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A review of the complex interplay between chemoresistance and lncRNAs in lung cancer

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Abstract
Lung Cancer (LC) is characterized by chemoresistance, which poses a significant clinical challenge and results in a poor prognosis for patients. Long non-coding RNAs (lncRNAs) have recently gained recognition as crucial mediators of chemoresistance in LC. Through the regulation of key cellular processes, these molecules play important roles in the progression of LC and response to therapy. The mechanisms by which lncRNAs affect chemoresistance include the modulation of gene expression, chromatin structure, microRNA interactions, and signaling pathways. Exosomes have emerged as key mediators of lncRNA-driven chemoresistance, facilitating the transfer of resistance-associated lncRNAs between cancer cells and contributing to tumor development. Consequently, exosomal lncRNAs may serve as biomarkers and therapeutic targets for the treatment of LC. Therapeutic strategies targeting lncRNAs offer novel approaches to circumvent chemoresistance. Different approaches, including RNA interference (RNAi) and antisense oligonucleotides (ASOs), are available to degrade lncRNAs or alter their function. ASO-based therapies are effective at reducing lncRNA expression levels, increasing chemotherapy sensitivity, and improving clinical outcomes. The use of these strategies can facilitate the development of targeted interventions designed to disrupt lncRNA-mediated mechanisms of chemoresistance. An important aspect of this review is the discussion of the complex relationship between lncRNAs and drug resistance in LC, particularly through exosomal pathways, and the development of innovative therapeutic strategies to enhance drug efficacy by targeting lncRNAs. The development of new pathways and interventions for treating LC holds promise in overcoming this resistance.

Keywords lncRNA, NSCLC, Exosome, RNAi, ASO

Background

Lung cancer (LC) is one of the most common cancers worldwide, with 1,825,000 new cases reported in 2012 alone [1]. A high incidence rate has been observed in North America, whereas a low incidence rate has been observed in Central Africa. These differences can be attributed to different risk factors and the availability of different diagnostic methods [2]. Approximately 47,235 newly diagnosed cancer cases were recorded in the UK in 2016, accounting for 13% of all cancer cases in the country. The incidence rates for males and females were generally the same, whereas the incidence rate was higher for females in Northern Ireland [3]. Considerable attention has been paid to the prevention, management, and treatment of this cancer, because it poses a threat to millions of people worldwide.

Based on histology, LC can be divided into two main categories: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) [4]. It is estimated that 80% of all LC are NSCLC (Heighway and Betticher, 2004). In addition to being more aggressive than SCLC, NSCLC presents a challenging treatment issue for clinicians,

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because the prognosis of patients with this disease is poor [5]. A major challenge for doctors is the early diagnosis of LC, as most cases are diagnosed at an advanced stage. It is more difficult to treat LC in later stages, and there is a high potential for therapy resistance [6–8].

LC treatment is challenging due to chemotherapy resistance. Upon treatment failure and poor patient outcomes, cancer cells become resistant to cytotoxic chemotherapy drugs. Molecular alterations that cause drug resistance in cancer cells are well established [9]. Several factors contribute to the mechanisms underlying chemoresistance. By altering the molecular structure, drugs are effluxed more effectively, they are inactivated more rapidly, they are scavenged by enzymes, DNA is repaired, targets are modified, and apoptosis is evaded.

Due to the tendency for LC to be detected at a late stage, it is associated with increased drug sensitivity and a long natural history of tumors that are typically highly heterogeneous at the molecular level. As a result, there is an increased risk of developing acquired mutations that are resistant to chemotherapy.

Overcoming chemoresistance in LC patients can improve outcomes. Several strategies are currently being investigated, including the use of exosome inhibitors, targeting specific resistance mechanisms, combining therapies, and exploiting the vulnerabilities of chemotherapy-resistant cancer cells.

Main text

lncRNAs and chemoresistance in lung cancer

LncRNA transcripts of more than 200 nucleotides that are not translated into proteins. It is widely acknowledged that Chemoresistance and cancer biology are both affected by long non-coding RNAs (lncRNAs). They also play key roles in the pathogenesis and progression of LC. Several mechanisms are involved in these effects, such as epigenetic regulation, which affects cell proliferation and differentiation [10, 11]. Abnormally expressed lncRNAs are recognized as significant contributors to the development of LC and they offer promise as diagnostic, therapeutic, and prognostic biomarkers. Over the past few years, researchers have identified and extensively studied many lncRNAs in LC [12].

Mechanisms of lncRNA-mediated chemoresistance

Despite the development of therapeutic strategies for LC, resistance to therapy is inevitable. Increasingly, LC treatments face the challenge of chemoresistance, and genetic changes appear contribute significantly to this process. Several mechanisms have been identified by which lncRNAs regulate chemoresistance in cancer cells. Some broad categories of mechanisms are discussed in the following sections (Fig. 1).

Direct impact of lncRNA on gene expression

An important mechanism by which lncRNAs influence drug resistance is through their ability to modulate the expression of related genes. Based on their subcellular localization, lncRNAs directly affect gene expression. lncRNAs engage in chromatin modification by binding to chromatin regulatory proteins, directly influencing gene regulation, altering the splicing and stability of mRNAs, and indirectly participating in transcriptional and post-transcriptional regulatory mechanisms by interacting with other RNAs and proteins [13–15]. The activities of lncRNAs, such as metastasis-associated lung adenocarcinoma transcript 1 (*MALAT1*), maternally expressed 3 (*MEG3*), and *H19*, play important roles in the regulation of the cell cycle, particularly through their effects on key proteins, such as p21 and p53 [16–18]. Alternatively, lncRNAs, such as *H19*, pituitary tumor-transforming (*PINT*), lincRNA-p21, and PPARα-binding non-coding RNA in diabetes (*PANDA*), are upregulated by p53, showing the complex interaction between lncRNAs and major regulatory pathways [18–22].

HOX transcript antisense RNA (*HOTAIR*) illustrates how lncRNAs function as both enhancers and inhibitors of gene expression, demonstrating the dual roles of lncRNAs in gene regulation. By interacting with chromatin-modifying complexes, *HOTAIR* alters the chromatin structure, which in turn affects gene transcription. Specifically, *HOTAIR* recruits polycomb repressive complex 2 (PRC2) and LSD1/CoREST/REST complexes to target genomic locations [23]. By modifying histones, including methylation and demethylation, these complexes facilitate chromatin condensation and suppress the expression of certain target genes, while activating others associated with resistance mechanisms.

In addition to modulating chromatin states, *HOTAIR* also influences the binding affinity of transcription factors to DNA, which controls the transcription of several genes essential for drug resistance, including those that inhibit apoptosis and drug efflux and support cell survival [24]. The regulatory capabilities of *HOTAIR* in cancer, particularly those related to cellular survival and drug metabolism, contribute to a resistant phenotype, while its expression in breast and liver cancers is affects clinical outcomes and induces resistance to chemotherapy [25]. *HOTAIR* plays an important role in the orchestration of complex epigenetic programs that may serve as targets for therapeutic approaches aimed at overcoming cancer-related resistance.

lncRNAs modulate the activity of RNA-binding proteins

Another mechanism by which lncRNAs regulate chemoresistance is by modulating the activity of RNA-binding proteins (RBPs), which are essential for mRNA stability, translation, and splicing, thus influencing the expression

