Role of noncoding RNA in drug resistance of prostate cancer

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Abstract
Prostate cancer is one of the most prevalent forms of cancer around the world. Androgen-deprivation treatment and chemotherapy are the curative approaches used to suppress prostate cancer progression. However, drug resistance is extensively and hard to overcome even though remarkable progress has been made in recent decades. Noncoding RNAs, such as miRNAs, lncRNAs, and circRNAs, are a group of cellular RNAs which participate in various cellular processes and diseases. Recently, accumulating evidence has highlighted the vital role of non-coding RNA in the development of drug resistance in prostate cancer. In this review, we summarize the important roles of these three classes of noncoding RNA in drug resistance and the potential therapeutic applications in this disease.

Facts
- Androgen-deprivation treatment and chemotherapy are indispensable treatments for metastatic prostate cancer (PCa). However, drug resistance is hard to avoid.
- Anti-tumor drugs cause a change in the expression of noncoding RNA, thus affecting the drug sensitivity of PCa.
- Noncoding RNAs are proposed as candidate biomarkers to predict the drug response of PCa.
- Noncoding RNAs are proposed as a potential therapeutic target to reverse drug resistance of PCa.

Open questions
- How do noncoding RNAs mediate drug resistance in PCa?
- How can noncoding RNAs be used as biomarkers to predict the drug response of PCa?
- How can noncoding RNAs be used to design drug targets and reverse the drug resistance of PCa?

Introduction
Prostate cancer is the most commonly diagnosed malignancy in men worldwide1. It is particularly prevalent in the West, while the incidence is lower in Eastern Asian2. Apart from race, lifestyle factors such as smoking, body mass index, and physical activity also contribute to prostate cancer3. Because of the coverage of screening and early detection, there are more than 1.2 million newly diagnosed prostate cancer patients annually and more than 350,000 deaths worldwide4. Androgen deprivation treatment (ADT) is the initial treatment used for prostate cancer5. Moreover, it is reported that androgen deprivation treatment combined with chemotherapy drugs can improve the survival of prostate cancer6. Hence, it is urgent to uncover the detailed molecular mechanism of drug resistance in prostate cancer, and thus find a way to maximize the benefits of chemotherapy.

Early research on carcinogenesis focused mainly on protein-coding genes, because proteins are considered...
central to molecular biology. However, many noncoding RNAs species have been discovered due to the development of transcriptional sequencing. In addition, it has been verified that numerous noncoding RNAs participate in many vital cellular functions and in disease, especially in cancer. According to their size, noncoding RNAs can be divided into two groups: (1) small noncoding RNAs (sncRNAs), with length less than 200 nucleotides, including microRNAs and piRNAs, (2) long noncoding RNA (lncRNAs), including circRNAs and pseudogenes.

In this review, we discuss the characteristics and vital role of noncoding RNAs, especially miRNA, lncRNA, and circRNA, in drug resistance of prostate cancer. These noncoding RNAs are potential therapeutic targets for treating drug resistance in prostate cancer (Fig. 1).

Evidence acquisition
We accessed PubMed to search English-language articles up to October 2020, using a combination of the following terms: noncoding RNA, or microRNA, or miRNA, or lncRNA, or long noncoding RNA, or circular RNA, or circRNA, and prostate cancer, and drug resistance or chemoresistance.

MicroRNA and drug resistance
MiRNA is a type of conserved small noncoding RNA whose length is about 18–22 nucleotides. Mature miRNA can directly target the 3′ untranslated region (UTR) of mRNA, as some target to the 5′ UTR or to the coding sequence, in a sequence-specific manner. As a result, miRNA can downregulate the expression level of mRNAs...
by hampering the translational process or mRNA decay\textsuperscript{11,12}. Thus, miRNA has been shown to take part in carcinogenesis by regulating the expression level of important oncogenes or tumor suppressor genes\textsuperscript{13–15}. miRNAs also play a vital role in drug resistance. Here, we present some crucial miRNAs involved in drug resistance of prostate cancer.

