Research Progress of Non-coding RNAs in Tumor Drug Resistance

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Abstract. In recent years, research of non-coding RNAs(ncRNAs)' role in tumor drug resistance has made significant progress. Studies have revealed that various types of ncRNAs contribute to the emergence of tumor drug resistance through diverse mechanisms. NcRNAs are also showing promise as biomarkers for predicting drug resistance in various tumors. Furthermore, therapeutic strategies based on ncRNAs offer new opportunities to overcome drug resistance, although their clinical translation faces considerable challenges. This review is concentrated on the classification of ncRNAs, their roles in tumor drug resistance, their value as biomarkers, proposed therapeutic strategies, and the challenges and prospects for clinical translation.

Keywords: Non-coding RNA, Tumor drug resistance, Biomarker, Therapeutic application.

1. Introduction

Malignant tumors represent a significant threat to human health. Based on Global Cancer Statistics 2022, the worldwide prevalence and mortality associated with cancer remain alarmingly high and are expected to escalate. The growing population base and accelerated aging contribute to age-related cancer incidence and mortality, which are key factors driving the increasing global cancer burden, including in China [1-2].

Contemporary anti-cancer treatments encompass chemotherapy agents, molecular targeting therapies, and immune checkpoint inhibitors. Initially, these drugs often significantly inhibit tumor progression. However, as treatment continues, cancer cells can develop drug resistance. This occurs through various mechanisms, such as gene mutations, epigenetic reprogramming, and cellular signaling pathway rewiring. Drug resistance leads to disease recurrence and exacerbation, severely impacting patient prognosis.

Therefore, researchers have extensively and deeply explored the mechanisms underlying tumor drug resistance. In recent years, scientists have found that non-coding RNAs (ncRNAs) serve as a key driver in tumor drug resistance, becoming a research hotspot [3]. NcRNAs constitute over 90% of the genomic transcripts. They are vital for regulating gene expression. Furthermore, ncRNAs significantly modulate tumor cell responses to therapy. They achieve this through diverse approaches, including antisense oligonucleotides, small-molecule inhibitors, RNA interference, and CRISPR/Cas9 systems. This paper reviews ncRNA types and characteristics. It also summarizes their key roles in tumor drug resistance and related diagnostic and therapeutic strategies. Our review is based on existing research and literature retrieval. We also propose future research directions. Our goal is to offer new insights and theoretical bases for overcoming tumor drug resistance.

2. Classification of ncRNAs

NcRNAs refer to RNA molecules that lack the capability of coding for proteins. Nevertheless, they execute indispensable functions in modulating gene expression, sustaining cell functions, and governing the physiological homeostasis and pathological perturbations in organisms. In human's genome, less than 2% of the sequences get transcribed into coding RNA, while over 98% are converted into ncRNAs [4]. Contrary to protein - coding mRNA, ncRNAs mainly exert regulatory effects on gene expression and cellular activities via interactions with DNA, RNA, or proteins. Depending on their length, structural features, and functional roles, ncRNAs can be categorized into

multiple types. Examples cover major ncRNA categories, including long non-coding RNA (lncRNA), microRNA (miRNA), circular RNA (circRNA), as well as small RNAs such as small nucleolar RNA (snoRNA), small interfering RNA (siRNA), and Piwi-interacting RNA (piRNA).

2.1. Long non-coding RNA (lncRNA)

LncRNAs are longer than 200 nucleotides in length and by the lack of capacity to encode proteins. Previously considered "transcriptional noise" due to their non-coding nature, recent studies have revealed their spatio-temporal cell-specific expression and low sequence conservation. LncRNAs can regulate chromatin conformation through cis/trans-acting mechanisms and act as miRNA sponges, participating in post-transcriptional regulation and signaling pathways in tumor cells [5-7]. For instance, MRP, a 153-amino acid tumor metastasis-related protein, is encoded by lncRNA LY6E-DT in breast cancer. It enhances the interaction between heterogeneous nuclear ribonucleoprotein C1/C2 (HNRNPC) and EGFR mRNA, stabilizing EGFR mRNA and elevating EGFR protein levels [8].

