Potential Regulatory Roles of MicroRNAs and Long Noncoding RNAs in Anticancer Therapies

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MicroRNAs and long noncoding RNAs have long been investigated due to their roles as diagnostic and prognostic biomarkers of cancers and regulators of tumorigenesis, and the potential regulatory roles of these molecules in anticancer therapies are attracting increasing interest as more in-depth studies are performed. The major clinical therapies for cancer include chemotherapy, immunotherapy, and targeted molecular therapy. MicroRNAs and long noncoding RNAs function through various mechanisms in these approaches, and the mechanisms involve direct targeting of immune checkpoints, cooperation with exosomes in the tumor microenvironment, and alteration of drug resistance through regulation of different signaling pathways. Herein we review the regulatory functions and significance of microRNAs and long noncoding RNAs in three anticancer therapies, especially in targeted molecular therapy, and their mechanisms.

MicroRNAs (miRNAs) and long noncoding RNAs (lncRNAs) are important noncoding RNAs (ncRNAs), which display a remarkable variety of biological functions.1 ncRNAs can be classified by length (small, 18–200 nt; long, >200 nt) or by function (housekeeping ncRNAs and regulatory ncRNAs), with research over the last two decades largely focusing on regulatory ncRNAs.2 miRNAs, which are ~22 nt long, are the most widely studied class of regulatory ncRNAs, and these molecules mediate post-transcriptional gene silencing in animals by controlling the translation of mRNAs into proteins.3 lncRNAs, longer than 200 nt, are another subtype of regulatory ncRNAs that have a broad repertoire of functions in chromatin modification as well as in transcriptional, post-transcriptional, and translational regulation.4–7

miRNAs and lncRNAs are expressed at different levels in multiple cell and tissue types; they are also involved in tumorigenesis and the progression of aggressive cancer phenotypes.8 These molecules are identified as either carcinogenic or carcinostatic; are associated with cell growth, proliferation, migration, invasion, and apoptosis; and can even alter immune functions.9–10 RNA sequencing has confirmed that miRNA and lncRNA profiles can serve as highly sensitive and specific diagnostic and prognostic biomarkers. Because these molecules can be detected in diverse tumor tissues compared to normal samples and are associated with different clinicopathologic character-

miRNAs and lncRNAs Participate in Chemotherapy

Although chemotherapy remains a mainstay of anticancer treatment, the multi-organ toxicity and chemoresistance associated with this treatment strategy continues to be problematic.11

Recent studies of miRNAs and lncRNAs have indicated their latent therapeutic value for successful clinical translation. Results have confirmed that miRNAs and lncRNAs function as crucial regulators in different drug therapies, including chemotherapy, immunotherapy, and targeted molecular therapy, and the associated mechanisms have been investigated.

In this review, we discuss the ectopic expression of miRNAs and lncRNAs in multiple cancers and how they function in the three types of anticancer therapies, especially in targeted molecular therapy.

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In this review, we discuss the ectopic expression of miRNAs and lncRNAs in multiple cancers and how they function in the three types of anticancer therapies, especially in targeted molecular therapy.
Bcl-2, miR-374b-5p and miR-15 were found to enhance the chemosensitivity of cancer cells by modulating apoptotic pathways.27,28 While investigating the role of lncRNAs involved in temozolomide (TMZ)-resistant glioma, Jia et al.29 and Cai and colleagues30 found that knockdown of lncRNAs H19 and MALAT1 reversed chemoresistance to TMZ by inhibiting or promoting their downstream targets. As a crucial regulator, lncRNA PVT1 directly acts on multiple drug resistance-associated molecules. Silencing of PVT1 downregulates the levels of multidrug resistance 1 (MDR1) and multidrug resistance protein 1 (MRP1) as well as the expression of antiapoptotic B cell lymphoma-2 (Bcl-2), but it upregulates levels of proapoptotic Bax and cleaved caspase-3.31 Mechanistically, the effects of lncRNAs TP53TG1, UCA1, MALAT1, and TUSC7 occur in an miRNA-dependent manner in which these molecules suppress expression of miRNAs, thus blocking relevant signaling pathways.22,24,30,32 In summary, the regulatory roles of miRNAs and lncRNAs have been widely investigated (Table 1), and these functions are important for chemoresistance. The modulatory effects of these molecules mainly impact transcription and apoptosis, indicating that miRNAs and lncRNAs are potential targets that may improve drug efficacy.

