Molecular Therapy
Nucleic Acids
Review

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.[2,3]

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.[4] These molecules are identified as either carcinogenetic or carcinostatic; are associated with cell growth, proliferation, migration, invasion, and apoptosis; and can even alter immune functions.[5–10] 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 characteristics, differentially expressed miRNAs and lncRNAs can be employed to assess the pathogenesis of diseases, including non-small-cell lung cancer (NSCLC), gastric cancer (GC), colorectal cancer (CRC), and melanoma, as well as clinical prognosis.[11–16]

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.

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.[17]

Accumulating evidence shows that ncRNAs have an important role in cellular sensitivity to chemotherapy due to their specific regulatory features. The significance of miRNAs in anticancer chemotherapy has been demonstrated by multiple studies, and the associated mechanisms include regulation of different targets.[18] For example, miR-197, miR-130b, and lncRNA MALAT1 confer cisplatin resistance in NSCLC by targeting the signal transducer and activator of transcription 3 (STAT3) and Wnt/β-catenin pathways, and lncRNA TP53TG1 enhances cellular sensitivity through the miR-18a/PTEN axis.[19–22] In contrast, miR-125a-5p and lncRNA TUSC7 are able to reverse cisplatin resistance in esophageal squamous cell carcinoma (ESCC) by reducing the levels of STAT3 and miR-224, respectively.[23,24] miR-503 and miR-623 inhibit resistance to different drugs by regulating cyclin D1-3 (CCND1-3),[25,26] and targeting

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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/β-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	99
	miR-29c	inhibition	USP22	GEM	100
	miR-374b-5p	inhibition	Bcl-2	GEM	27
BC	miR-503	inhibition	CCND2, CCND3	EPI, PTX	25
	lncRNA LINP1	promotion	–	ADM, 5-FU	101
	miR-17	promotion	DEDD	DDP, 5-FU	102
GC	miR-218	inhibition	mTOR inhibitor	DDP	103
	miR-623	inhibition	CCND1	5-FU	26
CRC	miR-191	promotion	Wnt/β-catenin pathway	5-FU	104
	miR-519b-3p	inhibition	ARID4B mRNA	CAPE/OXA/5-FU	105
	miR-15	inhibition	NF-κB, Bcl-2	5-FU/OXA	28
	lncRNA PVT1	promotion	MDR1, MRP1, Bcl-2, Bax, cleaved caspase-3	DDP	31
	lncRNA MALAT1	promotion	EZH2	OXA	106
	lncRNA UCA1	promotion	miR-204-5p	5-FU	32
Glioma	lncRNA H19	promotion	Wnt/β-catenin pathway	TMZ	29
	lncRNA MALAT1	promotion	MiR-101	TMZ	30
	lncRNA DANCR	promotion	AXL/PI3K/Akt/ NF-κB	DDP	107
ESCC	miR-125a-5p	inhibition	STAT3	DDP	23
	lncRNA TUSC7	inhibition	MiR-224	DDP, 5-FU, and ADM/PTX	24
HCC	miR-16	inhibition	NF-κB	PTX	108
OC	miR-630	promotion	APAF-1	PTX	109
	miR-142-3p	inhibition	Sirtuin 1	DDP	110

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.

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 colleagues[30] 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 pro-apoptotic 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.[25] In addition, exosome-transferred miR-21 derived from M2-polarized macrophages

Table 2. miRNAs and lncRNAs 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	↓	↑	50
Glioma	miR-138	↓	↓ (PD-1)	48
Nasopharyngeal carcinoma	AFAP1-AS1	↑	↑ (PD-1)	49

confer cisplatin resistance in GC, suggesting a new therapeutic strategy for GC patients[34–36] (Table 1).

miRNAs and lncRNAs Participate in Immunotherapy

The breakthrough of immune checkpoint therapy, which involves the use of monoclonal antibodies against the receptor cytotoxic T lymphocyte antigen-4 (CTLA-4), programmed cell death protein 1 (PD-1), and PD-1 ligand (PD-L1), represents a turning point in cancer immunotherapy.[37] Notably, therapeutic success in clinical trials has been achieved with pembrolizumab, which targets the PD-1/PD-L1 pathway.[38,39]