2.2. MicroRNA (miRNA)

Endogenous single - stranded non - coding RNAs, miRNAs, have a length that falls in the range of 19 to 25 nucleotides. They mainly control gene expression post-transcriptionally by binding, often in a partial manner, to the messenger RNA (mRNA) of specific target genes. This binding can either inhibit translation or promote mRNA degradation. MiRNAs are essential in regulating tumor cell proliferation, apoptosis, and differentiation. Altered miRNA expression in tumor tissues exhibits a close association with how tumors initiate and progress. For example, miR-324-3p is notably downregulated in glioblastoma tissues, and its diminished expression can promote tumor cell proliferation through the activation of the Wnt/β-catenin signaling pathway [9].

2.3. Circular RNA (circRNA)

CircRNAs belong to the category of non-coding RNAs. They feature covalently closed structures. These RNAs are generated through the back-splicing of precursor mRNAs (pre-mRNAs). Additionally, they are broadly distributed across cellular environments. This closed circular architecture endows them with substantial stability, rendering them impervious to exonucleolytic degradation. This allows circRNAs to accumulate within cells and exert diverse biological functions. CircRNAs play significant roles in gene regulation. CircRNAs modulate the activity or subcellular distribution of RNA-binding proteins (RBPs), thereby impacting gene expression processes [10]. For example, circRNA-cEMSY mediates the mitochondrial aggregation of the RBP TDP-43 in lung adenocarcinoma cells. This aggregation leads to mitochondrial DNA leakage, activating the cGAS-STING pathway, which subsequently modulates the tumor microenvironment [11].

2.4. Small nucleolar RNA (snoRNA)

SnoRNAs typically range in length from 60 to 300 nucleotides. These RNAs originate from the transcription of introns in vertebrates. They can be divided into two main categories: SNORDs (also called C/D box snoRNAs) and SNORAs (known as H/ACA box snoRNAs). In addition, snoRNAs form complexes with nucleolar proteins, which are referred to as snoRNPs. SNORDs direct rRNA 2'-O-methylation via conserved sequences; SNORAs facilitate RNA pseudouridylation through H/ACA boxes. Some cleave into smaller RNAs or regulate mRNA splicing, functioning in rRNA/snRNA/mRNA regulation to affect protein synthesis. In lung adenocarcinoma, SNORD60 involves tumor progression [12]. SnoRNA knockdown inhibits NSCLC (e.g., H1299) growth/colony formation, indicating roles in promoting proliferation via cell cycle regulation [13].

2.5. Small interfering RNA (siRNA)

SiRNAs have an important function. Their function involves the regulation of gene expression. These molecules, approximately 20 to 25 nucleotides long, possessing a two-nucleotide extension at the 3' terminus, are generated from long double-stranded RNAs by Dicer enzymes cleavage. Mediated

by siRNA, the RNA-induced silencing complex (RISC) is guided to specifically target and degrade complementary messenger RNA (mRNA), inhibiting gene expression. Zou et al. demonstrated that delivering siRNA into colorectal cancer cells via carriers like liposomes leads to the degradation of CD44 mRNA by RISC, resulting in CD44 protein depletion. Ultimately, this approach significantly reduced tumor volume and decreased lung metastasis rates in nude mouse models, confirming that siRNA can restrain tumor cell growth and migration [14].

2.6. Piwi-interacting RNA (piRNA)

PiRNAs have a characteristic length. Their length usually falls between 26 and 31 nucleotides. They are uniquely expressed in germline cells. To date, a vast number of piRNAs, amounting to tens of thousands, have been identified within the human genome. They need to bind to PIWI proteins to carry out their regulatory roles. For instance, Yao et al. discovered that piR-651 promotes the highly metastatic phenotype of lung cancer cell lines [15].

3. Mechanisms of Non-coding RNAs in Tumor Drug Resistance

LncRNAs, miRNAs, and circRNAs are types of ncRNAs that partake in intricate regulatory mechanisms underlying cancer drug resistance. Their mechanisms encompass various aspects, such as modulating drug metabolism and transport, cellular apoptosis, signaling pathways, and protein-related mechanisms.

3.1. Regulation of Drug Metabolism and Transport

Cancer cell drug resistance often correlates with altered drug transport, absorption, and metabolism, particularly through mechanisms regulating intracellular drug accumulation. Certain lncRNAs can enhance the expression level of ABC transporters. These transporters include ABCB1, MRP1, and ABCG2. For instance, lncANRIL promotes MDR1 and MRP1 expression in gastric cancer cells, while lncHOTAIR induces ABCG2 expression in breast cancer cells [16].