**miRNA and resistance to anti-androgen drugs**

Indeed, androgen-deprivation treatment was one of the earliest hormonal therapies in oncology\textsuperscript{16,17}. Since the discovery of the androgen receptor (AR), ADT has been an indispensable treatment for prostate cancer. The first generation of antiandrogen drugs, Cyproterone (CPA), is a type of steroidal drugs, which competitively binds to the AR and AR-v7. Expect from miR-212, miR-361–3p was also reported to increase the enzalutamide resistance and dramatically improve patient survival.

**miR-221 and miR-222**

Growing evidence elucidates that miRNAs have a vital role in anti-androgen drugs resistance (Table 1). Pimenta et al. reported that miR-23b and miR-27b can sensitize castration prostate cancer cells to flutamide by targeting CCNG1\textsuperscript{21}. Another group revealed that miR-221 and miR-222, which are significantly up-regulated in CRPC cells, can maintain the castration resistance phenotype in prostate cancer\textsuperscript{22}. In addition, miR-663 is involved in the prostate cancer castration phenotype. miR-663 significantly alters the effect of the AR signal but does not alter the expression of the AR to induce castration-therapy resistance. Evaluation of 117 prostate cancer patients’ specimens also confirmed that miR-663 was upregulated in CRPC patients and could be a prognostic indicator for clinical recurrence\textsuperscript{23}.

Meanwhile, some miRNAs can also target AR and androgen splicing variant 7 (AR-V7) to re-sensitize drug resistant prostate cancer cells\textsuperscript{24,25}. miR-212 was found downregulated in prostate cancer tissues compared to adjacent tissues. Moreover, overexpression of miR-212 can restrain the castration resistance of prostate cancer by inhibiting hnRNPH1 and in turn reducing the expression of the AR and AR-V7\textsuperscript{24}. Expect from miR-212, miR-361–3p was also reported to increase the enzalutamide sensitivity of prostate cancer via targeting the AR-V7. MiR-361–3p can directly bind to the 3’ UTR of AR-V7 and MKNK2 in hypoxia conditions to sensitize prostate cancer cells to enzalutamide\textsuperscript{25}.

**miR-32–3p**

Apart from those miRNAs which have a role in the castration phenotype, miRNAs also could be promising prognostic biomarkers in castration-resistant prostate cancer (Table 2). Huang et al. analyzed miRNA expression in two independent cohorts, including a screening cohort which contained 23 patients and a follow-up cohort with 100 patients. They found that high expression levels of miR-1290 and miR-375 were associated with a poor survival rate. What’s more, miR-1290 and miR-375 also have good performance in prediction of CRPC stage\textsuperscript{26}.

**miRNA and resistance to taxane**

**Table 1** MiRNA and castration resistance in prostate cancer.

| MiRNAs          | Expression | Genes and pathways       | Reference |
|-----------------|------------|--------------------------|-----------|
| miR-23b and     | Down       | CCNG1                    | 21        |
| miR-27b         |            |                           |           |
| miR-221 and     | Up         | P21/Kip1                 | 22        |
| miR-222         |            |                           |           |
| miR-212         | Down       | hnRNPH1/AR, AR-V7        | 24        |
| miR-150–5p and  | Down       | SPOCK1                   | 25        |
| miR-150–3p      |            |                           |           |
| miR-616         | Up         | TFPI-2                   | 26        |
| miR-663         | Up         | KCNC4, DHR57, NKX3.1,    | 27        |
|                 |            | DHCR24, PSMA7            |           |
| miR-32          | Up         | BTG2                     | 28        |
| miR-361–3p      | Down       | AR-V7 and MKNK2          | 29        |
| miR-4719 and    | Up         | IL-23                    | 30        |
| miR-6756–5p     |            |                           |           |
| miR-4638–5p     | Down       | Kidins220                | 31        |
| miR-100–5p      | Up         | MTOR                     | 32        |