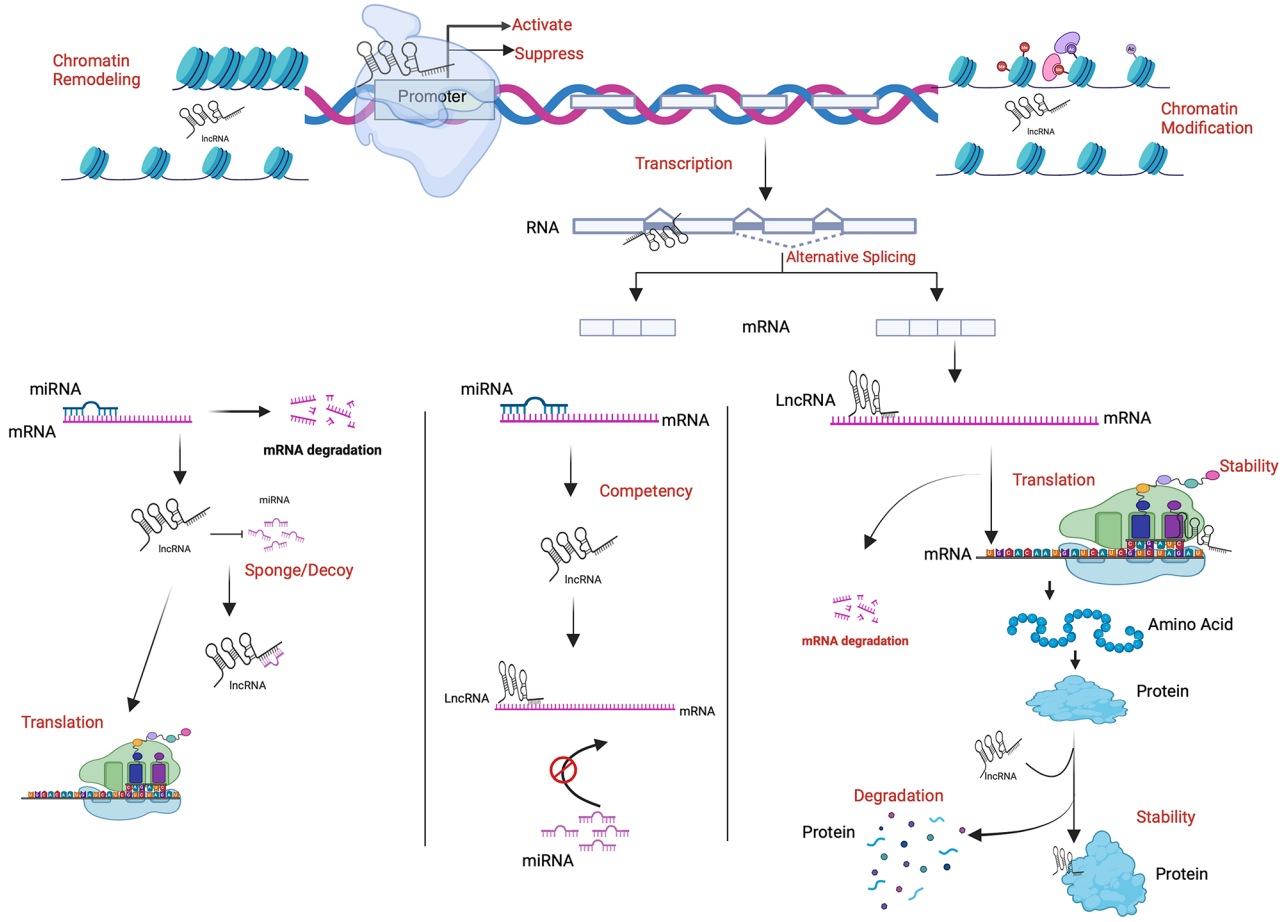

Fig. 1 Schematic illustration of the mechanisms by which lncRNAs affect chemoresistance. This figure was designed with BioRender.com

of proteins related to drug resistance. In cellular systems, lncRNAs and RBPs play key roles in regulating gene expression. The interaction between these two genes is key to the post-transcriptional regulation of mRNA and directly affects the synthesis of cancer-relevant proteins by regulating mRNA stability [26]. Researchers have demonstrated that RBPs modulate mRNA stability via post-transcriptional mechanisms, which are crucial for the initiation and progression of malignant tumors and their resistance to treatment [27, 28]. It is important to note that, although RBPs typically bind to mRNAs, they can also interact with lncRNAs. Both lncRNAs and RBPs exhibit abnormal expression patterns in tumors, which may alter tumor behavior and responses to treatment [29, 30]. Recent studies have shown that lncRNAs regulate mRNA stability by interacting with RBPs, which significantly contributes to cancer progression and drug resistance [31–33].

lncRNAs are significant regulators of post-translational modifications of RBPs. PLK1 is phosphorylated and activated by anaplastic lymphoma kinase (ALK) 5' UTR pseudogene –associated lncRNA (*APAL*), which is vital for the survival of NSCLC cells. One study highlighted the crucial role of lncRNAs in cancer cell survival and identified *APAL* as a potential therapeutic target for a variety of cancers. They found that *APAL* knockdown caused mitotic catastrophe and substantial apoptosis in human lungs. In contrast, *APAL* overexpression accelerated cell cycle progression, enhanced proliferation, and inhibited the induction of apoptosis by chemotherapy. Based on the results of mechanistic studies, it appears that *APAL* facilitates the interaction between PLK1 and Aurora A, which in turn enhances the ability of Aurora A to phosphorylate PLK1. In vivo experiments have shown that targeting *APAL* inhibits LC xenografts [34].

lncRNAs can cause the intracellular localization of RBPs. For example, the lncRNA *AC020978* interacts with *PKM2* and promotes its translocation from the nucleus to the cytoplasm, resulting in enhanced proliferation and glycolytic metabolism in NSCLC [35]. According to the findings of the that study, *AC020978* was significantly upregulated in NSCLC and its upregulation was associated with advanced TNM stage and poor clinical outcomes, indicating that it can serve as an independent prognostic indicator. In NSCLC, *AC020978* confers an aggressive phenotype and poor prognosis. Thus, it may

be beneficial to target AC020978 in the treatment of patients with NSCLC [35].

lncRNAs interact with microRNAs

In addition to other mechanisms underlying the regulation of chemoresistance by lncRNAs, lncRNAs can function as molecular sponges for microRNAs (miRNAs), thus inhibiting their activity. The ability of lncRNAs to sequester miRNAs prevents them from repressing their target mRNAs, including genes associated with survival and resistance to chemotherapy. As competing endogenous RNAs (ceRNAs), lncRNAs can indirectly modulate mRNA expression via a sponge mechanism [36]. It has been shown that lncRNA-mediated sponge interactions and their protein-coding targets can be involved in various malignancies, including gastric cancer [37], glioblastoma multiforme [38], pancreatic cancer [39], ovarian cancer [40], and breast cancer [41].

As a prominent miRNA sponge, the parentally expressed lncRNA *H19* indirectly regulates the expression of downstream target genes, thus facilitating cancer progression in a variety of tumor types. Within a single cancer type, *H19* exhibits versatility by sponging various miRNAs to mediate different regulatory outcomes [39]. Due to its highly conserved secondary structure, *H19* can bind to miRNAs and proteins, allowing it to act as a ceRNA. Furthermore, *H19* can recruit and bind to the enhancer of zeste homolog 2 (*EZH2*) or function through its derivative *miRNA-775* to inhibit the expression of target genes [42]. Recent studies have recently highlighted the role of H19 as a ceRNA that indirectly regulates downstream mRNAs that play critical roles in promoting or inhibiting tumorigenesis. According to one study [43], *H19* regulates cisplatin resistance in human lung adenocarcinoma cells.