Furthermore, other non-coding RNAs, like miRNAs, are also closely involved in regulating drug transporters. In hepatocellular carcinoma, for example, miRNAs can influence drug concentrations by modulating transmembrane transporters. Aberrant regulation of the miR-383/MCUR1 axis can result in overexpression of P-gp and elevated ATP levels, which facilitate the efflux of anticancer drugs and contribute to chemotherapy resistance. Conversely, miR-145 binds directly to the 3’-UTR of P-gp and BCRP genes, inhibiting their protein expression to enhance cellular sensitivity to drugs [17].

3.2. Regulation of Cell Apoptosis

Cellular apoptosis is a critical mechanism for cancer cells' response to drugs. Non-coding RNAs regulate key genes involved in apoptosis, allowing tumor cells to evade programmed cell death, survive, and develop drug resistance. For example, lncARA exerts its influence on breast cancer cells by interfering with Cyclin B1 - mediated G2/M phase arrest. This interference causes the cells to pause before division, thereby disrupting the normal apoptotic processes. Likewise, lncPANDA exerts a downregulatory effect on pro-apoptotic factors like FAS and BIK. As a result, cells become more tolerant to DNA damage, and the frequency of apoptosis is diminished [16].

miR-106b-5p targets and represses the tumor suppressor gene BTG3. This action elevates the expression of its downstream molecules, namely cyclin E1, CDK2, and the anti-apoptotic Bcl-XL. miR-518d-5p exerts an inhibitory effect on its target gene c-Jun. As a result, PUMA expression is dampened, and apoptosis is suppressed. MiR-483-3p modulates genes and curtails PI3K/AKT pathway activation and lowers the levels of p-AKT and Bcl2 proteins. This triggers apoptosis induction and enhances the responsiveness of tumor cells to gemcitabine [18].

3.3. Regulation of Signaling Pathways

In the molecular mechanisms of tumor drug resistance, aberrant modulation of signaling cascades takes center stage. Take oral squamous cell carcinoma as an example: lncRNA CASC2 acts on the FZD8 gene, reducing FZD8 expression. Lowered FZD8 dampens activation of the Wnt/β-catenin signaling cascade, a process often associated with chemoresistance in tumor cells. Blocking this pathway can lessen cellular resistance to cisplatin [19].

Furthermore, miRNAs can influence drug resistance by modulating key molecules in signaling cascades. miR-125b-5p, by degrading ATXN1 mRNA, releases its inhibition on Snail, activating EMT-related signaling axes and inducing drug resistance. Additionally, miR-92b mediates sorafenib resistance by inhibiting PTEN, which activates the PI3K/AKT/mTOR pathway. Moreover, miRNAs like miR-30a-5p can suppress autophagy by reducing Beclin-1 and ATG5 expression, affecting the susceptibility of tumor cells to drug-based therapies [17].

circMAPKBP1 targets and inhibits the expression of miR-17-3p. As miR-17-3p negatively regulates TGF-β2, this interaction activates the miR-17-3p/TGF-β2 signaling pathway, which then activates autophagy, promotes tumor progression, reduces the efficacy of cisplatin, and ultimately leads to drug resistance [20]. Small nucleolar RNA host gene 1 (SNHG1) is also linked to tumor drug resistance. SNHG1 binds with miR-23b-3p at PTEN's 3' untranslated region, preventing miR-23b-3p from degrading PTEN and thereby upregulating PTEN. Increased PTEN inhibits the AKT signaling cascade, which in turn reduces tumor cell proliferation, promotes apoptosis, enhances sensitivity to gemcitabine, and ultimately alleviates drug resistance [21].

3.4. Protein-Related Mechanisms

3.4.1. Regulation of Protein Degradation

In the intricate regulatory network of tumor cell drug resistance, the regulation of protein degradation serves as a pivotal molecular mechanism. This process profoundly influences cellular responses to drugs by precisely controlling the stability of oncoproteins and tumor suppressor proteins. The Ubiquitin-Proteasome System (UPS), along with the Autophagy-Lysosome Pathway, as core pathways for protein degradation, can contribute to tumor cell drug resistance. They achieve this by targeted degradation of tumor suppressor proteins, thereby weakening their anti-tumor functions, or by aberrantly accumulating oncoproteins that drive the drug-resistant phenotype. Conversely, intervention in protein degradation processes can re-establish the expression homeostasis of critical proteins, such as tumor suppressor proteins and drug target proteins, thus reversing drug resistance. For instance, lncRNA CASC2 upregulates SOCS1 levels by hindering the UPS-mediated degradation of the tumor suppressor protein SOCS1. This action inhibits abnormally activated oncogenic pathways like JAK/STAT, thereby enhancing cellular sensitivity to cisplatin and capecitabine [19].