Taxane, composed of paclitaxel and docetaxel, is a class of well-known anti-tumor drugs which affect the intrinsic instability of microtubules\textsuperscript{27,28}. Paclitaxel (PXL) was the first taxane to become clinically available. It can arrest the cell cycle by binding to the tubulin, which in turn stabilizes the microtubule structure\textsuperscript{29}. Docetaxel (DXL) is the first-line drug to treat metastatic castration-resistant prostate cancer (mCRPC) and provides a significant advantage in CRPC survival\textsuperscript{30}. However, taxane therapy inevitably encounters the problem of resistance, despite a good response to initial treatment\textsuperscript{31}. Hence, a deeper understanding of the underlying mechanism of taxane resistance would provide opportunities to overcome taxane resistance and dramatically improve patient survival.
Several miRNAs have been reported as upregulated in three paclitaxel-resistant cell lines, including miR-200b-3p, miR-375, and miR-34b-3p. In addition, the downstream genes of miRNAs, LARP1, and CCND1 are increased in paclitaxel-resistant cell lines, which could be the potential cause of resistance. It has been found that miR199a, which is downregulated in prostate cancer tissues, is suppressed by docetaxel resistance. MiR-195 was reported to be downregulated in the DOC-resistant prostate cancer cells compared to the DOC-sensitive prostate cancer cells. In addition, high expression of miR-195 lowers the IC50 of DOC through decreasing the expression level of CLU. miR-204 can also directly inhibit the expression of ZEB1 and then attenuate docetaxel resistance. A well-known miRNA which has been comprehensively studied in various types of cancer, has been proved to play a vital role in docetaxel resistance of prostate cancer. Xu et al. revealed that miR-143 could target the EGFR/RAS/MAPK pathway to enhance the docetaxel sensitivity of prostate cancer cells, and this is a potential site for the treatment of docetaxel-resistant prostate cancer. In another study analyzing 30 prostate cancer patients’ specimens, miR-200b was identified as a tumor-suppressor gene and promoter of chemosensitivity in prostate cancer.

miRNA and resistance to cisplatin

Since prostate cancer often becomes refractory to hormonal treatment and taxane drugs, medical providers frequently turn to alternative therapies to treat advanced prostate cancer patients. Cisplatin, a chemotherapy drug that halts tumor progression by leading to cancer cell apoptosis, is proved to have a moderate effect on metastatic castration-resistant prostate cancer. Although cisplatin is not considered to use solely, it is conformed that cisplatin has a significant synergistic effect with other chemotherapy drugs.

It has been reported that miR-205 can enhance cisplatin toxicity in prostate cancer. MiR-205 can impair the autophagic pathway of prostate cancer by downregulating the lysosome-associated protein RAB27A/LAMP3 and eventually overcome the cisplatin resistance. Conversely, another six oncogenic miRNAs, which derive from the miR-17–92 cluster, promote chemoresistance through activating the AKT pathway (Table 3).

| Table 2 Clinical application of miRNA in prostate cancer. |
|---------------------|-------|---------------------|---------------------|
| MiRNAs            | Expression | Potential clinical application | Reference |
| miR-1290 and miR-375 | Up     | Prognostic markers | 26 |
| miR-216a          | Up     | Prognostic markers | 104 |

| Table 3 MiRNA and chemoresistance in prostate cancer. |
|---------------------|-------|---------------------|---------------------|
| MiRNAs            | Expression | Genes and pathways | Drug     | Reference |
| miR-148a          | Down   | MSK1                | Paclitaxel | 34 |
| miR-199a          | Down   | YES1                | Paclitaxel | 33 |
| miR-34a           | Down   | JAG1/Notch1         | Paclitaxel | 35 |
| miR-375           | Up      | SEC23A/YAP1         | Docetaxel | 36 |
| miR-323           | Up      | P73                 | Docetaxel | 37 |
| miR-181a          | Up      | A8C81               | Docetaxel | 7 |
| miR-195           | Down   | CLU                 | Docetaxel | 39 |
| miR-27a           | Up      | PS3                 | Docetaxel | 105 |
| miR-204           | Down   | ZEB1                | Docetaxel | 40 |
| miR-143           | Down   | KRAS                | Docetaxel | 41 |
| miR-193a-5p       | Up      | Bach2               | Docetaxel | 38 |
| miR-138           | Up      | Kindlin-2           | Docetaxel | 106 |
| miR-200b          | Down   | Bmi-1               | Docetaxel | 42 |
| miR-205           | Down   | RAB27A/LAMP3        | Cisplatin | 47 |
| miR-17-92 cluster | Down   | AKT pathway         | Cisplatin | 48 |