Based on a recent study, lncRNA small nucleolar RNA host gene 14 (SNHG14) is upregulated in NSCLC cells and is responsible for resistance to chemotherapy treatments involving cisplatin. Upon silencing *SNHG14*, NSCLC cells were found to be significantly more sensitive to cisplatin. By decreasing *miRNA-133a* expression levels, *SNHG14* promotes the expression of the homeobox protein Hox-B13 (HOXB13) [44]. NSCLC cells are sensitized to cisplatin when doublecortin-like kinase 1 (DCLK1) is downregulated by *miRNA-330-5p*. *SNHG1* downregulates *miRNA-330-5p* expression and upregulates DCLK1 to exert tumor-suppressive activity Accordingly, silencing *SNHG1* reverses the resistance of NSCLC cells to cisplatin. There is also evidence that the lncRNA X-inactive specific transcript (*XIST*) interacts with *miRNA-101-3p* in LC [45]. Overexpression of *XIST* in lung tumors promotes cisplatin resistance by glucose uptake, acidification rates, and lactate production, and by inducing glycolysis enhances the growth of lung tumors. Through its role as a ceRNA, XIST inhibits the expression of miRNA-101-3p and contributes to cisplatin resistance [45]. Restoration of *miRNA-101-3p* expression can abrogate the tumor-promoting function of *XIST* in LC and increase the sensitivity of LC to cisplatin. In addition to *miRNA-101-3p*, *XIST* also regulates the response of NSCLC cells to chemotherapy by regulating *miRNA-520*. Through its ability to sponge *miRNA-520*, *XIST* increase cisplatin resistance and inhibit apoptosis by modulating Bcl-2-associated X (*BAX*) expression and the p53 pathway [46].

lncRNAs regulate biological processes

Additionally, lncRNAs have been increasingly observed as pivotal regulators of various biological processes, including cell survival, apoptosis, and drug metabolism. A growing body of evidence supports the contribution of lncRNAs, such as *XIST*, to the progression and metastasis of cancer. *XIST* is dysregulated in various tumor types, including NSCLC. According to in vitro studies, knockdown of *XIST* inhibits the proliferation of NSCLC cells and enhances their sensitivity to cisplatin (DDP) through apoptotic and pyroptotic pathways [47]. The oncogenic properties of *XIST* and its ability to facilitate DDP resistance have been attributed largely to its interaction with the TGF-β effector protein SMAD2. This interaction prevents SMAD2 from translocating to the nucleus, thereby inhibiting *p53* and *NLRP3*, two key transcription factors that regulate the apoptosis and pyroptosis processes, respectively. Based on experiments using DDP-resistant NSCLC cell lines and mouse xenograft models, it can be concluded that *XIST* is oncogenic and inhibits programmed cell death, thereby increasing DDP chemoresistance [47].

Growth arrest-specific transcript 5 (*GAS5*) is an lncRNA that promotes apoptosis of cancer cells. This primarily affects the sensitivity of the LC to chemotherapy. *GAS5* promotes cisplatin sensitivity in LC by inhibiting autophagy [48]. It also promotes gefitinib-induced LC cell death by inhibiting insulin-like growth factor 1 receptor (IGF-1R) [49]. Furthermore, maternally expressed 3 (MEG3) increases the sensitivity of LC cells to cisplatin by increasing p53 and β-catenin levels and cell survival [50]. In LC, experiments using nuclear enhanced abundant transcript 1 (NEAT1) revealed that the interaction between NEAT1 and copper transporter 1 (CTR1) facilitated the internalization of cDDP (platinum-based chemotherapies, such as cisplatin) in tumor cells, thereby increasing cisplatin sensitivity [51].

lncRNAs modulate signaling pathways

One way that lncRNAs exert their regulatory effects is by modulating critical signaling pathways that contribute to the development of chemoresistance. The relationship

between lncRNAs and cancer regulatory pathways has been studied previously, but few comprehensive studies have been conducted [52]. Several malignant diseases, such as breast cancer [53], prostate cancer [54], gastric cancer [55], and pancreatic cancer [56] are constitutively activated via the PI3K/Akt/FOXO and NF-B pathways [56].

For example, the lncRNA *Linc00152* has been shown to promote gastric cancer growth by activating the EGFR-dependent PI3K/Akt pathway [57]. Similarly, the lncRNA *BC087858* enhances LC invasion and drug resistance to epidermal growth factor receptor (EGFR) inhibitors by activating the PI3K/Akt pathway [58]. Through the same signaling cascade, the lncRNA *MALAT1* has been implicated in cholangiocarcinoma progression [59].

A positive feedback loop between the lncRNA plasmacytoma variant translocation 1 (*PVT1*) and Wnt/β-catenin signaling has been documented in the context of gemcitabine resistance in pancreatic cancer. In addition to providing insights into the mechanisms by which lncRNAs regulate autophagy, this study demonstrated how lncRNAs interact with autophagy-related proteins. Such cooperation between lncRNAs, autophagy, and Wnt/β-catenin signaling pathways may mitigate the effects of chemotherapeutic stress [60].

During the past few years, researchers have begun to examine the effects of natural compounds on lncRNAs and how they interact with NF-κB signaling pathways. In addition, silencing of the lncRNA nuclear factor I/A-like protein (*NKILA*) negates the anticancer effects of baicalein, indicating that *NKILA* plays a critical role in mediating these effects. As well, the NF-κB nuclear translocation inhibitor JSH-23 was found to diminish the effects of *NKILA*, thereby establishing a connection between the actions of baicalein, lncRNA *NKILA*, and NF-κB signaling pathways [61].

There is evidence that the downregulation of *HOTAIR* promotes the sensitivity of cells to anticancer drugs, resulting in the suppression of cell viability, arrest of the cell cycle, and the prevention of tumor development [62]. There is also evidence that the lncRNA *AC006050.3-003* plays a significant role in the development of chemoresistance [63]. In addition, *AK126698* has been found to induce cisplatin resistance in LC cells by targeting the Wnt pathway [64]. Urothelial cancer-associated 1 (UCA1)-induced cancer cells acquire resistance to epidermal growth factor receptor tyrosine kinase inhibitors [65].

lncRNAs are currently under investigation for their involvement in chemoresistance in LC. Several lncRNA targets have demonstrated the potential to address the challenge of chemoresistance (Table 1).

Several mechanisms appear to participate in the promotion of chemoresistance in LC, including the regulation of gene expression, activation of signaling pathways, and ceRNAs. Targeting these specific lncRNAs may improve treatment outcomes in patients with LC by overcoming drug resistance. Understanding the roles of lncRNAs in chemoresistance has advanced significantly; however, several challenges remain.

Exosomes: mediators of lncRNA-driven chemoresistance in lung cancer

Cells secrete nano-sized vesicles called exosomes, which play important roles in intercellular communication. Different molecules are transported by exosomes, including proteins; lipids; and nucleic acids, such as lncRNAs.

lncRNAs are transferred between cells by exosomes and they play an essential role in the development of chemoresistance in LC. Various cellular processes, including proliferation, differentiation, and survival, are regulated by lncRNAs. Moreover, lncRNAs contribute to resistance to chemotherapy and targeted therapies [66–68]. To promote chemoresistance, exosomes act as messengers that transfer lncRNAs from resistant tumor cells to sensitive cells.

Exosomal lncRNAs are involved in mediating drug resistance in LC. An example of an exosomal lncRNA is *RP11–838N2.4*, which can be packed into exosomes to decrease the sensitivity of cells to chemotherapy drugs [67]. Recent studies have identified two lncRNAs, maternally expressed gene 3 (*MEG3*) and ETS1-associated transcript 1 (*MLETA1*), high-metastasizing LC cells and their secreted exosomes are upregulated in these pathways. Moreover, lncRNA *MLETA1* plays a role in promoting LC metastasis and cell motility by regulating the expression of EGFR and insulin-like growth factor 1 receptor (IGF1R) and sponging *miR-186-5p* and *miR-497-5p.1* [66].

UFC1, also known as urothelial cancer-associated 1 (*UCA1*), is an exosomal lncRNA that inhibits apoptosis and cell cycle arrest and induces the proliferation and metastasis of lung tumor cells. EZH2 accumulates at the promoter of phosphatase and tensin homolog (*PTEN*) as a result of its of interaction with EZH2. A significant reduction in PTEN expression leads to NSCLC progression [69]. Moreover, investigated the relationship between exosomal lncRNA *H19* and erlotinib resistance in LC. *H19* can be loaded into exosomes and transferred to LC, which may reduce sensitivity to erlotinib. To achieve this goal, exosomal lncRNA *H19* inhibits *miRNA-615-3p* expression to enhance autophagy-related 7 (ATG7) expression in LC cells, thereby causing the cells to become resistant to erlotinib [70].