3.4.2. Regulation of Protein-Protein Interactions

Circular RNAs (circRNAs) can encode proteins and interact with other proteins, thereby regulating tumor cell drug resistance. For example, circATG4B encodes circATG4B-222aa, which competitively binds to TMED10, releasing its inhibition on ATG4B. This enhances ATG4B-mediated LC3-II conversion, promoting autophagy-induced oxaliplatin resistance in colorectal cancer cells [22]. Additionally, in pancreatic ductal adenocarcinoma, circRREB1 engages with PGK1 and YBX1 and drives tumor progression [23].

3.5. Regulation of Metabolic Enzymes

Metabolic enzymes exert a pivotal regulatory function in the mechanisms underlying tumor cell chemoresistance. These enzymes can directly or indirectly partake in drug resistance through the modulation of tumor cell metabolic homeostasis and activating downstream signaling pathways. Their functions can rely on classical metabolic activities or be achieved through non-metabolic mechanisms [24].

piR-39980 enhances tumor cell sensitivity to DOX by targeting cholesterol biosynthesis enzyme FDFT1, which inhibits CYPOR and the EIF3H/HIF1α axis, thereby boosting DOX cytotoxicity. Furthermore, piR-39980 significantly attenuates the oncogenicity of tumor cells by inhibiting their migration, proliferation, and tumor spheroid-forming capabilities. PiR-39980 is capable of shifting cell populations from the growth phase (S phase) to the apoptotic phase (Sub-G1 phase), which further enhances the anti-tumor effect of DOX and overcomes tumor cell resistance to DOX [25].

3.6. Regulation of Cancer Immune Checkpoints

Of immune checkpoints, the regulatory mechanisms contributing to tumor cell drug resistance primarily involve alterations in tumor cell antigen presentation capabilities, aberrant signaling pathways, and tumor microenvironment remodeling. Tumor cells can evade T cell recognition by reducing antigenicity or downregulating Major Histocompatibility Complex (MHC) expression. Abnormal signaling pathways like IFN-γ and WNT/β–catenin can mediate drug resistance by regulating PD-L1 expression or inhibiting immune cell activity. Immunosuppressive cell populations, including Tregs (i.e., regulatory T cells) and MDSCs (namely, myeloid-derived suppressor cells), as well as substances like indoleamine 2,3-dioxygenase 1 (IDO1) within the tumor microenvironment, can promote tumor immune escape by secreting inhibitory factors or directly suppressing effector T cell function [26].

Research has revealed that piRNA-137463 is markedly overexpressed in tumor tissues and links tightly to unfavorable patient prognosis. Inhibiting piRNA-137463 can significantly reduce the tumor cells' abilities to proliferate, migrate, and invade, and enhance T cell cytotoxicity by increasing IFN-γ secretion. Simultaneously, piRNA-137463 inhibits the cholesterol synthesis pathway through the LOC100128494/miR-24-3p/INSIG1 axis, reducing lipid raft formation and PD-L1 expression, thereby reversing immune escape. Animal experiments have confirmed that targeting piRNA-137463 (AntagopiRNA-137463) inhibits tumor growth and metastasis, and significantly enhances the response rate to anti-PD-1 therapy [27].

