study start date: January 1, 2017; Actual study completion date: July 31, 2021 | Completed |
| Kidney cancer | NCT04946266 | Prospective validation of the prognostic value of long non-coding MFI2-AS1 RNA in localized clear cell kidney cancers | University Hospital, Strasbourg, France | Actual study start date: December 1, 2021; Estimated study completion date: December 2024 | Recruiting |
| Rectal cancer | NCT03962088 | Timisnar - biomarkers substudy (Timisnar-mirna) | Azienda Ospedaliera SS. Antonio e Biagio e Cesare Arrigo di Alessandria, Italy | Actual study start date: April 1, 2019; Estimated study completion date: April 1, 2024 | Recruiting |
| Pan-cancer | NCT02780375 | Feasibility study testing transcriptional responses as an indicator of individualized responses to radiation effects | Institute of Cancer Research, UK | Actual study start date: September 12, 2016; Actual study completion date: July 17, 2018 | Completed |
| Multiple myeloma | NCT04811898 | A Dose Escalation Study of LNA-i-miR-221 for Cancer Treatment (LNA-i-miR221) | TASSONE PIERFRANCESCO, Azienda Ospedaliera Universitaria Mater Domini, Catanzaro | Actual study start date: January 14, 2019; Actual study completion date: December 29, 2021 | Completed |

macrophage M2 polarization. Reduced MM2P expression impedes cytokine-driven macrophage M2 polarization, thereby attenuating the characteristic promotion of neovascularization by M2-like tumor-associated macrophages. In epithelial ovarian cancer, M2-like macrophages secrete epidermal growth factor (EGF), leading to the inhibition of lncRNA LIMT expression and promotion of cancer metastasis through the epidermal growth factor receptor (EGFR)-extracellular regulated protein kinase (ERK) signaling pathway [448]. Furthermore, lncRNAs exert a regulatory effect on cancer development by influencing NK cells. Fang et al. [434] found that the lncRNA GAS5 plays a suppressive role in tumor growth. Overexpression of GAS5 modulates the miR-544/RUNX3 axis, thereby augmenting the cytotoxicity of NK cells against liver cancer cells.

Dendritic cells (DCs) are pivotal regulators of the immune system and act as essential intermediaries between innate and adaptive immunity. Their role encompasses not only antigen presentation but also the transmission of co-stimulatory signals and cytokine production to regulate adaptive immune responses [449]. Within the tumor microenvironment, compromised antigen cross-presentation function of DCs hinders the activation of anti-tumor immune responses, facilitating tumor development. Therefore, lncRNAs have emerged as significant contributors. Specifically, lnc-DC, a distinct lncRNA found in DC, exhibits altered expression in the tumor microenvironment. Downregulation of lnc-DCs correlates with a reduced capacity of DCs to stimulate T-cell activation and differentiation, ultimately diminishing the effectiveness of the anti-tumor immune response [450]. The lnc-DC has been