By mediating cell-cell communication, exosomes have been suggested to exert profound effects on the development of drug resistance.33 Indeed, by transferring miR-503 from the endothelium to the tumor microenvironment, thus interfering with interaction between breast cancer (BC) cells and the microenvironment, endothelial exosomes contribute to chemotherapeutic response in BC.33 In addition, exosome-transferred miR-21 derived from M2-polarized macrophages

### Table 1. miRNAs and lncRNAs Involved in Chemotherapy

| Cancer Type | ncRNA       | Regulation of Chemoresistance | Target                  | Drug          | Reference |
|-------------|-------------|--------------------------------|-------------------------|---------------|-----------|
| NSCLC       | miR-197     | promotion                      | CKS1B/STAT3             | DDP           | 19        |
|             | miR-130b    | promotion                      | Wnt/b-catenin pathway   | DDP           | 20        |
|             | lncRNA MALAT1 | promotion                   | STAT3                   | DDP           | 21        |
|             | lncRNA TP53TG1 | inhibition                 | miR-18a/PTEN           | DDP           | 22        |
| PC          | miR-455-3p  | promotion                      | TAZ                     | GEM           | 23        |
|             | miR-29c     | inhibition                     | USP22                   | GEM           | 24        |
|             | miR-374b-5p | inhibition                     | Bcl-2                   | GEM           | 25        |
| BC          | miR-503     | inhibition                     | CCND2, CCND3            | EPI, PTX      | 26        |
|             | lncRNA LINP1 | promotion                   | ~                       | ADM, 5-FU     | 27        |
|             | miR-17      | promotion                      | DEDD                    | DDP, 5-FU     | 28        |
| GC          | miR-218     | inhibition                     | mTOR inhibitor          | DDP           | 29        |
|             | miR-623     | inhibition                     | CCND1                   | 5-FU          | 30        |
|             | miR-191     | promotion                      | Wnt/b-catenin pathway   | 5-FU          | 31        |
|             | miR-519b-3p | inhibition                     | ARID4B mRNA             | CAPE/OXA/5-FU | 32        |
| CRC         | miR-15      | inhibition                     | NF-kB, Bcl-2            | 5-FU/OXA      | 33        |
|             | lncRNA PVT1 | promotion                      | MDR1, MRP1, Bcl-2, Bax, cleaved caspase-3 | DDP | 34        |
|             | lncRNA MALAT1 | promotion                   | EZH2                    | OXA           | 35        |
|             | lncRNA UCA1 | promotion                      | miR-204-5p              | 5-FU          | 36        |
| Glioma      | lncRNA H19  | promotion                      | Wnt/b-catenin pathway   | TMZ           | 37        |
|             | lncRNA MALAT1 | promotion        | MIR-101                 | TMZ           | 38        |
|             | lncRNA DANCR | promotion                  | AXL/PI3K/Akt/ NF-kB     | DDP           | 39        |
| ESCC        | miR-125a-5p | inhibition                     | STAT3                   | DDP           | 40        |
|             | lncRNA TUSC7 | inhibition                 | MIR-224                 | DDP, 5-FU, and ADM/PTX | 41        |
| HCC         | miR-16      | inhibition                     | NF-kB                   | PTX           | 42        |
| OC          | miR-630     | promotion                      | APAF-1                  | PTX           | 43        |
|             | miR-142-3p  | inhibition                     | Sirtuin 1               | DDP           | 44        |