PD-L1 is a cell surface glycoprotein that maintains immunologic homeostasis; but, PD-L1 is overexpressed on tumor cells as well as immune cells in many cancers. Blockade of the PD-1/PD-L1 pathway reverses immune escape in tumors, and it provides strategies for cancer immunotherapy. As a biomarker of a response to immune checkpoint blockade, PD-L1 expression on tumor cells has been assessed in the prediction of therapeutic efficacy and chemoresistance.[40]

Altered expression of miRNAs in PD-1/PD-L1 immune checkpoint blockage and various cellular processes in cancer has recently gained attention (Table 2).[41] 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.[42–45]

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 cells through PD-1/PD-L1 checkpoint blockage.[46] 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 anticancer immune responses by inhibiting PD-L1 expression, thus weakening the aggressive features of OSCC.[47] In addition to PD-L1, PD-1 is also an effective target for PD-1/PD-L1 pathway blockade. miR-138 exhibits antiglioma efficacy by decreasing PD-1 expression, resulting in substantial tumor regression and a 43% increase in median survival time.[48] 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.[49]

Most miRNAs play a positive role in anticancer immunology 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.[50]

Other immunologic mechanisms together with immune checkpoint blockade involve the anticancer functions of ncRNAs. For example, it has been demonstrated that ncRNAs 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, ncRNAs also present the best targets for immunotherapy[51] (Table 2).

miRNAs and lncRNAs 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).[52–54] In addition, the use of miRNAs and lncRNAs in targeted molecular therapy primarily involves the alteration of cellular sensitivity to drugs. Below we summarize the modulatory effects of miRNAs and lncRNAs 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;[52] they also occur in other types of malignancies.[55,56] Anticancer targeted molecular therapeutic drugs mainly include gefitinib, erlotinib, and cetuximab targeting EGFR;[57] trastuzumab and pertuzumab targeting HER2;[58] and afatinib and lapatinib targeting both EGFR and HER2.[56,57] Lapatinib, a tyrosine kinase inhibitor (TKI), was approved based on improvements in progression-free survival (PFS)[58] and alleviation of side effects.[56] In a survival analysis of HER2-positive BC, overall survival (OS) was significantly

Table 3. miRNAs and lncRNAs Involved in the Resistance to Lapatinib, Gefitinib, Erlotinib, Pertuzumab, Cetuximab, and Trastuzumab

Drug	Cancer Type	Regulation of Resistance	ncRNA	Target	Reference
Lapatinib	HER2(+) BC	inhibition	miR-630	IGF1R	111
	triple-negative BC		miR-7	Raf-1/MAPK/IL-6	77
	HER2(-) BC			EGFR	78
Lapatinib + trastuzumab	HER2(+) BC+GC	inhibition	miR-16	CCNJ, FUBP1	112
Trastuzumab	HER2(+) BC	promotion	miR-7	EGFR/Src	76
			miR-21	IL-6/STAT3/NF-κB, PTEN/PI3K	71
				PTEN	72
			miR-221	PTEN	113
			lncRNA UCA1	miR-18a/YAP1	80
		inhibition	miR-375	IGF1R	114
			miR-194	TLN2	115
			miR-30b	CCNE2	116
			lncRNA GAS5	miR-21/PTEN	74
	HER2(+) GC	promotion	miR-125b	–	117
Trastuzumab + gefitinib	melanoma	inhibition	miR-217	CAGE	118
Gefitinib	NSCLC	promotion	miR-125b	–	119
			miR-21	PTEN, PDCD4, PI3K/Akt	73
			lncRNA UCA1	Akt/mTOR	63
			miR-630	YAP1/ERK	120
Erlotinib	NSCLC	promotion	miR-641	NF1/ERK	121
Cetuximab	CRC	promotion	lncRNA MIR100HG, miR-100, miR-125b	Wnt/β-catenin pathway	122
			miR-199a-5p, miR-375	PHLPP1	123
		inhibition	miR-7	EGFR	79
	HCC	inhibition	let-7a	STAT3	124
			miR-9	eIF-5A-2	125
Pertuzumab	OC	inhibition	miR-150	Akt	126