As research emphasizes the role that interactions between tumors and stromal cells play in immune evasion and cancer metastasis, attention is being paid to the tumor microenvironment [71]. Among the main

Table 1 lncRNAs targets with promise to overcome the obstacle of chemoresistance

LncRNA	Description	Mechanism of Resistance
PVT1	Pvt1 oncogene	• Induction of PVT1 by hypoxia promotes the resistance of LC to cisplatin through autophagy via the PVT1/*miR-140-3p*/ATG5 pathway [145]. • By regulating apoptosis and autophagy via the *miR-216b*/Beclin-1 pathway, PVT1 may act as a competitive endogenous RNA for *miR-216b*, thereby inhibiting the sensitivity of NSCLC to cisplatin [146].
HOTAIR	HOX transcript antisense RNA	• Through epithelial-mesenchymal transition (EMT), *HOTAIR* induces resistance to EGFR-tyrosine kinase inhibitors (TKIs) in NSCLC [147]. *In addition to regulating cell proliferation by activating apoptosis and EMT, HOTAIR expression has been associated with acquired and primary resistance to EGFR-TKIs* [147]. • The resistance to cisplatin is higher in patients with NSCLC with increased *HOTAIR* expression levels [148]. A high level of *HOTAIR* expression is associated with drug resistance in patients with NSCLC and is linked to an increase in KLF4 expression levels [148]. • It has been demonstrated that *HOTAIR* contributes to cisplatin resistance and the down-regulation of p21WAF1/CIP1 expression levels in human lung adenocarcinoma cells [88]. • *HOTAIR* contributes to gemcitabine resistance by inhibiting apoptosis [149].
H19	H19-imprinted maternally expressed transcript	• ***H19*increases resistance to cisplatin through modulation of the PI3K/AKT pathway** [150]. • Downregulation of the lncRNA *H19* promotes erlotinib resistance by upregulating PKM2 and phosphorylating AKT in EGFR-mutant LCs [151]. • Gefitinib resistance is associated with tumor-released lncRNA *H19*, which is packaged into exosomes and thereby contributes to NSCLC resistance [152].
ANRIL	**Antisense non-coding RNA in the INK4 locus**	• ***ANRIL*increases docetaxel resistance by promoting cell proliferation and survival** [153]. • ***ANRIL*expression levels are high in patients with gastric cancer who are resistant to cisplatin and 5-fluorouracil** [154]. • *ANRIL* knockdown inhibits cisplatin resistance by increasing *miR98* levels in LC cells [155].
MALAT1	Metastasis -associated lung adenocarcinoma transcript 1	• *MALAT1* participates in cisplatin resistance in LC by upregulating MRP1 and MDR1 via STAT3 activation [156]. • *MALAT1* promotes tumor growth in vivo and enhances gemcitabine resistance in NSCLC cells by targeting the *miR-27a-5p*/PBOV1 axis [157].
KCNQ1OT1	**KCNQ1 opposite strand/antisense transcript 1**	• Paclitaxel resistance is decreased when *KCNQ1OT1* is knocked down in lung adenocarcinomas [158]. • Apoptosis and the chemotherapy drug response are improved by inhibition of the lncRNA *KCNQ1OT1* in SCLC [159]. • In SCLC cells, *KCNQ1OT1* affects proliferation, apoptosis, and chemoresistance through its interaction with the JAK2/STAT3 axis [160].
SNHG12	**Small nucleolar RNA host gene 12**	• *SNHG12* contributes to multidrug resistance in NSCLC by promoting the activation of MAPK/Slug signaling by sponging *miR-181a* [161]. • lncRNA *SNHG12* increases the sensitivity of NSCLC cells to cisplatin by repressing *miR-525-5p* and promoting XIAP expression [162].
NEAT1	**Nuclear enriched abundant transcript 1**	• *NEAT1* mediates paclitaxel resistance in NSCLC by activating the Akt/mTOR signaling pathway [163]. • Shikonin suppresses *NEAT1* and Akt signaling during the treatment of paclitaxel-resistant NSCLC [164].
LANCL1-AS1	LANCL1 antisense RNA 1	• Overexpression of *LANCL1-AS1* results in an increase in the proliferation, migration, and invasion of cancer cells, and an increase in gemcitabine and vinorelbine sensitivity in NSCLC. Overexpression of *LANCL1-AS1* increases platinum resistance in NSCLC [165]. • The upregulation of *LANCL1-AS1* inhibits NSCLC progression by modulating the *miR-3680-3p*/GMFG axis [166].
MEG3	Maternally expressed gene 3	• Enhanced chemosensitivity caused by *MEG3* is linked to cell cycle arrest and increased apoptosis. Several transcription factors are involved in achieving this, including p53, β-catenin, and survivin, which is a target gene of the WNT/-catenin signaling pathway [50, 167, 168]. • A549/DDP LC cells with cisplatin resistance express significantly lower levels of *MEG3* than parental A549 cells [50]. • A decrease in autophagy levels is associated with an increase in the sensitivity of LC cells to vincristine chemotherapy when *MEG3* lncRNA expression levels are increased [169]. • The autophagy levels of resistant cells are higher than those of non-resistant cells; however, *MEG3* overexpression significantly reduces the expression of autophagy-related proteins in resistant cells [169].
PINT	Prostate-specific transcript	• By sponging *miR-543* and inducing PTEN expression, *PINT* can inhibit the proliferation and colony formation of NSCLC cells [170]. • There is a significant reduction in PINT levels in serum samples and tissues of NSCLC patients [171].

Table 1 (continued)