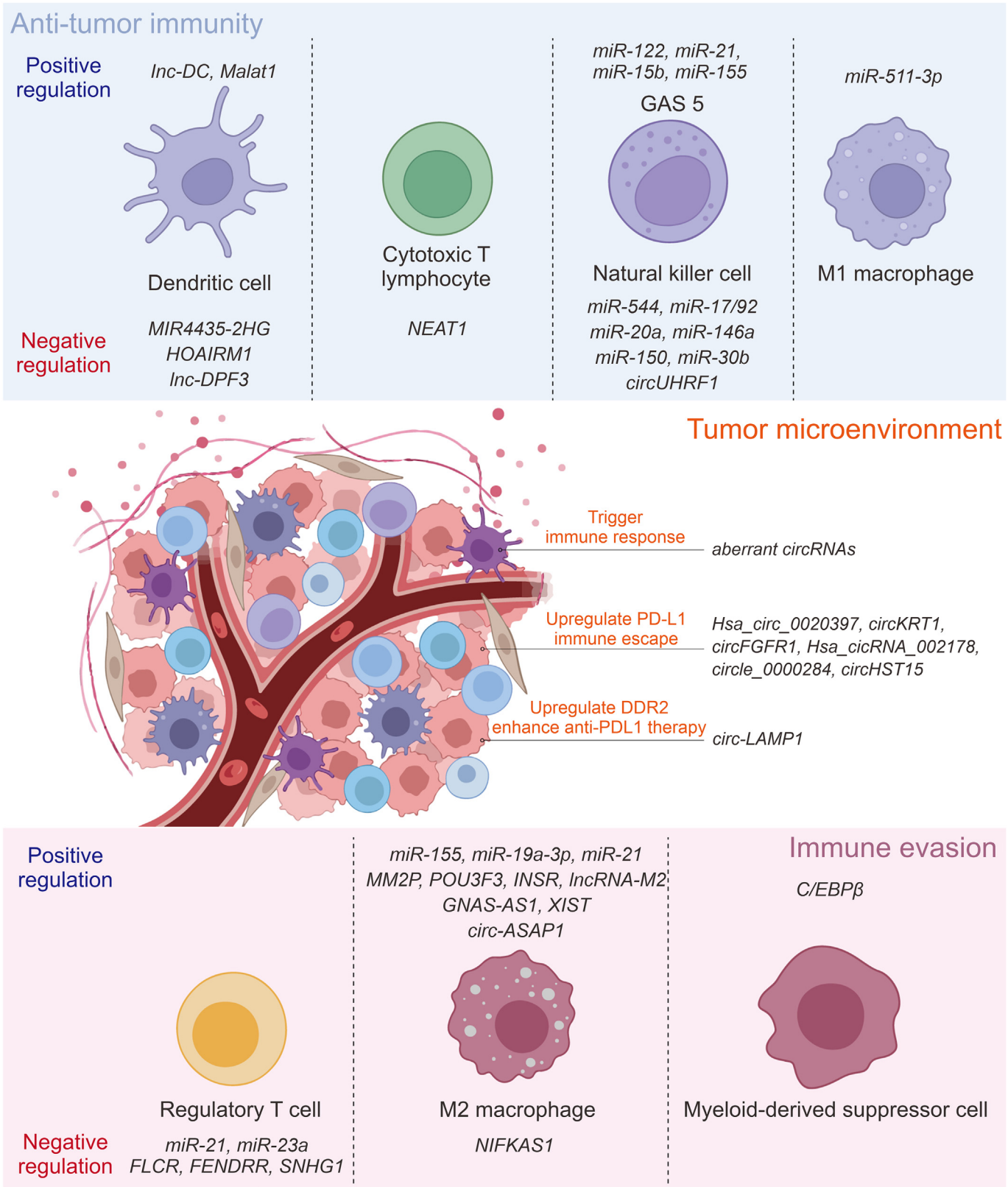


**Fig. 5.** Impact of three types of non-coding RNA (ncRNA) on tumor immunity.

implicated in modulating the secretion of key cytokines such as TNF-α, IL-12, IL-6, and IFN-γ [451,452], as well as activating SHP1 by promoting signal transducer and activator of transcription 3 (STAT3) dephosphorylation [453]. The knockdown of lncRNA DC results in reduced differentiation and antigen presentation abilities of DCs [453]. Elevated levels of MIR4435-2HG in myeloid DCs are linked to epigenetic modulation, resulting in heightened oxidative phosphorylation and glycolysis [454]. Downregulation of HOAIRM1 is essential for DC differentiation [455]. Additionally, lnc-DPF3 inhibits DC migration by reducing HIF1A and glycolysis [456], while inhibiting Malat1 increases the secretion of IL-6 and TNF-α, and IFN-γ, in DCs [457]. These findings underscore the intricate role of lncRNAs in fine-tuning the functions of DCs and consequently shaping immune responses.