| miR-1290 and miR-375 | Up | Prognostic markers | miR-375 could increase docetaxel resistance by targeting SEC23A and YAP1. Similarly, miR-323 was identified as having a high expression level in DOC-resistant cells by other groups. miR-323 significantly increased the inhibitory concentration (IC50) value for docetaxel in prostate cancer cell lines by repressing the expression level of P73. In addition, miR-193–5p was found to enhance drug resistance to docetaxel in prostate cancer by inhibiting Bach2 expression. Aside from elevated expression of miRNAs in docetaxel-resistant prostate cancer, there are several miRNAs which can reverse docetaxel resistance. MiR-195 was reported to be downregulated in the DOC-resistant prostate cancer cells compared to the DOC-sensitive prostate cancer cells. In addition, high expression of miR-195 lowers the IC50 of DOC through decreasing the expression level of CLU. miR-204 can also directly inhibit the expression of ZEB1 and then attenuate docetaxel resistance. A well-known miRNA which has been comprehensively studied in various types of cancer, has been proved to play a vital role in docetaxel resistance of prostate cancer. Xu et al. revealed that miR-143 could target the EGFR/RAS/MAPK pathway to enhance the docetaxel sensitivity of prostate cancer cells, and this is a potential site for the treatment of docetaxel-resistant prostate cancer. In another study analyzing 30 prostate cancer patients’ specimens, miR-200b was identified as a tumor-suppressor gene and promoter of chemosensitivity in prostate cancer.

miRNA and drug resistance

LncRNAs are a subset of non-coding RNAs whose length is more than 200nt. Although they share many
similarities with other protein-coding mRNA, lncRNAs generally have limited or no protein-coding capacity. LncRNAs can regulate processes such as chromatin remodeling, histone modifications, miRNAs sponging, mediation of complex formation and so on. However, with the deeper study of lncRNA, it has gradually been revealed that it is vital in tumorigenesis, including in prostate cancer. Furthermore, lncRNAs play an important part in drug resistance of prostate cancer. Here, we present some lncRNAs that are crucial in drug resistance of prostate cancer (Table 4).

LncRNA and resistance to anti-androgen drugs

Several lncRNAs have been reported as highly expressed in CRPC. BCAR4, which has a crucial role in tamoxifen-resistance breast cancer, can bind to the promoter region of GLI2 and activate the GLI2 downstream genes, making the prostate cancer cells less sensitive to androgen stimulation. Similarly, Lnc-SNHG17, which was identified as highly expressed in CRPC, can serve as a competing endogenous RNA (ceRNA) to sponge miR-144 in CRPC. Subsequently, inhibition of miR-144 upregulates the downstream target, CD51, to accelerate the CRPC cell proliferation and invasion.

Apart from the above lncRNAs, there are several well-known lncRNAs have been reported to participate in the progression of CRPC. LncRNA HOXD-AS1, which has been extensively studied in colorectal carcinoma, glioma, cervical cancer, and liver cancer, can promote castration by recruiting WDR5 to mediate histone 3 lysine 4 tri-methylation and then to regulate the downstream genes, such as PLK1, AURKA, and CDC25C. Another famous lncRNA, MALAT1, is involved in CRPC progression both in vivo and in vitro. Silencing of MALAT1 can inhibit CRPC cell proliferation by arresting the CRPC cell in the G0/G1 cycle. Moreover, xenografts assays produced the same results.