LncRNA	Description	Mechanism of Resistance
lincRNA-P21	Long intergenic noncoding RNA-p21	• *lincRNA-p21* expression levels are significantly low in NSCLC tumor tissues. This reduces the proliferation and migration of LC cells, while enhancing their apoptosis. *lincRNA-p21* and *miR-17-5p* expression levels are negatively correlated with *miR-17-5p* levels, thus counteracting the effects of *lincRNA-p21* overexpression [96]. *lincRNA-p21* inhibits the progression of NSCLC by directly targeting *miR-17-5p* [172]. • *lincRNA-P21* expression levels are positively correlated with poor patient outcomes. Studies in vitro have shown that inhibiting *lincRNA-P21* reduces the angiogenic capacity of cell supernatants and VEGF-A secretion. A high level of *lincRNA-P21* has been found to promote angiogenesis in tumors, suggesting that *lincRNA-P21* plays an angiogenesis-inducing role [173]. • A significant reduction in apoptosis was observed with an increase in *lincRNA-p21* levels, whereas a decrease in *lincRNA-p21* levels had the opposite effect. Expression levels of *PUMA*, a gene that has been identified as a direct target of *lincRNA-p21*, exhibit a negative correlation with *lincRNA-p21* expression levels in NSCLC specimens. A reduction in the anti-apoptotic effect of *lincRNA-p21* could be achieved by increasing the expression levels of *PUMA* [174].
XIST	X-inactive specific transcript	• Cisplatin-resistant A549 cells express a higher level of *XIST*. The lncRNA *XIST*/*miR-17*/autophagy pathway may provide a promising target for treating chemoresistant NSCLC. The lncRNA *XIST* is overexpressed in NSCLC tumor samples, and its knockdown results in a significant reduction in autophagy through the regulation of ATG7 [175]. • *XIST* knockdown inhibits the growth and improves the chemosensitivity of NSCLC cells by causing apoptosis and pyroptosis in vitro. Moreover, the oncogenic effects of XISTs and its role in promoting DDP chemoresistance resulted primarily from its interaction with the TGF-β effector SMAD2. The interaction inhibited the translocation of SMAD2 to the nucleus, preventing the transcription of p53 and NLRP3, which are key regulators of apoptosis and pyroptosis, respectively. Studies of mouse xenografts with DDP-resistant NSCLC cells confirmed that *XIST* has oncogenic properties and is capable of inhibiting programmed cell death, which contributes to DDP chemoresistance [47]. • *XIST* can be targeted as a competing endogenous RNA by *miR-101-3p*, which acts as a tumor suppressor, enhancing sensitivity to cisplatin. There is a correlation between *XIST* levels and glycolysis in LC cells, and glycolysis results in an increase in extracellular acidification, glucose uptake, and lactate production, while *miR-101-3p* suppresses glycolysis in LC cells. *XIST* silencing increases *miR-101-3p* levels and decreases the expression levels of key glycolysis enzymes, although this effect can be reversed by inhibiting *miR-101-3p* [176].
APAL	Antisense noncoding RNA in the INK4 locus	• *APAL* is highly expressed in patients with LC, and its depletion leads to mitotic catastrophe and increased apoptosis. Cell cycle progression, proliferation, and apoptosis induced by chemotherapy are all accelerated by increased levels of *APAL*. Based on mechanistic studies, *APAL* binds to PLK1 and Aurora A and promotes the phosphorylation of PLK1 by Aurora A [34].
UCA1/UFC1	**Urogenital carcinoma antigen 1**	• lncRNA *UCA1* is expressed at higher levels in gefitinib-resistant PC9 cells than gefitinib-sensitive PC9 cells. Its levels are also elevated in LC tissues from patients who have acquired resistance to EGFR-TKIs when compared with those who are susceptible or have primary resistance. A functional study showed that knocking down *UCA1* partially restored gefitinib sensitivity in PC9/R cells without the T790M mutation by promoting caspase 3 and caspase 8 expression, while H1975 cells possessing the T790M mutation remained resistant. lncRNA *UCA1* contributes to non-T790M acquired resistance to EGFR-TKIs by activating the AKT/mTOR pathway and promoting EMT in vitro and in vivo [65]. • A significantly higher mRNA expression level of *UCA1* and a significantly lower mRNA expression level of *TXNIP* have observed in lung adenocarcinoma tissue with cisplatin-insensitive compared to those with the lung adenocarcinoma tissue cisplatin-sensitive. Cisplatin resistance in lung adenocarcinoma is associated with the downregulation of TXNIP expression by *UCA1*. TXNIP interacts with various proteins, including TXN, DDIT4, and NLRP3 [177].
AC020978		• Both in vitro and in vivo, *AC020978* enhances the migration and invasion of NSCLC. It interacts with malate dehydrogenase 2 (MDH2) and helps to maintain the stability of MDH2. NSCLC cells overexpressing *AC020978* show decreased metastasis and 2-hydroxyglutarate (2-HG) metabolism when MDH2 is knocked down. AKT pathway activation by *AC020978* may serve as a prognostic biomarker, as it contributes to the progression and metastasis of NSCLC through the stabilization of MDH2 [178]. • In NSCLC, *AC020978* is upregulated and this is significantly associated with an advanced TNM stage and poor clinical outcomes; thus, it serves as a prognostic indicator. *AC020978* plays an important role in promoting cell growth and metabolic reprogramming. It has also been found that *AC020978* is upregulated in conditions of glucose starvation and hypoxia, and that it is directly transactivated by HIF-1α. The mechanism of action of *AC020978* revealed that it interacts directly with pyruvate kinase isozyme M2 (PKM2) and enhances the stability of the PKM2 protein. *AC020978* promotes the nuclear translocation of PKM2 and affects its ability to enhance HIF-1α transcriptional activity [35].

Table 1 (continued)

LncRNA	Description	Mechanism of Resistance
GAS5	Growth arrest-specific 5	• NSCLC tissues exhibit markedly reduced *GAS5* expression levels compared to adjacent normal tissues, and even lower levels are found in tissues from patients with progressive disease (PD). In A549 cells, silencing *GAS5* increases the IC50 of DDP, whereas overexpressing *GAS5* decreases it. When *GAS5* is knocked down in A549 cells, autophagy decreases, while *GAS5* overexpression in A549/DDP cells increases autophagy [48]. • A549-derived tumors in nude mice treated with gefitinib are inhibited by *GAS5* overexpression in addition to its pro-apoptotic properties. In addition, *GAS5* expression levels are inversely correlated with the expression levels of proteins related to the EGFR pathway and the IGF-1 receptor [49]. • Mechanistically, *GAS5* acts as a molecular sponge for *miR-217*, inhibiting the expression of LHPP (phospholysine phosphohistidine inorganic pyrophosphate phosphatase) [48].
AC006050.3-003		• Expression levels of the lncRNA *AC006050.3-003* are significantly reduced in patients with lung squamous cell carcinoma with a partial response compared to those with PD [63].
AK126698		• *AK001796* levels are higher in A549/DDP cells than in A549 cells. Silencing *AK001796* using a small interfering RNA reduces cellular resistance to cisplatin and cell viability, resulting in a significant increase in the proportion of A549/DDP cells in the G0/G1 phase. Knockdown of *AK001796* has also been shown to upregulate the expression levels of the apoptosis-related factors, CCNC and BIRC5, while downregulating the expression levels of the cell-cycle-related factors, CDK1 and GTSE5 [179]. • *AK126698* inhibits the activation of the Wnt/catenin pathway based on changes in Axin1, Catenin, c-myc, cyclin D1 and E-cadherin expression levels [180].
Linc00839		• *LINC00839* is upregulated in LC cells, and knocking it down leads to decreased viability, migratory capacity, and invasion, while increasing apoptosis. *LINC00839* is a target gene of *miR-519d-3p*, which shows reduced expression levels in response to *LINC00839* overexpression. *miR-519d-3p* inhibits JMJD6 at both the mRNA and protein levels. In addition, *miR-519d-3p* overexpression decreases the viability, migration, and invasiveness of LC cells and increases the rate of apoptosis. Overexpression of *LINC00839* increases JMJD6 mRNA and protein levels. By acting as a competitive sponge for *miR-519d-3p*, *LINC00839* promotes LC cell viability, invasion, and migration and reduces the apoptosis rates of A549 and H460 LC cells. These effects are reversed by knocking down JMJD6 [181].
NKILA	NF-κB-interacting lncRNA	• *NKILA* levels are significantly lower in NSCLC tumor tissues than adjacent noncancerous tissues, with lower levels associated with lymph node metastasis and an advanced TNM stage. *NKILA* expression is primarily regulated by the classical TGF-β signaling pathway in NSCLC cells. According to functional assays, *NKILA* inhibits NSCLC cell migration, invasion, and viability. An investigation of the mechanism of action revealed that *NKILA* inhibits Snail expression by inhibiting the phosphorylation of IκBα and the activation of NF-κB, which in turn suppresses the expression of markers associated of EMT [182].

components of the tumor microenvironment are cancer-associated fibroblasts (CAFs), which are involved in the process of promoting tumor development by secreting exosomes, extracellular membrane vesicles, DNA, and various forms of RNA, which serve as messengers between cells [72]. A number of studies have demonstrated that CAF-derived exosomal lncRNAs are involved in the progression of cancer and immune evasion [73–76].

MEG3 released from CAF-derived exosomes confers DDP resistance via regulation of the *miR-15a-5p*/CCNE1 axis in SCLC. The current study may provide a new potential therapeutic strategy for improving the clinical benefits of DDP. The combination of etoposide/topotecan plus DDP has been shown to be effective as the first-line chemotherapy for patients with SCLC [77]. Several additional exosomal lncRNAs involved in the regulation of LC progression are shown in Table 2.

Therapeutics based on targeting lncRNAs: a new approach in drug discovery

Targeting lncRNAs with drugs is a promising research topic. An lncRNA-targeted therapeutic approach aims to enhance therapeutic effects by modulating lncRNA expression or function. lncRNAs are involved in cancer progression and tumorigenesis at multiple stages and are widely expressed in LC [78]. These molecules play cretical roles in the development and regulation of a wide variety of molecular pathways associated with gene expression. Molecular-targeted therapies and chemotherapy have been reported to be associated with the dysregulation of lncRNAs. Since they are specific and sensitive to chemotherapeutic drugs, lncRNAs may serve as new therapeutic targets for NSCLC and may prove to be effective at curing it [79]. The methods employed to address chemoresistance by degrading, inhibiting, or modifying lncRNAs are presented in Fig. 2.