BC, breast cancer; GC, gastric cancer; NSCLC, non-small-cell lung cancer; CRC, colorectal cancer; OC, ovarian cancer; HCC, hepatocellular carcinoma; IGF1R, insulin growth factor receptor 1; MAPK, mitogen-activated protein kinase; IL-6, interleukin-6; CCNJ, cyclin J; FUBP1, far upstream element-binding protein 1; STAT3, signal transducer and activator of transcription 3; PI3K, phosphatidylinositol 3-kinase; PTEN, phosphatase and tensin homolog deleted on chromosome 10; TLN2, cytoskeleton protein talin2; CCNE2, cyclin E2; YAP1, Yes-associated protein 1; CAGE, cancer-associated gene; PDCD4, programmed cell death protein 4; NF1, neurofibromatosis 1; PHLPP1, PH domain and leucine-rich repeat protein phosphatase 1; eIF-5A-2, eukaryotic translation initiation factor 5A2.

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 IGF1R and PI3K activation.[60,61] Additionally, emerging evidence highlights the master regulatory roles of miRNAs and lncRNAs in the acquisition of resistance, and it suggests potential targets for development in targeted therapy (Table 3).[60,62–66]

miR-21, miR-7, and lncRNA 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, lncRNA GAS5 increases PTEN levels by competitively binding to miR-21 in a trastuzumab-resistant BC cell

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-1α	127
			miR-425-3p	–	82
			miR-34a	Bcl-2, Mcl-1	128
			miR-193b	Mcl-1	129
			Ad5-AlncRNA	miR-21, miR-153, miR-216a, miR-217, miR-494, miR-10a-5p	90
		promotion	miR-494	PTEN, PI3K/Akt	89
			miR-222	PI3K/Akt	130
			miR-21	PTEN, PI3K/Akt	88
			miR-181a	RASSF1	53
			lncTUC338	RASAL1	131
	RCC	inhibition	miR-27b	CCNG1	83
			miR-30a	Beclin-1	81
			miR-200c	HO-1	132
		promotion	lncRNA SRLR	NF-κB	133
			lncRNA NEAT1	miR-34a	134
Sunitinib	RCC	inhibition	lncRNA SARCC	AR/miR-143-3p	93
		promotion	miR-144-3p	ARID1A	92
			lncRNA ARSR	miR-34, miR-449	91

HCC, hepatocellular carcinoma; RCC, renal cell carcinoma; SRF, serum response factor; ADAM10, a distintegrin 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-activating protein (RasGAP) 1; RASAL1, RAS GTPase-activation protein (RasGAP) gene; CCNG1, cyclin G1; ARID1A, AT-rich interactive domain 1A; AR, androgen receptor.

line (SKBR-3/Tr cell), thus inhibiting cell proliferation. In addition, GAS5 expression can be elevated by mTOR activation in lapatinib-treated SKBR-3/Tr cells, identifying GAS5 as candidate drug target for trastuzumab-resistant BC.[74]

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.[75] 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.[76] 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.[77,78] Moreover, restoration of miR-7 expression inhibits Raf-1 signaling activation and EGFR expression, thereby restricting lapatinib-induced metastasis.[77] By directly targeting EGFR and Raf-1, miR-7 also inhibits cell resistance to cetuximab in CRC.[79]

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.[80] 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[63] (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).[53] 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.[81] While assessing this urgent problem, researchers were able to identify the predictive and therapeutic functions of miRNAs and lncRNAs in sorafenib treatment (Table 4).[82] 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.[83]