The regulation of tumor immunity, particularly in influencing T cells, is significantly influenced by the crucial role of lncRNAs. For instance, lncRNAs such as POU class 3 homeobox 3 (POU3F3) [458] and insulin receptor precursor (INSR) [459] promote the M2 polarization of TAMs, differentiation of cancer-associated fibroblasts (CAFs), and the secretion of immunosuppressive cytokines such as IL-10, transforming growth factor-beta (TGF-β), and IL-35. These factors contribute to the direct enhancement of Treg differentiation by maintaining an immunosuppressive microenvironment that compromises the anti-tumor activity of $CD8^+$ cytotoxic T lymphocytes. Preclinical studies exploring the modulation of lncRNA NEAT1 in cancer immunotherapy have demonstrated promise in preserving the cytotoxicity and reducing apoptosis of CD8 T cells [460]. TAMs, as pivotal components of the tumor microenvironment, significantly influence tumor prognosis, and recent research has highlighted the critical role of lncRNAs in TAM polarization, primarily mediated through the STAT3 signaling pathway [461]. lncRNA-M2 is a notable example that promotes M2 polarization through the protein kinase A (PKA)/cAMP-responsive element binding protein (CREB) axis [462]. Additionally, several other ncRNAs, including guanine nucleotide-binding proteins α-stimulating active peptide anti-sense RNA 1 (GNAS-AS1) [463,464], X-inactive-specific transcript (XIST) [465], and MM2P [447], are implicated in mediating the M2 polarization of TAMs within the tumor microenvironment. Conversely, certain ncRNAs, such as nucleolar proteins interacting with the FHA domain of MKI67 tissue-sensing RNA 1 (NIFK AS1), inhibit M2 polarization by activating the Notch homolog 1 (Notch1) or Jagged1 (Jag1) pathway. This regulatory mechanism has also been observed in endometrial cancer [466]. Among the various cytokines, IL-6 is a pleiotropic cytokine that promotes Th2/17 programming in the tumor microenvironment. The lncRNA-C, transcribed from the antisense strand of CCAAT/enhancer-binding protein (C/EBPβ), plays a crucial role in promoting the differentiation and immunosuppressive activities of myeloid populations within tumors. This lncRNA-C/EBPβ acts by silencing C/EBPβ, influencing the expression of key factors such as arginase1 (Arg-1), nitric oxide synthase 2 (NOS2), COX2, NADPH oxidase 2 (NOX2), and IL-4. Consequently, it drives the differentiation of myeloid-derived suppressor cells (MDSCs) into polymorphonuclear (PMN-MDSC), contributing to further tumor development in a TGF-β-dependent manner [467,468]. Tumors often undergo significant infiltration by Tregs, leading to a dampened response from effector T cells. This orchestrated effect involves key factors such as cytotoxic T lymphocyte-associated protein 4 (CTLA-4), IL-10, and TGF-β, collectively contributing to the suppression of anti-cancer T cells, DC cells, and NK cells [469,470]. The lncRNA-Foxp3 long gene ncRNA (FLCR) is part of a class of ncRNAs that negatively regulates the expression of forkhead box protein P3 (FOXP3), a key biomarker of Tregs. Similarly, lncRNA-FOXF1 adjacent non-coding developmental regulatory RNA (FENDRR) [471] and lncRNA small nucleolar RNA host gene 1 (SNHG1) play roles in preventing Treg differentiation, thereby mitigating the immune evasion potential of tumors [472].

### 4.3. circRNA and tumor immunity

circRNAs primarily exert anti-tumor effects by modulating the expression of immune and immunotherapeutic markers, mainly through miRNA sponging. For example, circRNAs have the capacity to trigger the expression of PDL1 receptors, leading to impaired immune surveillance of tumor cells, resistance to anti-PDL1 therapy, and an unfavorable prognosis. This is achieved through their role as miRNA sponges, which dampen the expression of PDL1 receptors in tumor cells. In colorectal cancer, hsa _circ_0020397 absorbs miR-381-3p, contributing to its intricate regulatory network [473]. Similarly, in oral squamous cell carcinoma (OSCC), circKRT1 facilitates the absorption of miR-495-3p. Additionally, in non-small cell lung cancer (NSCLC), circFGFR1, Hsa_cicRNA_002178, circle_0000284, and circHST15 play crucial roles by absorbing miR-388-3p, miR-34, miR-377, miR-155-5p, and miR-194-5p, respectively [474–477]. These interactions ultimately lead to the overexpression of programmed cell death ligand 1 (PD-L1) in cancer cells, resulting in immune escape. Moreover, circUHRF1 secreted by extracellular vesicles derived from HCC is involved in upregulating the expression of TIM-3 by quenching miR-449c-5p in NK cells, further contributing to immune evasion and poor prognosis during PD1 therapy. Conversely, circ-LAMP1 inhibits miR-615-5p, leading to DDR2 upregulation, with the consequent effect of enhancing sensitivity to PD-L1 therapy [478], thus compromising anti-PDL1 treatment and prognosis in T-cell lymphoblastic lymphoma (T-LBL) tissue [479,480]. circRNAs play a crucial role in directing the movement of TAMs within the tumor microenvironment. For instance, circ-ASAP1 orchestrates macrophage infiltration in HCC by modulating the miR-326/miR-532-5p-CSF-1 axis. In endometrial cancer, HSA_cir_0001610 is transported to endometrial cancer cells via exosomes derived from tissue-related macrophages, thereby reducing radiosensitivity by sequestering miR-139-5p [481]. Additionally, circRNAs have emerged as potential adjuvants, effectively inducing antigen-specific activation of B and T cells and fostering anti-tumor immunity [482].