NSCLC, non-small-cell lung cancer; PC, pancreatic cancer; BC, breast cancer; GC, gastric cancer; CRC, colorectal cancer; ESCC, esophageal squamous cell carcinoma; OC, ovarian cancer; HCC, hepatocellular carcinoma; APAF-1, apoptotic protease activating factor-1; CCND1-3, cyclin D1-3; DEDD, death effector domain-containing DNA-binding protein; EZH2, enhancer of zeste homolog 2; MDR1, multidrug resistance 1; MRP1, multidrug resistance protein 1; PTEN, phosphatase and tensin homolog deleted on chromosome 10; STAT3, signal transducer and activator of transcription 3; TAZ, transcriptional co-activator with PDZ-binding motif; TMZ, temozolomide; PI3K, phosphatidylinositol 3-kinase; USP22, ubiquitin-specific peptidase 22; Bcl-2, B cell lymphoma-2; DDP, cisplatin; GEM, gemcitabine; EPI, epirubicin; PTX, paclitaxel; 5-FU, 5-fluorouracil; CAPE, capecitabine; OXA, oxaliplatin; TMZ, temozolomide; ADM, adriamycin; PTX, paclitaxel.
angiogenesis. And the epithelial-mesenchymal transition (EMT), as well as tumor-promoting traits, such as cell migration, invasion, proliferation, apoptosis, and the restoration of which enhances the drug sensitivity of ovarian cancer cells through PD-1/PD-L1 checkpoint blockade. Tumor-infiltrating lymphocytes (TILs) in oral squamous cell carcinoma (OSCC) are sites where immune escape arises, an effect that can be reversed by blocking the PD-1/PD-L1 pathway. miR-197 enhances antitumor immune responses by inhibiting PD-L1 expression, thus weakening the aggressive features of OSCC. In addition to PD-L1, PD-1 is also an effective target for PD-1/PD-L1 pathway blockade. miR-138 exhibits antitumor efficacy by decreasing PD-1 expression, resulting in substantial tumor regression and a 43% increase in median survival time. In addition, co-expression of PD-1 and lncRNA AFAP1-AS1, which is associated with the poorest prognosis in nasopharyngeal carcinoma patients, suggests that this molecule is an ideal candidate for future clinical trials of anti-PD-1 immunotherapy.

Most miRNAs play a positive role in anticancer immunity by targeting immune checkpoints; however, there are also miRNAs that carry out the opposite functions. For example, miR-17-5p post-transcriptionally upregulates PD-L1 in metastatic melanoma, leading to significantly enhanced invasive properties.

Other immunologic mechanisms together with immune checkpoint blockades involve the antitumor functions of miRNAs. For example, it has been demonstrated that miRNAs drive exosome-mediated MAPK signaling by activating CD97 and proinflammatory cytokine production by activating cells of the mononuclear phagocytic system; because they are translated into short polypeptides, miRNAs also present the best targets for immunotherapy (Table 2).

### miRNAs and IncRNAs Are Involved in Targeted Molecular Therapy

Targeted therapy is personalized treatment that involves the application of agents targeted toward specific molecular features of cancer cells, thereby minimizing toxicity and decreasing the cost of cancer care. These unique molecular targets that recognize and eliminate cancer cells are genetic alterations that are primarily mutated versions of epidermal growth factor receptor (EGFR), epidermal growth factor receptor 2 (HER2), vascular endothelial growth factor (VEGF), vascular endothelial growth factor receptor 2 (VEGFR2), and v-Raf murine sarcoma viral oncogene homolog B (BRAF). In addition, the use of miRNAs and IncRNAs in targeted molecular therapy primarily involves the alteration of cellular sensitivity to drugs. Below we summarize the modulatory effects of miRNAs and IncRNAs on resistance to agents that have been approved in China.