Meanwhile, lncRNA can directly bind to the androgen receptor to affect castration. Lnc-HOTAIR has been found to interact with the AR and prevent it from ubiquitination and degradation, and thus drives CRPC progression. Another lncRNA, Lnc-LBCS, can directly interact with hnRNPK and AR mRNA to form a complex and inhibit translation of the AR. Therefore, inhibiting the expression of LBCS can activate AR signaling to sustain the trait of castration.

LncRNA and resistance to taxane

Similarly, lncRNAs have a unique role in taxane resistance. Linc00518 was previously found to be highly expressed both in cancer cell lines and tumor tissues previously. Recent studies revealed that linc00518 can promote paclitaxel resistance through a sponge mechanism. Linc00518 regulates GATA6 expression and promotes paclitaxel resistance by competitively binding to miR-216b-5p. Another lncRNA, CCAT1, also appears to enhance paclitaxel resistance in prostate cancer. Similarly, CCAT1 can sponge miR-24-3p and

| LncRNAs          | Expression | Genes and pathways | Drug           | Reference |
|------------------|------------|--------------------|----------------|-----------|
| HOXD-AS1         | Up         | WDR5/H3K4me3       | Bicalutamide   | 60        |
| LncRNA-HOTAIr    | Up         | AR                 | Androgen       | 62        |
| Lnc-LBCS         | Down       | hnRNPK/AR          | Androgen       | 107       |
| LncRNA-BCAR4     | Up         | GLI2               | Androgen       | 54        |
| LncRNA-SNHG6     | Up         | miR-186/CD51       | Androgen       | 55        |
| Linc00675        | Up         | MDM2/GATA2/AR      | Androgen       | 108       |
| Linc00518        | Up         | miR-216b-5p/GATA   | Paclitaxel     | 63        |
| LncRNA-CCAT1     | Up         | miR-24-3p/FSCN1    | Paclitaxel     | 64        |
| LncRNA-NEAT1     | Up         | miR-34a-5p and miR-204-5p/ASCL4 | Docetaxel | 70 |
| LncRNA-MALAT1    | Up         | miR-145-5p/AKAP12  | Docetaxel      | 63,71     |
| LncRNA-DANCR     | Up         | miR-34a-5p/JAG1 or miR-135a | Docetaxel | 65 |
| LncRNA-CASC2     | Down       | miR-183/SPRY2      | Docetaxel      | 66        |
| LncRNA-HORAS5    | Up         | BCL2A1             | Cabazitaxel    | 109       |
| LncRNA-HOTTIP    | Up         | Wnt/B-catenin      | Cisplatin      | 72        |
| LOXL1-AS1        | Down       | miR-let-7a-5p/EGFR | Doxorubicin    | 76        |
thus upregulate FSCN1 expression to promote pacli-
taxel resistance64.

Besides taking part in paclitaxel resistance, IncRNA also
plays a vital role in prostate cancer resistance to docetaxel. IncRNA DANCR is signi-
cficantly upregulated in docetaxel-resistant prostate cancer. Silencing of DANCR
re-sensitized DTX-tolerant prostate cancer cells to doc-
etaxel treatment. Further studies found that DANCR
suppressed the miR-34a-5p-induced JAG1 degradation to
trigger docetaxel resistance65. Another IncRNA, CASC2,
also functions as a ceRNA for miR-183 to positively
upregulate the expression of SPRY2, a key antagonist of
RTK signaling, and enhance the cytotoxicity of docetaxel
in prostate cancer66. Another famous IncRNA NEAT1,
which is encoded from the familial tumor syndrome
multiple endocrine neoplasia type 1 locus, is shown to
exert oncogenic effects in many malignancies, including
non-small-cell lung cancers, gastric cancers, and esopha-
geal cancers67–69. A recent study showed that NEAT1
contributes to docetaxel resistance by upregulating ACSL
expression; it sponges miR-34a-5p and miR-204-5p in
prostate cancer70. Interestingly, IncRNA-MALAT1, which
is proved to be involved in CRPC progress, enhances
docetaxel resistance both in vivo and in vitro. Further
research veri-


cfied that MALAT1 upregulates AKAP12
expression via directly targeting miR-145-5p to promote
DTX-chemoresistance71.