In addition to their role as miRNA sponges, tumor cells generate numerous aberrant circRNAs during carcinogenesis, which are often driven by genetic mutations and other factors. Notably, these newly formed circRNAs can function as tumor antigens. Exosomes are secreted by tumor cells and transport these aberrant circRNAs to immune cells, thereby triggering an immune response and activating anti-tumor immunity. This novel mechanism underscores the multifaceted involvement of circRNAs in orchestrating the immune responses against cancer [483].

## 5. Clinical application of ncRNA in cancer

miRNAs are highly attractive potential biomarkers and have been isolated from most body fluids, including tears, saliva, serum, plasma, urine, and semen. Furthermore, miRNAs circulate in a highly stable cell-free form; therefore, they can be readily detected by specific and sensitive quantitative real-time polymerase chain reaction (PCR) in small-volume samples. In addition, miRNAs are highly conserved among species and can be used in pre-clinical animal models. Tumor cells can release miRNAs into the circulation, which can be used as biomarkers for cancer diagnosis and progression. miRNAs are non-invasive biomarkers for cancer diagnosis, screening, monitoring treatment, and predicting prognosis. Numerous studies have investigated the abnormal expression of human serum miRNAs in different tumors, including pancreatic, liver, and colorectal carcinomas. As the most common

primary liver cancer, HCC is the third leading cause of cancer-related deaths worldwide. Treatments for HCC include sorafenib, *trans*-arterial chemoembolization, surgical resection, and local therapies, such as radiofrequency ablation. However, most patients experience tumor recurrence or progression. It is important to identify serum biomarkers for HCC because clinical staging systems cannot precisely predict the outcomes of patients with HCC. By comparing the circulating levels of miRNAs in patients with chronic liver disease, healthy volunteers, and patients with HCC, NCT03227510 established miRNAs as biomarkers for a diagnostic tool for HCC patients. HCC and type II diabetes mellitus (T2DM), two of the most prevalent diseases worldwide, share common predisposing pathological conditions. NCT04767750 investigated the relationship between lncRNA H19 and insulin-like growth factor 1 receptor (IGF-1R) mRNA gene expression in blood samples of HCC and T2DM patients and explored the potential of a pathophysiological link between HCC and DM that may support a therapeutic target for both diseases [484]. In another study, NCT05088811 investigated the role of the long ncRNAs WRAP53 and urothelial carcinoma-associated 1 (UCA1) as potential biomarkers for the diagnosis of HCC [485,486].