### EGFR and HER2 Mutations and Their Corresponding Agents

EGFR and HER2 are two common oncogenic mutations found in lung cancer and BC; they also occur in other types of malignancies. Antitumor targeted molecular therapeutic drugs mainly include gefitinib, erlotinib, and cetuximab targeting EGFR, trastuzumab and pertuzumab targeting HER2, and afatinib and lapatinib targeting both EGFR and HER2. Lapatinib, a tyrosine kinase inhibitor (TKI), was approved based on improvements in progression-free survival (PFS) and alleviation of side effects. In a survival analysis of HER2-positive BC, overall survival (OS) was significantly

| Table 2. miRNAs and IncRNAs Involved in the PD-1/PD-L1 Immune Checkpoint |
|-----------------------------|----------------|------------------|
| Cancer Type                | ncRNA          | Expression | Regulation of PD-L1 (PD-1) | Reference |
| Bone marrow stromal niche  | miR-25-93-106b | ↑           | ↓                          | 42        |
| Colorectal cancer          | miR-138-5p     | ↓           | ↓                          | 43        |
| Laryngeal cancer           | miR-217        | ↓           | ↓                          | 44        |
| Lung adenocarcinoma        | miR-200        | ↓           | ↑                          | 45        |
| Ovarian cancer             | miR-424(322)   | ↓           | ↓                          | 46        |
| Oral squamous cell carcinoma | miR-197     | ↑           | ↓                          | 47        |
| Melanoma                   | miR-17-5p      | ↓           | ↑                          | 48        |
| Glioma                     | miR-138        | ↓           | ↓ (PD-1)                   | 49        |
| Nasopharyngeal carcinoma   | AFAP1-AS1      | ↑           | ↑ (PD-1)                   | 50        |

Additional expression of miRNAs in PD-1/PD-L1 immune checkpoint blockade and various cellular processes in cancer has recently gained attention (Table 2). miR-25-93-106b, miR-138-5p, miR-217, and miR-200 were found to suppress the expression of PD-L1, thus rescuing decreased tumor immunity and inhibiting multiple metastatic traits, such as cell migration, invasion, proliferation, apoptosis, and the epithelial-mesenchymal transition (EMT), as well as angiogenesis.

Additionally, miRNAs can enhance curative effects and restore immune functions indirectly through interaction with PD-L1. miR-424(322) regulates the PD-1/PD-L1 and CD80/CTLA-4 pathways in ovarian cancer by decreasing PD-L1 and CD80 expression, restoration of which enhances the drug sensitivity of ovarian cancer.
better in patients who were treated with the neoadjuvant lapatinib followed by the adjuvant trastuzumab than in those treated with trastuzumab alone (hazard ratio [HR], 0.32; p = 0.019).59 The addition of trastuzumab, a humanized monoclonal antibody, to carboplatin-paclitaxel was well tolerated by HER2-positive patients and increased PFS (12.6 months [experimental] versus 8.0 months [control], p = 0.005).55

However, numerous cases of acquired resistance reveal the limitation of targeted therapy. For example, acquired resistance to TKIs inevitably occurs in almost all NSCLC patients, and the major mechanisms include T790M, MET, and HER2/3 mutations as well as IGFR1 and PI3K activation.60,61 Additionally, emerging evidence highlights the master regulatory roles of miRNAs and IncRNAs in the acquisition of resistance, and it suggests potential targets for development in targeted therapy (Table 3).60,62–66

| Drug          | Cancer Type | Regulation of Resistance | ncRNA     | Target                          | Reference |
|---------------|-------------|--------------------------|-----------|---------------------------------|-----------|
| Lapatinib     | HER2(+) BC  | inhibition               | miR-630   | IGF1R                           | 111       |
|               | triple-negative BC | inhibition        | miR-7     | Raf-1/MAPK/IL-6                  | 78        |
|               | HER2(-) BC  | inhibition               | miR-16    | CCNJ, FUBP1                      | 112       |
|               |             | promotion                | miR-21    | IL-6/STAT3/ NFκB, PTEN/PI3K     | 117       |
|               |             | inhibition               | miR-22    | PTEN                            | 111       |
| Trastuzumab   | HER2(+) BC  | inhibition               | miR-21    | IGF1R                           | 114       |
|               | HER2(+) GC  | promotion                | miR-21    | PTEN                            | 111       |
|               | melanoma    | inhibition               | miR-21    | CAGE                            | 117       |
| Gefitinib     | NSCLC       | promotion                | miR-21    | PTEN, PDCD4, PI3K/Akt           | 77        |
|               |             | inhibition               | miR-630   | Akt/mTOR                        | 83        |
| Erlotinib     | NSCLC       | promotion                | miR-641   | NF1/ERK                         | 112       |
| Cetuximab     | CRC         | promotion                | miR-7     | EGFR/Sec                        | 75        |
|               | HCC         | inhibition               | miR-9     | eIF-5A-2                        | 75        |
| Pertuzumab    | OC          | inhibition               | miR-150   | Akt                             | 126       |