With recent advancements in genome editing technologies, such as clustered regularly interspaced short palindromic repeats (CRISPR)-associated protein 9 (CRISPR-Cas9) technology, it has become possible to silence the transcription of lncRNA genes through CRISPR interference [156, 157]. Using this technique, a transcriptional-repressor-fused dead-Cas9 protein is directed to a specific gene promoter via guide RNAs to silence the gene [158]. CRISPR/Cas9 has been used to

Table 2 The exosomal lncRNAs in regulating progression of lung cancer cells

Exosomal lncRNA	Descriptive	Remark
TBILA- AGAP2-AS1	TGF-beta Induced LncRNA Transcript-ArfGAP With GTPase Domain, Ankyrin Repeat and PH Domain-2 Antisense RNA 1	Elevated levels of exosomal lncRNAs have been found in patients with NSCLC. The individual lncRNAs TBILA and *AGAP2-AS1* serve as more effective diagnostic tools than when used in combination [184]. *AGAP2*-AS1 enhances NOTCH2 expression through the downregulation of miRNA-296, contributing to the induction of radioresistance [185].
FOXD3-AS1	Forkhead Box D3 Antisense RNA 1	Exosomes derived from LC cells that contain *FOXD3-AS1* stimulate ELAVL1 expression and activation of the PI3K/Akt signaling pathway, which promotes LC progression [188].
GAS5	Growth Arrest Specific 5	*GAS5* is downregulated in patients with NSCLC. Low expression levels of *GAS5* create an environment conducive to lymph node metastasis and larger tumor size in NSCLC [192].
H19		*H19* enhances erlotinib resistance and reduces the expression levels of *miRNA-615-3p*, leading to the upregulation of ATG7 and the promotion of LC progression [70].
LINC00662	Long Intergenic Non-Protein Coding RNA 662	*LINC00662* prevents apoptosis and encourages proliferation, cell cycle progression, and invasion by sponging miRNA-320d, thereby enhancing E2F1 expression [191].
MLETA1	Malignant Lymphoma Expressed Transcript 1	lncRNA *MLETA1*, which is highly expressed in metastatic LC cells and their exosomes, facilitates cancer cell invasion and migration. By reducing *MLETA1* levels, cell motility and metastasis are reduced. Exosomes containing *MLETA1* also stimulate metastasis in recipient cells, an effect that is inhibited by locked nucleic acid–mediated silencing of *MLETA1*. *MLETA1* works as a competing endogenous RNA, regulating the expression of EGFR and IGF1R by sequestering *miR-186-5p* and *miR-497-5p* [66].
MMP2–2		TGF-β stimulates the release of exosomes containing lncRNA *MMP2–2*, which promotes the migration and invasion of cancer cells through the upregulation of MMP2 [183].
MSTRG.292666.16		Silencing lncRNA MSTRG.292666.16 reduced osimertinib resistance in H1975R cells. These results suggest that exosomal lncRNA MSTRG.292666.16 may be linked to osimertinib resistance in NSCLC [189].
PCAT-1	Prostate Cancer Associated Transcript 1	The development of a pre-metastatic niche facilitates LC migration and invasion. Elevated expression of *miRNA-182* and *miRNA-217* decreases the levels of *p27* and CDK6, thereby contributing to immunosuppressive activity [186].
RP11–838N2.4		Exosomes carrying lncRNA *RP11-838N2.4* are responsible for the transfer of erlotinib resistance from one cell to another. Knockdown of *RP11-838N2.4* reverses this effect in vitro, and recipient cells exposed to these exosomes developed resistance. Elevated serum levels of exosomal *RP11-838N2.4* correlate with erlotinib resistance in patients with NSCLC, suggesting this lncRNA could be a therapeutic target [193].
SCIRT	Stem Cell Induced Regulator of Transcription	lncRNA SCIRT levels were elevated in exosomes from cancer cells, possibly contributing to miR-665 integration into these exosomes with the aid of hnRNPA1. Exosomal miR-665 interacts with HEYL, a transcription factor downstream of the Notch pathway, enhancing LC cell invasion and migration [187].
SOX2OT	SOX2 Overlapping Transcript	*SOX2OT* induces the bone metastasis of LC cells by sponging *miRNA-194-5p* to upregulate RAC1 expression [190].
SNHG15	Small Nucleolar RNA Host Gene 15	The enrichment of *SNHG15* in exosomes is associated with an unfavorable prognosis [185].
UFC1/ UCA1	Ubiquitin Fold Modifier 1-Associated Long Non-Coding RNA/ Urothelial Carcinoma Associated 1	*UFC1* is delivered by exosomes derived from NSCLC cells and promotes the proliferation, migration, and invasion of NSCLC cells. Exosome-mediated transfer of *UFC1* promotes NSCLC progression through the epigenetic silencing of PTEN mediated by EZH2 [69].

target nuclear-enriched abundant transcript 1 (NLUCAT1), which is constitutively upregulated in lung adenocarcinomas under oxidative stress and hypoxic conditions. This results in a decrease in cell proliferation and invasion, as well as an increase in sensitivity to cisplatin-induced apoptosis [80]. Induced pluripotent stem cells and cancer cells are represented by seven human cell lines, were used to selectively deactivate lncRNAs via CRISPR interference. Approximately 500 lncRNAs were found to be critical to the proliferation of cancer cells. Most of these lncRNAs identified as essential for only one cell type, underscoring the specificity of their functions [159]. Knockdown of six different lncRNAs has been achieved using dCas9-KRAB, with >80% efficiency observed for five lncRNAs, according to Gilbert et al. [81].

Loss of function may also be accomplished by steric inhibition of RNA-protein interactions or by inhibiting the formation of secondary structures. An RNA-binding small molecule or an **antisense oligonucleotide** (ASO) can be applied in this situation [82].

An effective method for targeting and degrading lncRNA is to use small interfering RNAs (siRNAs) or ASOs. Pathogenic RNAs can be knocked down via post-transcriptional RNA degradation. The cleavage pathway can be triggered by Dicer- and argonaute-dependent siRNAs. In