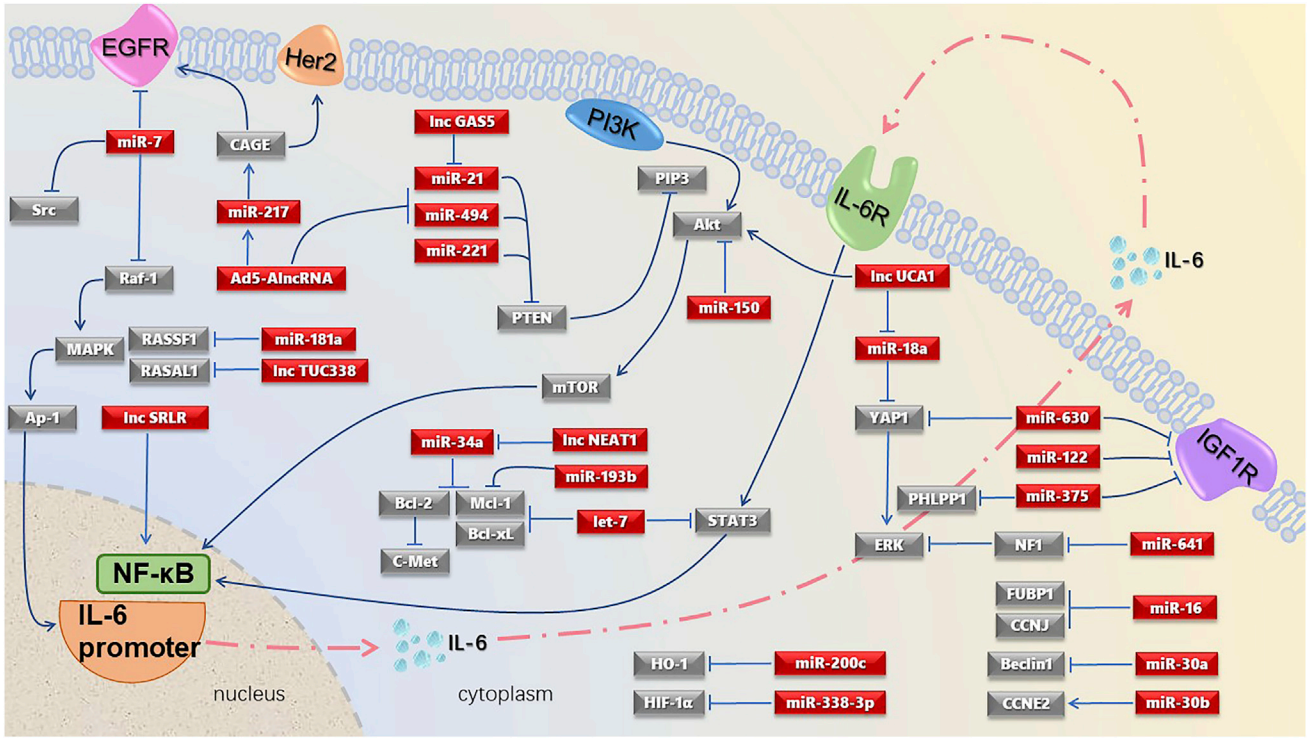

Figure 1. miRNAs and lncRNAs in Targeted Therapy with Explicit Targets and Pathways

These pathways mainly comprise the Raf-1/MAPK/IL-6 axis, IL-6/STAT3/NF-κB axis, and PI3K/Akt/mTOR axis, and they center on targets of PTEN, IGF1R, and ERK. Among the ncRNAs involved, miR-7, miR-21, miR-630, and lncRNA UCA1 play important roles.

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 targets[91–93] (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.[54,94–96] 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, lncRNA, exosome, PD-1/PD-L1, immunotherapy, chemoresistance, targeted therapy, lapatinib, gefitinib, trastuzumab, sorafenib, HER2, EGFR, and similar terms.

Conclusions

miRNAs and lncRNAs, 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 blockage therapy directly by altering the expression of PD-1/PD-L1. Overexpressing miRNAs and lncRNAs 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 lncRNAs 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.[3] However, more work on the therapeutic value of exosome-associated ncRNAs in cancer is needed. Second, miRNA-miRNA and miRNA-lncRNA 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 lncRNAs 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, lncRNA, 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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