Considering that the sensitivity of miRNAs as diagnostic biomarkers of HCC can be up to 80%, NCT02448056 established an miRNA biomarker platform as a diagnostic or prognostic tool for HCC. The investigators will also compare the miRNA expression levels in the serum before and after treatment and then correlate the miRNA expression between the serum and HCC tissue. Based on the response of skin fibroblasts after irradiation, NCT03000764 seeks to identify the molecular signature of pathological radiation-induced fibrosis by comparing two groups of patients with different radio sensitivities. This signature uses the expression levels of ncRNAs, particularly lncRNAs, snRNAs, snoRNAs, and microRNAs, as biomarkers of breast cancer. NCT03779022 found that the concentrations of some circulating miRNAs in human breast cancer are correlated with tumor development and progression and that aberrant miRNA expression is involved in drug resistance to various chemotherapeutic agents in breast cancer. Therefore, this study used serum miRNAs as early markers of breast cancer [487]. After predicting high-risk triple-negative breast cancer by the mRNA-lncRNA integrated signature, NCT02641847 compared the efficacy and safety of docetaxel combined with doxorubicin and cyclophosphamide, followed by gemcitabine combined with cisplatin, and doxorubicin combined with cyclophosphamide, followed by docetaxel. NCT04671498 distinguishes breast cancer patients from non-cancer volunteers by investigating a new type of screening test for circulating small-non-coding RNA in the blood. This study also provides a new method for breast cancer screening and diagnosis by classifying subgroups of breast cancer patients with various conditions.

Hematological cancers, caused by the malignant transformation of the lymphatic system and bone marrow cells, are typically divided into three major clusters: lymphoma, leukemia, and multiple myeloma. Some hematological malignancies are aggressive, and early diagnosis is essential for survival. However, the current diagnostic methods have various limitations, including insufficient sensitivity, time-consuming procedures, and a high level of expertise. Using recently developed high-throughput sequencing technologies, NCT01556828 identified genetic changes associated with the initiation, progression, and treatment response of cutaneous and hematologic disorders. These genetic changes may lead to improved diagnostic, prognostic, and therapeutic options for cutaneous and hematological disorders. NCT02791217 has developed new miRNAs as biomarkers for the early detection and relapse of hematological malignancies. AML is a heterogeneous disorder characterized by clonal expansion of myeloid progenitors (blasts) in the bone marrow and peripheral blood. The X-inactive specific transcript RNA was one of the first lncRNAs discovered in the early 1990s. NCT04288739 studied the human XIST gene and its relationship with immunophenotyping in AML patients; this is the first study to detect its prognostic role and immunophenotypic association in AML [488]. miRNA-124 is a tumor suppressor, and a decrease in its expression level is a typical sign of a tumor. NCT05477667 studies the role of miRNA-124 as a biomarker for the development of non-Hodgkin lymphoma and AML [489].

Early detection of prostate cancer mainly involves digital rectal examination (DRE) and testing of the level of prostate-specific antigen (PSA) in the blood. However, PSA is not a specific biomarker for prostate cancer. NCT04835454 identified new biomarkers, including microRNAs, sncRNAs, proteins, and metabolites, which are important for the early detection of prostate cancer and can increase the accuracy of diagnosis and reduce false positives in PSA testing [490]. The miR Scientific Sentinel® Prostate Cancer Classifier Platform (Sentinel® PCC4 Test) tested 442 sncRNAs that were extracted from urinary exosomes (NCT04100811). Disease status was determined as either no molecular evidence of prostate cancer (NMEPC) or molecular evidence (MEPC) of low-, intermediate-, or high-risk aggressive prostate cancer. NCT05141383 established a diagnostic, prognostic, and active surveillance test for prostate cancer by analyzing lncRNAs as biomarkers in three cohorts of patients: prostate cancer, suspected cancer without biopsy confirmation or with prostatic hyperplasia, and healthy donors. This biological analysis will help researchers improve the prognosis and diagnostic management of patients with prostate pathologies using biomarkers and genetic markers.

Most cancer-related deaths are caused by distant metastases. Tumor cells release a large number of exosomes containing tumor markers, which can then spread to distant locations. Recent studies have shown that exosomes derived from cancer cells contain specific markers. Studies on miRNAs are of particular interest. NCT04523389 investigates specific miRNAs in circulating exosomes derived from the blood samples of patients with colon cancer that could be used as biomarkers for early prognosis (survival and progression). Another study, NCT04269746, evaluated the diagnostic value of long non-coding RNA (CCAT1) expression in the peripheral blood of patients [491].

Thyroid cancer is the most prevalent endocrine malignancy. Early detection is key to successful treatment and mortality reduction, as survival rates may decrease from 100% in stages I and II to 50% in stage IV. Pathological analysis using fine-needle aspiration biopsies has some limitations, such as difficulty in sampling small tumors and bleeding, making biomarkers essential for diagnosis. NCT03469544 is currently conducting a study on the lncRNA HOTAIR as a biomarker of thyroid cancer. NCT04594720 aims to identify potential mRNAs and lncRNA biomarkers to differentiate papillary thyroid cancers from benign thyroid tumors.