LncRNA and resistance to cisplatin
It is reported that IncRNAs are also involved in cisplatin
resistance. Lnc-HOTTIP is evidently highly expressed in
prostate cancer samples compared to controls. Interest-
ingly, HOTTIP also sustains prostate cancer cisplatin
resistance through decreasing the apoptosis of PCa cells.
Furthermore, the mRNA and protein levels of Cyclin D1,
CDK4, and β-catenin are reduced significantly by silen-
cing the expression of HOTTIP, indicating that HOTTIP
is involved in cisplatin resistance through regulating
Wnt /β-catenin signaling72.

LncRNA and resistance to other drugs
Both taxanes and anthracyclines have been well studied
in CRPC. However, little attention has been focused on
anthracyclines in prostate cancer compared to taxanes73.

Doxorubicin is belonging to anthracyclines which is the
first-line clinical drug for CRPC. Doxorubicin exerts its
anti-tumor effect on a molecular level by blocking DNA
replication and transcription to induce cancer cell apop-
tosis74,75. It is reported that IncRNA LOXL1-AS1 can
promote doxorubicin resistance through the IncRNA
LOXL1-AS1/miR-let-7a-5p/EGFR axis. And inhibition of
IncRNA LOXL1-AS1 can be a potential strategy for drug-
resistant prostate cancer patients76.

CircRNA and drug resistance
Circular RNA is a subset of noncoding RNAs that is
produced by a non-canonical splicing event called back-
splicing. During back-splicing, a downstream 5
splice site is joined to an upstream 3
splice site to form circular
RNAs77,78. Due to differences in their production, struc-
ture, and turnover, circular RNAs have many unique and
important biological functions79. CircRNAs can function
as decoys for miRNAs or proteins, act as scaffolds for
circRNA-protein complex and recruit protein to speci-
fic loci80–82. In addition, some circRNAs can also be trans-
lated to produce small unique peptides83,84. In-depth
research has gradually lead to a recognition that circRNAs
play a vital role in chemoresistance in prostate cancer. We
will list some representative circRNAs involved in drug
resistance in prostate cancer below (Table 5).

CircRNA and resistance to anti-androgen drugs
Several circRNAs have been found to suppress
enzalutamide-resistance prostate cancer cell progression. hsa_circ_0001427 have been found down-regulated in
PCa specimens with higher Gleason scores, and the
results from cell lines also confirmed that hsa_circ_0001427 is decreased in Enz-resistant CRPC cells
compared to Enz-sensitive CRPC cells. Mechanism assays
revealed that hsa_circ_0001427 can regulate AR-v7
expression by sponging miR-181c-5p. These results sug-
gested that hsa_circ_0001427/miR-181c-5p/AR-
v7 signaling could be a potential target for treatment of
Enz-resistant PCa65. In addition, a circRNA microarray
assay was performed to identify differentially expressed
circRNAs between the Enz-resistant cell line and
sensitive cell line. Hundreds of circRNAs, such as hsa_circ_0001721 and hsa_circ_0004870 were
differentially expressed. Also, hsa_circ_0004870 was confirmed negatively correlated with AR and AR-v7 expression.

CircRNA and resistance to taxane
Circular RNA hsa_circ_0000735 is upregulated in docetaxel-resistant PCa tissues and cells. Functional assays have verified that silencing of hsa_circ_0000735 restrains DTX resistance and inhibits tumor progression. Moreover, hsa_circ_0000735 can serve as a sponge for miR-7, which is downregulated in DTX-resistant PCa, to promote PCa chemoresistance. Another circRNA, circFOXO3, which is one of the most studied circRNAs, has been found to inhibit prostate cancer progression and docetaxel resistance through enhanced FOXO3 expression and repression of EMT.

Conclusions and future perspectives
Since noncoding RNAs play significant roles in tumorigenesis, more and more attention has been focused on the relationship between noncoding RNA and chemoresistance. Accumulating evidences reveal that noncoding RNA (including miRNAs, lncRNAs, and circRNAs) has been involved in chemoresistance through targeting multiple signaling pathways (Fig. 2). Therefore, correcting the aberrant expression of noncoding RNA could be a promising strategy to overcome the chemoresistance of prostate cancer.