miR-21, miR-7, and IncRNA UCA1 Regulate Drug Resistance

miR-21, which promotes cell proliferation and invasion and is upregulated in many cancers, is one of the most widely investigated miRNAs.67–70 In HER2-positive BC, miR-21 was found to be inversely correlated with the expression of PTEN and PDCD4; by triggering an interleukin-6 (IL-6)/STAT3/nuclear factor κB (NF-κB)-mediated signaling loop and activating the PI3K pathway, it is also related to decreased trastuzumab sensitivity.71 Blocking the action of miR-21 with antisense oligonucleotides (ASOs) re-sensitized resistant cells to the therapeutic effects of trastuzumab.72 Similarly, miR-21 downregulates the expression of PTEN and PDCD4 and activates the PI3K/Akt pathway in gefitinib-resistant NSCLC cell lines, and inhibiting miR-21 with ASOs suppresses tumor growth in nude mice treated with gefitinib.73 Serving as a molecular sponge for miR-21, IncRNA GAS5 increases PTEN levels by competitively binding to miR-21 in a trastuzumab-resistant BC cell.
miR-7 is another well-investigated miRNA that has been identified as both a tumor suppressor and promoter in a number of malignancies, such as BC, hepatocellular carcinoma (HCC), CRC, NSCLC, glioma, and melanoma. miR-7 also plays an indispensable role in drug resistance. Reestablished miR-7 expression abolishes HER2Δ16, the oncogenic isoform of HER2, and it induces cell proliferation and migration while sensitizing HER2Δ16-expressing cells to trastuzumab therapy. The off-target activity of lapatinib in inducing EGFR expression in BC was unexpectedly found to enhance metastasis, and this resistance-related phenotype was attributed to miR-7 downregulation. Moreover, restoration of miR-7 expression inhibits Raf-1 signaling activation and EGFR expression, thereby restricting lapatinib-induced metastasis. By directly targeting EGFR and Raf-1, miR-7 also inhibits cell resistance to cetuximab in CRC.

Previous studies have demonstrated the role of dysregulated miRNA expression in drug resistance, but, to date, few studies have examined lncRNAs. Nonetheless, Zhu et al. found that the lncRNA UCA1 desensitized BC cells to trastuzumab by impeding miR-18a repression of Yes-associated protein 1 (YAP1). In another study, UCA1 knockdown restored gefitinib sensitivity in cells with acquired resistance and no T790M mutations, and it inhibited activation of the Akt/mTOR pathway and EMT (Table 3).

### miRNAs and lncRNAs Are Involved in the Effects of Sorafenib and Sunitinib

Sorafenib, the first systemic drug for patients with advanced HCC, inhibits the activity of multiple kinases, such as Raf kinase, VEGFR2, and platelet-derived growth factor receptor (PDGFR). This drug also increases the survival rate of renal cell carcinoma (RCC) patients. Regardless, poor primary response and acquired resistance remain the major obstacles for effective treatment with sorafenib. While assessing this urgent problem, researchers were able to identify the predictive and therapeutic functions of miRNAs and lncRNAs in sorafenib treatment (Table 4). By activating p53-dependent apoptosis, miR-27b was found to enhance the response to sorafenib in HCC and RCC, and the direct target of miR-27b was cyclin G1 (CCNG1), a negative regulator of p53.