Furthermore, epithelial ovarian cancer is the most lethal female reproductive malignant tumor because 80% of tumors metastasize beyond the ovary at the time of diagnosis, leading to largely unsuccessful screening efforts aimed at improving the identification of early-stage disease. Considering that sncRNAs hold significant promise as biomarkers for ovarian cancer predisposition, NCT01187602 will first compare serum-derived sncRNAs in women with and without a hereditary risk of ovarian cancer. Then, they defined serum-derived sncRNAs that correlate with ovarian cancer disease status. Another study, NCT03738319, analyzed the expression of lncRNAs and miRNAs in patients with high-grade serous ovarian cancer (HGSOC) and benign gynecologic diseases, and miRNAs/lncRNAs were used as biomarkers to detect HGSOC.

Pancreatic cancer (PC) is a popular disease worldwide. Endoscopic ultrasonography has been a breakthrough in personalized treatment by obtaining histopathological samples through a fine-

needle biopsy or aspiration. These analyzed samples offer the possibility of detecting miRNA profiles. NCT04765410 conducted a study of 60 patients with solid pancreatic masses to evaluate tissue miRNA expression in aggressive pancreatic adenocarcinoma, focusing on survival and response to treatment. In another study, NCT04584996 explored the expression of circRNAs in patient biomaterials (including blood, bile, tissue, and biopsy samples) as biomarkers for the diagnosis, prognostication, association with clinicopathological features, and survival outcomes of pancreatic cancer, as well as their ability to predict and monitor the response to surgery and/or chemotherapy.

Oral lichen planus (OLP) is one of the most common chronic mucocutaneous diseases and is considered a premalignant lesion owing to its high potential for malignant transformation. Examination of miRNAs in OLP patients has indicated that miR-93 plays an important role in carcinogenesis. Additionally, its expression was found to be increased in the saliva of OSCC patients. Furthermore, miR-412-3p is beneficial for cancer prediction and is highly expressed in the extracellular vesicles of OSCC patients. Therefore, in NCT05400057, researchers assess miR-93 and miR-412-3p as novel tumor markers in patients with OLP.

Based on the fact that ncRNAs are involved in many biological activities, including tumor growth and metastasis, the prospective translational study NCT03102268 was designed to characterize ncRNAs as useful diagnostic tools from exosomes in cholangiocarcinoma in both pre-clinical and clinical phases [492].

Conventional tumor markers for the non-invasive diagnosis of lung cancer exhibited insufficient specificity and sensitivity to facilitate the detection of early lung cancer (ELC). Therefore, the identification of ELC-specific exosomal lncRNA biomarkers that are highly sensitive and stable for noninvasive diagnosis of ELC is crucial. In the NCT03830619 study, exosomes were isolated from the plasma of 30 lung cancer patients and five healthy individuals, as well as from the culture media of four cancer cells and four human bronchial epithelial cells. Subsequently, the lung cancer-specific exosomal lncRNAs were identified.

NCT04946266 will conduct an exploratory analysis of the plasma expression level of MFI2-AS1 to use lncRNA as a biomarker for the diagnosis of kidney cancer before tissue analysis and patient follow-up.

For locally advanced rectal cancer, neoadjuvant chemoradiotherapy (nCHT) followed by surgery is the main protocol used to reduce the tumor size (downsizing) and induce the primary tumor and lymph nodes to earlier disease stages (downstaging). Extensive pathological examination of tumor regression grading (TRG) and lymph node status (ypN) from the tumor specimen after surgery helped to retrospectively visualize individual tumor sensitivity to nCHT. However, valid biomarkers are needed to monitor tumor responses because the response of patients to nCHT is heterogeneous. Therefore, miRNAs) are currently under investigation in NCT03962088 as blood-based biomarkers [493].