Compared with protein-coding genes, which have been extensively utilized as tumor therapy targets, noncoding RNA therapy has several advantages. Many proteins (80–85%) are “undruggable” due to lack of suitable structural features to interact with drug-like chemical compounds. Noncoding RNAs, on the other hand, exist in nearly 98% of the genome. Therefore, noncoding RNAs could be more accessible targets for tumor therapy. Also, nearly all traditional drugs for cancer therapy are facing drug resistance, whereas there are no drug resistance reports for noncoding RNA therapy so far. In addition, after chemical modification of noncoding RNA,
the half-time of ncRNA drugs is longer than that of small molecules or antibodies.\textsuperscript{92,93} Like antisense oligonucleotides (ASOs) with 2′-O-methoxyethyl modification in the backbone, can be more resistance to nucleases degradation.\textsuperscript{94,95}

Despite the promising prospect for tumor therapy, there are still various obstacles for noncoding RNA therapy. Taking miRNAs as an example, though there are various ongoing clinical trials, no miRNAs have yet been applied in clinical use. There are still several difficulties to be overcome. First, it is of great concern to identify the best miRNA candidates for cancer therapy. Since noncoding RNAs normally targeting many sites, it is quite difficult to avoid an off-target effect in cells. Moreover, noncoding RNA may have the opposite effects in different tissues. As an example, miR-375 can promote docetaxel resistance in prostate cancer, as mentioned above. However, miR-375 has been reported to facilitate osteosarcoma progression\textsuperscript{96}, suggesting that it plays a different role in different systems. Thus, ncRNA therapy should comprehensively consider the overall effect of agents in the human body. Secondly, a more efficient delivery system is also required to maintain the therapeutic oligonucleotides treatment efficiency and decrease toxicity to other organs. Even though great efforts have been made to design distinct RNA oligos or different polymer coatings to treat tumors more specifically, viral agents (for example, CRISPR–Cas systems) or nanoparticles agents are still the most commonly employed delivery methods for noncoding RNA therapy.\textsuperscript{97} Thus, toxicity and immune responses are still difficult to overcome. In summary, there is still a long way to go before noncoding RNA therapy can be applied in practice. As for IncRNAs and circRNA, more researches should be conducted to better understand the underlying mechanism in chemoresponse of prostate cancer.

Currently, there are several ongoing ncRNA therapy clinical trials using locked nucleic acid (LNA) technology to manipulate the expression of noncoding RNAs. One of the most famous miRNA formulations, MRX34 (a liposomal of miR-34a mimic) has undergone phase I clinical trials in the U.S and Korea with advanced hepatoma, melanoma, renal cell carcinoma, and other cancers. Although 16 of 46 patients remained in stable conditions for at least 4 weeks, these clinical trials were ultimately terminated due to several adverse immune-related effects. However, another LNA-technology-based drug, which targets miR-122 in hepatitis C infection patients, has been proved to effectively reduce the HCV RNA in phase II trials without unmanageable adverse events. These active ncRNA-related clinical trials show that noncoding RNA has good prospects for treatment of cancer, infection, and other “undruggable” diseases. Ultimately, the off-target toxicity and immune response are still the ongoing challenges for clinical treatment.

Looking forward, with the development of noncoding RNA delivery systems and fewer off-target effects, we imagine that whole-genome sequencing (including noncoding RNA) may be necessary for individual cancer therapy in the near future. We also believe that noncoding RNA therapy could be an effective supplement for traditional treatments.

Author contributions
G.L. and L.X.: Conceptualization, supervision; L.D. and R.W.: Writing—original draft preparation; D.S. and S.C.: Writing—reviewing and editing; H.W.: Visualization, Validation; L.W.: Review and Editing; Z.L. and Q.Z.: Writing and Editing.

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Conflict of interest
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