### Table 4. miRNAs and lncRNAs Involved in Sorafenib and Sunitinib Resistance

| Drug     | Cancer Type | Regulation of Resistance | ncRNA   | Target                  | Reference |
|----------|-------------|--------------------------|---------|-------------------------|-----------|
| Sorafenib | HCC         | inhibition               | miR-27b | CCNG1                   | 83        |
|          |             |                          | let-7   | Bcl-xL, Mcl-1           | 84        |
|          |             |                          | miR-122 | ADAM10, SRF, IGF1R      | 85,86     |
|          |             |                          | miR-338-3p | HIF-1z            | 127       |
|          |             |                          | miR-425-3p | –                     | 32        |
|          |             |                          | miR-34a | Bcl-2, Mcl-1           | 129       |
|          |             |                          | miR-193b | Mcl-1                  | 129       |
|          |             |                          | Ad5-AIncRNA | miR-21, miR-153, miR-216a, miR-217, miR-494, miR-10a-5p | 10        |
|          |             | promotion                | miR-494 | PTEN, PI3K/Akt          | 85        |
|          |             |                          | miR-222 | PTEN, PI3K/Akt          | 90        |
|          |             |                          | miR-21  | PTEN, PI3K/Akt          | 90        |
|          |             |                          | miR-181a | RASSF1                 | 53        |
|          |             |                          | IncTUC338 | RASAL1                | 131       |
|          | RCC         | inhibition               | miR-27b | CCNG1                   | 83        |
|          |             |                          | miR-30a | Beclin-1                | 87        |
|          |             |                          | miR-200c | HO-1                   | 122       |
|          | promotion   |                          | IncRNA SRLR | NF-κB         | 133       |
|          |             |                          | IncRNA NEAT1 | miR-34a    | 134       |
|          | RCC         | inhibition               | IncRNA SARCC | AR/miR-143-3p | 94        |
|          |             | promotion               | miR-144-3p | ARID1A                | 94        |
|          |             |                          | IncRNA ARSR | miR-34, miR-449      | 91        |

HCC, hepatocellular carcinoma; RCC, renal cell carcinoma; SRF, serum response factor; ADAM10, a distinctintegrin and metalloprotease family 10; IGF1R, insulin growth factor receptor 1; Bcl-2, B cell lymphoma-2; Bcl-xL, B cell lymphoma-extra large; Mcl-1, myeloid cell leukemia-1; HIF-1α, hypoxia-inducible factor-1; HO-1, heme oxygenase-1; RASAL1, RAS GTPase-activation protein (RasGAP) 1; RASAL1, RAS GTPase-activation protein (RasGAP) gene; CCNG1, cyclin G1; ARID1A, AT-rich interactive domain 1A; AR, androgen receptor.
Another miRNA that potentiates sorafenib-induced apoptosis in HCC is let-7, which reduces expression of the antiapoptotic Bcl-2 protein Bcl-xL and Mcl-1. Another miRNA that potentiates sorafenib-induced apoptosis in HCC is let-7, which reduces expression of the antiapoptotic Bcl-2 protein Bcl-xL and Mcl-1.84 miR-122 appears to sensitize HCC cells to sorafenib by targeting distintegrin and metalloprotease family 10 (ADAM10), serum response factor (SRF), and IGF1R.85,86 Moreover, exosomes derived by adipose tissue-derived mesenchymal stem cells help to deliver miR-122 into HCC cells, further promoting the chemosensitivity of these cells.87 miR-494 and miR-21, which are both upregulated in HCC and reinforce sorafenib resistance, directly suppress the expression of PTEN but activate the PI3K/Akt-signaling pathway, thereby contributing to the promotion of proliferation, migration, and invasion.88,89

Although these potential antiresistance targets have been identified, it is a challenge to restore sensitivity by regulating only one miRNA, because it may sequentially activate other compensatory pathways. Accordingly, Tang et al.90 generated an artificial lncRNA expressed by an adenoviral vector (Ad5-AlncRNA), which simultaneously targets multiple miRNAs, including miR-21, miR-153, miR-216a, miR-217, miR-494, and miR-10a-5p. As mentioned above, these miRNAs participate in the mechanisms underlying sorafenib resistance, and, thus, targeting multiple miRNAs may be a promising strategy for overcoming such resistance.