In a study conducted by NCT02780375, which focuses on patients undergoing standard radiotherapy at The Royal Marsden for breast, lung, gastrointestinal, and genitourinary tumors, peripheral blood samples will be gathered with informed consent. The analysis will assess responses from panels, consisting of up to 800 coding and non-coding RNAs in these samples, to pinpoint indicators of individualized responses to the effects of radiation [494].

Although ncRNAs hold significant promise as cancer treatment targets and are currently the subject of extensive research and clinical trials, the transparency of their results from such trials is limited. This restriction arises because of confidentiality issues and ongoing research. In this paper, we present several clinical trial results that are available for review.

In a case-control analysis involving 100 ovarian cancer patients and 100 cancer-free women from the East Azerbaijan population in Iran, researchers systematically investigated two specific single nucleotide polymorphisms (SNPs) in the lncRNA-HOTAIR gene (rs1899663 G > T and rs4759314 A > G). As reported by Saeedi et al. [495], these findings indicate a significant association between distinct genetic variants of the lncRNA-HOTAIR gene and increased susceptibility to ovarian cancer in the Iranian population of East Azerbaijan. These results suggest that lncRNA-HOTAIR could potentially be considered a therapeutic target for ovarian cancer.

The genotypes of two specific TINCR SNPs, rs2288947 and rs8113645, were investigated in 125 surgically treated patients with bladder cancer and in 125 controls using Sanger sequencing. Additionally, a dual-luciferase reporter gene assay was employed to assess the binding of miR-1247-3p and miR-30c-2-3p to the lncRNA TINCR. The study concluded that the TINCR rs2288947 A > G variant is associated with an increased risk of bladder cancer, whereas the rs8113645 C > T variant is associated with decreased susceptibility. These SNPs have also been linked to TINCR expression [496]. This suggests a genetic association between specific TINCR SNPs and susceptibility to bladder cancer, providing insights into potential markers for disease risk assessment.

In one study (NCT04811898), Tassone et al. [497] examined the safety and efficacy of a novel locked nucleic acid (LNA) miR-221 selective inhibitor (LNA-i-miR-221) in patients with refractory advanced cancers. This investigation progressed to a first-in-human, open-label, dose-escalation phase 1 trial involving individuals with progressive cancer. The treatment cycle consisted of a 30-min intravenous infusion of LNA-i-miR-221 over four consecutive days, and all patients underwent evaluation for the phase 1 primary endpoint. The study outcomes revealed an excellent safety profile, promising bio-modulatory properties, and anti-tumor activity. These results set the foundation for further clinical exploration of LNA-i-miR-221. This study suggests that LNA-i-miR-221 has potential as a safe and effective treatment for refractory advanced cancer, warranting additional investigation in phase II trials. The relevant clinical trials have been summarized in Table 5 and can be accessed on the following websites: https://clinicaltrials.gov/.

## 6. Conclusion

With the advancement of gene sequencing technology, researchers have discovered the significant roles of ncRNAs, including circRNAs, lncRNAs, and miRNAs, in normal physiological processes and in the onset and progression of diseases, specifically cancer. Abnormal expression of ncRNAs is closely associated with the growth, proliferation, invasion, and metastasis of malignant tumors. ncRNAs are promising targets for cancer therapy and can serve as biomarkers for cancer prediction and prognosis to guide clinical decision-making. This emerging field has great potential for cancer treatment and warrants further investigation.

Despite their promise, targeting ncRNAs in cancer therapy faces several challenges. A major challenge is the delivery of ncRNA-based therapeutics to tumor cells. ncRNA-based therapeutics are typically delivered using nanoparticle-based systems or viral vectors. However, these delivery systems face several challenges, including off-target effects and activation of the immune system. Additionally, there are concerns regarding the specificity and toxicity of ncRNA-based therapeutics.

In conclusion, ncRNAs hold great promise as novel targets for cancer therapy. miRNAs and lncRNAs have been shown to regulate key oncogenic and tumor suppressor pathways, and the modulation of their expression may lead to tumor growth inhibition and increased sensitivity to chemotherapy. However, the development

of ncRNA-based therapeutics faces several challenges, including delivery and specificity issues. Further research is needed to address these challenges and realize the full potential of ncRNAs as targets for cancer therapy.

## CRediT author statement

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## Declaration of competing interest

The authors declare that there are no conflicts of interest.

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