4. Non-coding RNAs as Biomarkers for Tumor Drug Resistance

In non-small cell lung cancer (NSCLC), the lncRNA TRIDENT functions as a biomarker for drug resistance and prognosis. Notably, TRIDENT is highly expressed in EGFR-mutant NSCLC, with its expression level showing a significant correlation to patient outcomes. Among 998 NSCLC patient samples analyzed, TRIDENT expression in the EGFR-mutant subgroup was markedly elevated compared to the wild-type subgroup ($P < 0.0001$), as demonstrated by research findings. Furthermore, patients with high TRIDENT expression displayed shorter disease-free survival (Logrank test, $p = 0.0038$, HR = 1.4). Mechanistically, TRIDENT interacts with the TRIM28 protein, promoting its phosphorylation at S473 and S824 sites, which enhances DNA damage repair capability. Depletion of TRIDENT results in the buildup of DNA damage within tumor cells and significantly enhances their sensitivity to chemotherapeutic drugs. From a clinical translation perspective, TRIDENT expression is regulated by EGFR activation; targeted drugs like gefitinib and osimertinib can significantly downregulate its level, suggesting that its dynamic levels might reflect EGFR pathway activity and drug response. Moreover, the synergistic effect of TRIDENT and TRIM28 phosphorylation (e.g., phosphomimetic mutants can reverse the drug sensitivity induced by knockdown) further supports its potential as a predictive biomarker for drug resistance [28].

Circular RNA (circRNA) circ_0000098 and miR-494 play crucial roles in hepatocellular carcinoma (HCC) drug resistance and progression. Research demonstrates that in 58 pairs of HCC tissues, circ_0000098 exhibited significantly higher expression levels compared to adjacent non-tumor tissues. Moreover, patients exhibiting high circ_0000098 expression levels showed decreased survival rates. Mechanistically, circ_0000098 functions by sponging miR-383, thereby relieving its inhibition on the mitochondrial calcium uptake protein MCUR1, which promotes ATP synthesis and P-gp expression. This enhances the drug efflux capability of HCC cells against doxorubicin;

overexpression of circ_0000098 can reverse miR-383-induced downregulation of ATP and P-gp. In animal experiments, knockdown of circ_0000098 led to a 58% diminution of tumor volume and a 2.8-fold increase in γH2AX damage, suggesting accumulated DNA damage. On the other hand, miR-494 promotes HCC cell survival under metabolic stress by targeting and inhibiting G6pc expression, inducing a glycolytic phenotype, and remodeling lipid metabolism. Clinical data analysis revealed that high levels of miR - 494 in serum are implicated in sorafenib resistance, indicating its potential to assess tumor metabolic status and treatment response. Both circ_0000098 and miR-494 regulate HCC resistance and progression through the circ_0000098/miR-383/MCUR1 axis and the miR-494/G6pc pathway, respectively, illustrating their potential to act as diagnostic biomarkers and therapeutic targets [29-30].

Additionally, researchers analyzed tissue and fluid samples from various cancer patients, comparing RNA expression differences among drug-resistant and sensitive tumor cells. Combining cell experiments and animal models, they discovered that lncRNA CCAT2 is highly expressed in colorectal cancer, where it correlates with chromosomal instability. This increased chromosomal aberration leads to resistance to 5-fluorouracil and oxaliplatin. Similarly, low expression of miR-27a in bladder cancer cells contributes to cisplatin resistance [31].

In summary, ncRNAs play critical roles in tumor drug resistance mechanisms. Their unique expression characteristics and involvement in intercellular communication make them promising candidates for tumor drug resistance biomarkers. This potential can aid in clinically predicting treatment responses, monitoring drug resistance, and guiding personalized therapies.

5. Therapeutic potential of Non-coding RNAs in Tumor Drug Resistance

NcRNAs exert regulatory effects on cancer development via diverse mechanisms, emerging as promising pharmaceutical targets or therapeutic entities. The following sections outline the key research progress in targeting ncRNAs for cancer drug resistance therapy, incorporating cutting-edge technologies such as antisense oligonucleotides (ASOs), RNA interference (RNAi), and the CRISPR/Cas9 system.

5.1. Antisense Oligonucleotides (ASOs)

ASOs exert control over gene expression by attaching to target RNAs via complementary base pairing interactions. In the field of tumor drug resistance, ASOs can reverse resistance by targeting aberrant non-coding RNAs or mutation-associated RNAs. For instance, to address cetuximab resistance caused by abnormal splicing of EGFR exon 4, an ASO targeting rs737540-T at chromosome 13q32.2 was designed. The combination of 20 μg/ml ASO with 100 μmol/L cetuximab significantly inhibited tumor cell proliferation, and in animal models, tumor volume decreased by approximately 40%. Mechanistically, rs737540-T recruits TARDBP to induce EGFR exon 4 skipping, producing a resistant variant, while the ASO blocks this binding to restore normal splicing. Currently, the clinical application of ASOs faces challenges including poor delivery effectiveness, poor in vivo stability, and potential non-target toxicity, necessitating the development of novel carriers to improve targeting [32].