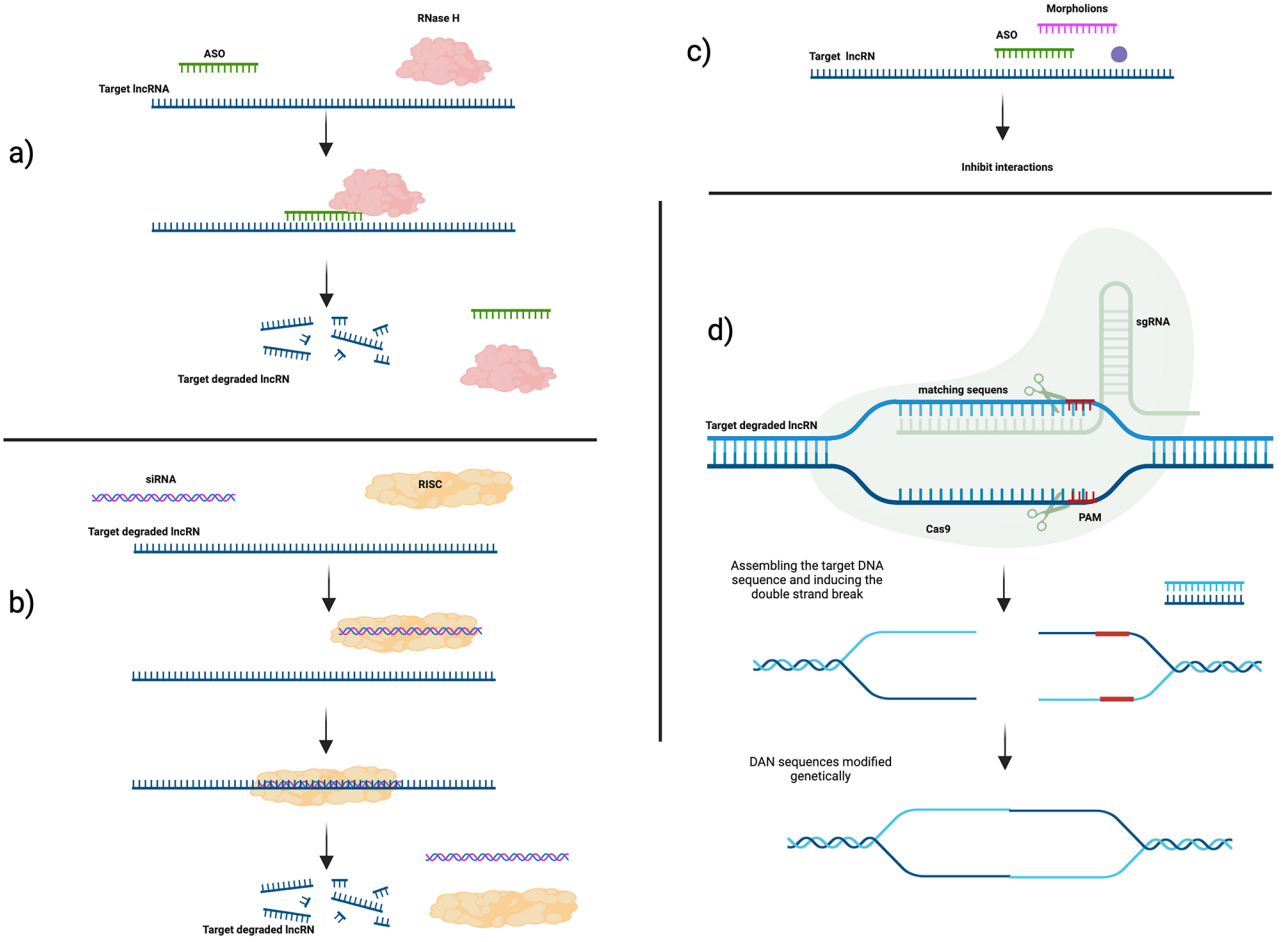

Fig. 2 Examples of advances in targeting lncRNAs and the potential therapeutic benefits of this approach. Antisense oligonucleotides (ASOs) and small interfering RNAs (siRNAs) are capable of degrading long non-coding RNA (lncRNA) molecules in different ways. **(a)** An ASO is a synthetic nucleic acid strand that is designed to bind specifically to the complementary bases of an lncRNA. Binding of the ASO-RNA complex to a lncRNA facilitates degradation by RNase H, as RNA-DNA hybrids are cleaved by RNase H. **(b)** siRNAs are usually short double-stranded RNA molecules, with one strand matching the sequence of the target lncRNA. After entering the cell, the siRNA is incorporated into an RNA-induced silencing complex (RISC). The lncRNA is degraded once it has been bound by the Argonaute protein component of the RISC. **(c)** Steric inhibitors, such as small molecules, morpholinos, or uniformly modified ASOs, can be used to inhibit lncRNA-protein interactions. ASOs bind to nascent lncRNA transcripts. Consequently, mature lncRNA levels can be reduced, and their activity can be effectively inhibited. A morpholino is a synthetic molecule that binds to a lncRNA and prevents other molecules from accessing the sequence. This method is stable and resistant to nucleases, allowing it to effectively inhibit lncRNA expression without degrading the target lncRNA. **(d)** CRISPR/Cas9 technology provides an efficient and flexible means of modulating lncRNA expression levels directly by targeting genomic DNA. Guide RNAs (gRNAs) are designed to match sequences upstream or within genes that encode the lncRNAs. The Cas9 endonuclease is directed by the gRNA to the specific location in the genome where double-strand breaks are generated. In the event that these breaks are introduced, insertions or deletions (indels) may be generated during the DNA repair process, typically as a result of non-homologous end joining. BioRender.com

addition, chemically modified ASOs can be used to target RNAse-H-dependent mechanisms to degrade the RNA of interest [82]. Targeted knockdown of *MALAT1* and *ANRIL* in LC cells reduces cell proliferation and increases apoptosis [83]. Using an ASO to knockdown *MALAT1* inhibits the migration of NSCLCs cells [83].

Drugs can alter the structure or function of lncRNAs to alter their interactions with other molecules and their downstream effects. In addition, the steric blockade of lncRNA promoters or genome editing can modify the transcription of these genes [82].

Because RNA-RNA and RNA-DNA duplexes are highly selective, scientists have explored therapeutic potential of oligonucleotide-based molecules. Nucleic-acid-based therapeutics are currently used in two ways. RNA interference (RNAi) uses double-stranded RNAs, whereas ASOs are single-stranded RNAs. Small-molecule inhibitors can target lncRNAs directly or by interfering with lncRNA-ribonucleoprotein interactions [82]. This approach has been used to successfully target *MALAT1* and decrease its expression levels by destabilizing the uncommon 3′-terminal element for nuclear expression

motif, which normally protects *MALAT1* from degradation [84].

There has been an increase in the stability and efficacy of nucleic acid therapeutics in recent years, as well as a reduction in off-target effects, resulting in the development of drugs for various diseases, including malignancies, at various stages of clinical development [85, 86].

RNAi-mediated gene silencing

The most promising method for selectively inhibiting target lncRNAs is through RNAi technologies (shRNAs, siRNAs, and ASOs), Due to the lncRNAs' localization or secondary structure, some may not be available. There is evidence that lncRNA-targeted RNAi is effective against cancer cell lines. It is required, however, that stable conditions be maintained in order to transport siRNAs to the target in vivo. Several lncRNA have recently been identified as promising therapeutic targets. The use of RNAi to silence *HOTAIR* may decrease the invasiveness and viability of pancreas, breast, and LC [87]. Additionally, it reduces p21 expression levels in lung adenocarcinoma cells, contributing to cisplatin resistance [88]. Furthermore, migration and cell invasiveness in NSCLC are significantly reduced by shRNA-mediated knockdown of *MALAT1* [89].

Cheng et al. recently investigated UCA1 protein levels prior to treatment in patients with EGFR-mutant NSCLC who had developed resistance to EGFR TKIs [65]. UCA1 may play a significant role in the development of resistance to EGFR TKIs. However, the use of siRNAs faces challenges due to unreliable delivery and potential off-target effects, which might limit their application. Consequently, inhibiting lncRNAs in vivo continues to be a challenging endeavor [90]. o overcome this limitation, various strategies have been developed, such as lipid-based nanoparticle delivery [91], conjugate-based delivery [92], and polymer-based delivery [93], .

The inherent vulnerability of double-stranded RNA to nucleases requires chemical modifications to prevent it from becoming a substrate for subsequent enzymatic degradation pathways [94]. Chemists have enhanced the pharmacological properties of siRNA-based drugs by incorporating 2′-O-methyl sugar residues and adding phosphorothioate linkages to the 3′ end of the RNAs [95].

In human prostate cancer cell lines, siRNAs targeting MALAT1 suppress cell proliferation, invasion, and migration, while also inducing cell cycle arrest [96]. In human breast cancer cell lines, siRNA-mediated knockdown of *HOTAIR* inhibits matrix invasion [97]. Furthermore, subcutaneous injection of human gastric cancer cell lines transfected with *HOTAIR*-specific shRNA prevented engraftment in nude mice [98]. A recent shRNA-based screening of a mouse model of leukemia identified several lncRNA species crucial for sustaining leukemia, with some promoting the development of leukemia stem cells [99].