Sunitinib is the mainstay of therapeutic options for advanced RCC patients. This drug is a multitarget receptor TKI that mainly inhibits VEGFR and PDGFR. However, 10%–20% of advanced RCC patients are inherently resistant to sunitinib therapy, and most of the remaining patients exhibit drug resistance and tumor progression after 6–15 months of therapy.91 In studies of sunitinib resistance in RCC, miR-144-3p and lncRNAs ARSR and SARCC were found to affect malignancy via different targets91–93 (Table 4).

miRNAs and lncRNAs Are Involved in the Effects of Imatinib and Vemurafenib

Little is known about the effect of ncRNAs on imatinib and vemurafenib resistance in solid tumors. Sensitivity of melanoma to the BRAF(V600E) inhibitor vemurafenib is positively regulated by miR-579-3p, miR-216b, and miR-7, and it is negatively regulated by miR-204-5p and miR-211-5p.94–96 Imatinib, a small-molecule inhibitor that targets several receptor tyrosine kinases, including KIT and PDGFR, is primarily applied in the treatment of chronic myelogenous leukemia (CML) and gastrointestinal stromal tumors (GISTs). One study on imatinib-resistant glioblastoma revealed that ectopic expression of miR-203 with miRNA mimics effectively sensitizes cells to chemotherapy by targeting SNAI2.97

In summary, this review compiles the available literature on the miRNAs and lncRNAs involved in targeted therapy that have certain...
and explicit targets and pathways (Figure 1). All relevant publications were retrieved from the PubMed database, with keywords such as miRNA, IncRNA, exosome, PD-1/PD-L1, immunotherapy, chemoresistance, targeted therapy, lapatinib, gefitinib, trastuzumab, sorafenib, HER2, EGFR, and similar terms.

Conclusions
miRNAs and IncRNAs, subcategories of ncRNAs, have primarily been investigated as biomarkers for predicting the initiation and development of cancer, but they have recently been discovered to be involved in the curative process of three clinically adopted therapies. These molecules enhance or suppress cancer cell responses to chemotherapy drugs and targeted drugs indirectly by modulating relevant pathways, and they also affect immune checkpoint blockade therapy directly by altering the expression of PD-1/PD-L1. Over-expressing miRNAs and IncRNAs by mimics and silencing these molecules by small interfering RNAs (siRNAs) verify their therapeutic capacity in suppressing aggressive cell phenotypes and alleviating drug resistance.

Furthermore, rapid advances in elucidating the roles of miRNAs and IncRNAs in anticancer therapies have revealed several opportunities and challenges to address in the future. One opportunity is cooperation with extracellular vesicles, especially exosomes. As mentioned above, exosome-mediated miR-503 reduced chemoresistance after it was transferred from endothelial cells to tumor cells.25 Studies have demonstrated the communication shuttle function of exosomes between cells and that exosome-associated ncRNAs fulfill important jobs in regulating gene expression in cancer.26 However, more work on the therapeutic value of exosome-associated ncRNAs in cancer is needed. Second, miRNA-miRNA and miRNA-IncRNA networks reveal the complexity of ncRNA-mediated mechanisms in anticancer therapies, providing a better understanding of the ncRNA-mediated drug response and creative research approaches.98 One outstanding problem is whether ectopic miRNAs and IncRNAs actually function in vivo, and more research utilizing convenient in vivo model systems are needed. Future studies will likely focus on ncRNA-based drug development and integrated clinical trials, which may lead to a cure for cancer. Additionally, the investigation of circular RNAs, another ncRNA research hotspot, is needed to improve our understanding of the ncRNA therapeutic network.

All relevant publications were retrieved from the PubMed database, with key words such as miRNA, IncRNA, exosome, PD-1/PD-L1, immunotherapy, chemoresistance, targeted therapy, lapatinib, gefitinib, trastuzumab, sorafenib, HER2, EGFR and similar terms.

AUTHOR CONTRIBUTIONS
M.X. designed the research and drafted the manuscript. L.M. and T.X. critically revised the manuscript. Y.P., Q.W., and Y.W. discussed and revised the manuscript. All authors read and approved the final manuscript.

CONFLICTS OF INTEREST
The authors have no conflicts of interest.

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