5.2. RNA Interference (RNAi)

RNAi is a technique that specifically degrades target gene mRNA through small interfering RNA (siRNA), thereby inhibiting gene expression. This method can be used to suppress tumor cell growth and invasion. For example, a study demonstrated that transfecting cervical cancer HeLa/C-33A cells with two siRNAs targeting ITGA5 significantly downregulated ITGA5 expression, inhibited cell proliferation, promoted apoptosis, and reduced invasiveness. Moreover, it boosted that of the epithelial marker E-cadheri, confirming its role via epithelial-mesenchymal transition modulation. Although RNAi holds significant potential in cancer therapy, it faces challenges such as the impact

of non-specific siRNA delivery on efficacy and a lack of standardized application. Its long-term safety and immunogenicity in normal tissues still require extensive research [33].

5.3. CRISPR/Cas9 System

The CRISPR/Cas9 gene-editing technology has been widely applied in the study of non-coding RNAs. For example, in research on oral squamous cell carcinoma (OSCC), this technology was employed to generate a systemic knockout mouse model of miR-181a-5p. Findings from this model demonstrated that the loss of miR-181a-5p leads to significant dysregulation of lipid metabolism–related proteins and tumor regulatory factors, along with enrichment of the PPAR signaling pathway. These alterations contribute to increased lipid droplet biogenesis and the development of an immunosuppressive microenvironment, thereby accelerating the malignant progression of OSCC. The results suggest that the absence of miR-181a-5p promotes tumor cell proliferation and drug resistance [34]. Despite the high editing efficiency of the CRISPR/Cas9 system in vivo, its clinical translation still faces risks of non-target effects, immunogenicity potential of viral vectors, and editing limitations in multi-gene drug resistance scenarios.

5.4. Targeting Non-coding RNA-Modifying Enzymes

Targeting non-coding RNA (ncRNA) modifying enzymes can regulate ncRNA function by interfering with RNA modification processes, thereby influencing tumor cell behavior. Taking m6A modification as an example, it can modulate ncRNA stability and function. For instance, the radiomimetic agent Zeocin selectively downregulates the protein level of the m6A methyltransferase METTL14 in a transcription-independent manner, reducing the total m6A level in glioma cells by nearly 50%. This, in turn, induces endogenous double-stranded RNA (dsRNA) production and activates the PKR/eIF2α pathway, significantly inhibiting tumor cell growth and migration. Targeting m6A modifying enzymes (e.g., METTL14) can regulate the modification status of ncRNAs and interfere with downstream gene regulation, as evidenced by Zeocin inhibiting METTL14 to alter RNA modifications and activate immunomodulatory pathways. Current challenges include insufficient specificity in targeting modifying enzymes and cellular heterogeneity in their functions, necessitating further optimization of target selection and intervention strategies [35].

These findings indicate that ncRNA modulation could represent a potential strategy for overcoming tumor drug resistance.

6. Conclusion

Non-coding RNAs exert a critical influence on tumor drug resistance. Functional analysis of various ncRNAs, including miRNAs, lncRNAs, and circRNAs, has elucidated their molecular mechanisms in forming tumor cell resistance by regulating signaling pathways, drug metabolism and transport, and ceRNA networks. Research has confirmed that non-coding RNAs (ncRNAs) hold promise as biomarkers for predicting drug resistance and the feasibility of targeting ncRNAs to reverse tumor resistance, offering new perspectives for studying tumor resistance mechanisms. However, current research still faces limitations such as low clinical translation efficiency, insufficient stability, and a lack of in vivo targeting specificity.

As single-cell sequencing and spatial transcriptomics advance, ncRNA spatiotemporal regulatory mechanisms in tumor drug resistance will be further elucidated. Combining gene editing and nano-delivery systems may overcome ncRNA-drug delivery bottlenecks. Future research can boost multi-omics integration to explore interactions between ncRNAs, tumor microenvironment, and immune system, building more precise drug resistance prediction models. Furthermore, collaborative efforts among industry, academia, and healthcare will accelerate the clinical translation of ncRNA-related diagnostic reagents and therapeutic drugs, bringing new hope for overcoming tumor drug resistance and improving patient prognosis.

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