ASO-based treatment

ASOs that target different mRNAs have been used to treat multiple diseases, including cancer [100]. Moreover, they have emerged as promising therapeutic approaches for targeting lncRNAs [101]. ASOs modify or suppress gene expression by mechanisms including steric hindrance, splicing alterations, initiating target degradation, and other pathways.

The advancement of ASO chemistry has played a significant role in the clinical success of ASOs across various applications. New-generation ASOs contain 15–20 nucleotides modified with phosphothioate linkages [102]. Numerous studies have shown that these ASOs can function as splice switchers, altering the splicing patterns of target RNAs by obstructing splicing enhancers or repressor-binding sites [86]. ASOs are single-stranded DNA molecules that promote lncRNA degradation via the enzyme RNase H and they can be used to silence and regulate lncRNAs. There are fewer off-target effects associated with ASOs than with siRNAs and they have a higher level of specificity [103].

In addition to knocking down cytoplasmic RNAs, ASOs are highly effective at knocking down nucleic RNAs. Several factors contribute to this phenomenon, including high levels of RNase H in the nucleus [104]. Several lncRNAs are highly concentrated in the nucleus [105], which makes ASOs an appealing method for lncRNA knockdown.

Moreover, the knockdown of MALAT1 using ASOs diminishes branching morphogenesis in three-dimensional organoids derived from MMTV-PyMT tumors, as well as in a mouse mammary tumor model that is amplified for the human epidermal growth factor receptor 2 (HER2) [106]. In addition to their effects in breast cancer, *MALAT1* ASOs elicit a potent anti-metastatic response in an LC xenograft model. In that study, the systemic knockdown of MALAT1 in nude mice receiving intravenous injections of human LC cells led to a reduction of over 70% in the number of cells migrating to the lungs compared to mice injected with control ASO [107].

ASOs targeting lncRNA *MALAT1* in cervical cancer and LC cells have been shown to weaken malignant phenotypes by causing cell cycle arrest [108]. To function of the lncRNA *MALAT1*, Tony et al. developed a loss-of-function model by knocking out *MALAT1* in lung tumor cells. Their findings revealed that animals treated with a *MALAT1* ASO exhibited significantly smaller tumor volumes and fewer lung nodules compared to those treated with a control ASO. As a result, the inhibition of MALAT1 by ASOs effectively prevented NSCLC

metastasis, suggesting a promising therapeutic strategy for the treatment of NSCLC [109].

Based findings, MALAT1 ASOs could represent a promising therapeutic option for metastatic disease across various cancer types; however, additional studies are needed [110]. Furthermore, research has demonstrated that a diverse array of Mammary Tumor Associated RNAs (MaTARs) can be effectively knocked down using ASOs in ex vivo organoid models, and this knockdown is linked to a significant antitumor response [111, 112]. Various preclinical studies are currently being conducted using patient-derived xenograft models and tumor organoids to move these studies closer to clinical trials.

Therapeutic limitations of nucleic acids

The application of nucleic acid-based therapies for treating a variety of disorders, including cancer, has gained considerable interest; however, it is important to approach this with caution. A key factor is that these molecules must successfully cross the plasma membrane of cells. Additionally, cellular nucleases and elements of the innate immune response to foreign RNA—such as Toll-like receptors (TLRs) and retinoic acid-induced gene I (RIG-I) RNA helicases—can impede the entry of these molecules into cells [113, 114].

Traditional siRNAs have been used to knockdown several lncRNAs in cell lines [94, 95]. However, conducting in vivo experiments with siRNAs poses challenges. Factors such as inefficient delivery methods and the low bioavailability of siRNAs in animal models contribute to their limited effectiveness [115, 116]. An RNA-based therapeutic approach has been used to target miRNAs, which were the first non-coding RNAs to be pharmacologically targeted [117]. However, the use of siRNAs/shRNAs to target lncRNAs in preclinical studies is limited.

Synthetic ASOs can also be entrapped in endosomes, significantly reducing their bioavailability [116, 118, 119]. In it is essential to verify that oligonucleotides have minimal or no off-target effects. Antisense therapeutics were discovered more than 20 years ago [120, 121], but have only recently achieved therapeutic success [86, 122] owing to the aforementioned factors.

The advancements in new-generation chemistries outlined above have been crucial in addressing numerous challenges to effective nucleic-acid-based therapies, such as enhanced uptake, improved stability, resistance to nucleases, and extended pharmacokinetics. The objective of ASO production is to identify sequences that are well tolerated and to avoid CpG motifs, which may elicit an immune response to overcome the effects of innate immune responses triggered by TLRs [123, 124].

It is also essential to consider the possibility of off-target effects. Bioinformatic analyses are necessary to eliminate sequences that may have off-target matches. Furthermore, with the advancement of gene editing techniques, it is possible to assess off-target effects by knocking down the target gene in cells lacking the target gene to assess whether any changes in gene expression occur.

Challenges in targeting lncRNAs for therapeutic applications

Several challenges must be overcome to effectively target lncRNAs, particularly when assessing their functions and validating in vivo therapeutic strategies. It is crucial to evaluate the expression of human lncRNAs in model organisms as part of this process, because it is imperative to understand the intricate interactions between lncRNAs and their target genes and proteins [125]. However, poor conservation of lncRNAs across species complicates this process. Several human lncRNAs lack homologs in mice [126, 127], and only a few orthologous lncRNAs have been identified in humans and mice [128]. To overcome these limitations, the development of engineered mouse models incorporating larger segments of the human genome, entire human chromosomes, or proteins substituted from those encoded in the mouse genome may be beneficial [129].

It is often difficult to obtain consistent results from lncRNA studies. For example, although *MALAT1* has been shown to regulate alternative splicing in human HeLa cells [130], other studies have demonstrated that the repression of *MALAT1* in cultured cells or mice does not affect the overall splicing or phosphorylation of serine- and arginine-rich proteins [108]. Furthermore, mice with defective *Neat-1*, *H19*, and *MALAT1* exhibit normal phenotypes [131]. Additionally, cell cycle arrest or apoptosis may occur when *MALAT1* is knocked down in certain cell lines. These discrepancies highlight the need for high-throughput functional analyses to provide a deeper understanding of the molecular mechanisms underlying the action of lncRNAs. CRISPR-Cas9 genome editing technology is an effective tool for identifying oncogenic lncRNAs, potential targets for therapeutic intervention, and mechanisms of drug resistance [132].

In some cases, lncRNAs exhibit tumor-specific expression patterns, although variations in their expression levels have been observed. Cancer heterogeneity may play a role in these differences, suggesting that a detailed analysis of cancer tissues would be more accurate than a simple assessment of bulk tissues [128]. Additionally, owing to the significant alternative splicing of lncRNAs, the general evaluation of tumor tissues may miss specific transcript isoforms. These challenges can be addressed by utilizing techniques such as fluorescent in situ hybridization using freshly frozen or fixed tumor specimens [133] as well as single-cell RNA sequencing [108, 134].

There are obstacles related to the toxicity and off-target effects of nucleic acid therapy. The modification of sugars to increase nucleic acid affinity can result in off-target cleavage after treatment with ASOs or small siRNAs [134–136] as a result of the tolerance for mismatches and hybridization within shorter regions of homology [137, 151]. The inflammatory properties of phosphothioated oligonucleotides have also been demonstrated. The transfection of HeLa cells with gapmer phosphorothioate-antisense oligonucleotides (PS-ASOs) containing 2′-F nucleoside modifications causes DNA damage and cell death [138, 139], as they demonstrated greater binding affinity to cellular proteins than PS-ASOs modified with 2′-O-methoxyethyl (2′-MOE) or constrained-ethyl-bicyclic-nucleic acids [139, 140]. Even a single nucleotide mismatch can significantly reduce RNase H1 activity, with three or more mismatches resulting in the complete loss of activity [141, 142]. Although bioinformatics tools can help predict and mitigate non-specific hybridization, only a fraction of designed ASOs effectively reduce target gene expression [143]. Although deep RNA sequencing approaches do not offer quantitative information, they may help minimize off-target effects [144].

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