Ge et al. Cancer Cell International (2024) 24:369
https://doi.org/10.1186/s12935-024-03549-1

Cancer Cell International

REVIEW Open Access

Comprehensive review of LncRNA-mediated therapeutic resistance in non-small cell lung cancer

Xin Ge[1,2†], Zichu Shen[2†] and Yuxin Yin[2,3*]

Abstract

Long non-coding RNAs (lncRNAs) are emerging as crucial regulators of gene expression through diverse mechanisms, including regulation of protein localization, sequestration of miRNAs, recruitment of chromatin modifiers, and modulation of signaling pathways. Accumulating evidence highlights their pivotal roles in tumor initiation, progression, and the development of therapeutic resistance. In this review, we comprehensively summarized the existing literature to identify lncRNAs associated with treatment responses in non-small cell lung cancer (NSCLC). Specifically, we categorized these lncRNAs based on their mechanisms of action in mediating resistance to chemotherapy, targeted therapy, and radiotherapy. Our analysis revealed that aberrant expression of various lncRNAs contributes to the development, metastasis, and therapeutic resistance in NSCLC, ultimately leading to poor clinical outcomes. By elucidating the intricate mechanisms through which lncRNAs modulate therapeutic responses, this review aims to provide mechanistic insights into the heterogeneous treatment outcomes observed in NSCLC patients and unveil potential therapeutic targets for overcoming drug resistance.

Keywords Long non-coding RNA, Non-small cell lung cancer, Chemotherapy, Targeted therapy, Radio therapy

Introduction

According to the latest statistical report [1], lung cancer ranks second in terms of estimated new cancer cases and first in terms of estimated cancer-related deaths. Furthermore, its five-year survival rate is relatively low compared to other cancers, standing at only 25% [2]. Nevertheless, the incidence of lung cancer and the number of deaths due to lung cancer are progressively decreasing annually [2], attributable to advancements in early diagnosis and treatment. The risk factors for lung cancer include smoking, air pollution, radiation exposure, and occupational exposure to asbestos, chloromethane, chromium, nickel, polycyclic aromatic hydrocarbons, etc. Among them, smoking is the most significant risk factor, accounting for over 80% of lung cancer cases [3].

Non-small cell lung cancer (NSCLC) represents the predominant form of lung cancer, comprising around 80% of total diagnosed incidences [4]. Subtypes of NSCLC include lung adenocarcinoma (LUAD), lung squamous cell carcinoma (LUSC), and large-cell carcinoma. LUAD, the most common subtype of NSCLC, is typically peripheral but grows rapidly. It can disseminate through the bronchial tree, invade the visceral pleura,

†Xin Ge and Zichu Shen equally contributed to this work.

*Correspondence:
Yuxin Yin
yinyuxin@hsc.pku.edu.cn
[1]Peking University First Hospital, Beijing 100034, China
[2]Institute of Systems Biomedicine, Department of Pathology, School of Basic Medical Sciences, Beijing Key Laboratory of Tumor Systems Biology, Peking-Tsinghua Center of Life Sciences, Peking University Health Science Center, Beijing 100191, China
[3]Institute of Precision Medicine, Peking University Shenzhen Hospital, Shenzhen 518036, China

and easily rupture, leading to intrapleural implantation. LUSC often occurs in the subsegmental bronchi and larger bronchi, mainly presenting as a central type. It is prone to lymphatic metastasis, and readily forms pulmonary cavities, infiltrating blood vessels and leading to hemoptysis. Large-cell carcinoma has a low incidence rate but a high degree of malignancy, resulting in poor prognosis.

Three-year survival rate for all stages of NSCLC combined increased from 25% for diagnoses during 2004 through 2006 to 38% for diagnoses during 2016 through 2018 [1]. This progress has largely been attributed to advancements in the treatment of NSCLC, particularly the utilization of targeted therapies [5]. Treatment approaches for NSCLC vary by stage, including surgery, chemotherapy, radiotherapy, targeted therapy, and immunotherapy [6]. Benefiting from the development of various treatment modalities, it is now possible to adopt combined therapy when choosing a treatment plan in clinical practice based on the specific conditions of the patient. For instance, neoadjuvant chemotherapy, which refers to systemic chemotherapy administered before surgery or radiotherapy, is aimed at reducing tumor volume, lowering the TNM staging, and increasing the success rate of resection. A meta-analysis has shown that neoadjuvant chemotherapy can significantly increase the overall survival rate of patients [7].

The genetic alterations in NSCLC vary according to different histological subtypes. In LUAD patients, epidermal growth factor receptor (EGFR) mutations are the most common, followed by ALK, KRAS, ROS1, BRAF, RET, and HER2. In LUSC patients, common genetic alterations include FGFR1, DDR2, PIK3CA, PTEN, and platelet-derived growth factor receptor [3]. The frequency of genetic alterations, the ranking and proportion of mutations vary among non-small cell lung cancer patients of different ethnicities [3]. With the development and popularization of molecular detection technologies, the clinical value of genotyping has been increasingly significant, and its role in guiding treatment and predicting prognosis cannot be neglected. The amplification refractory mutation system (ARMS), immunohistochemistry, polymerase chain reaction-related technologies, and fluorescence in situ hybridization (FISH) can all be used for molecular typing in patients with NSCLC. The popularity of genetic testing for NSCLC patients is gradually increasing [8], but it is more focused on EGFR mutations [9]. A retrospective [10] reviewed that genetic screening could effectively prolong the overall survival of patients with NSCLC (27.50 vs. 19.73 months; $P=0.007$), but there were significant differences in genetic screening rates between first-tier cities and second-tier and third-tier cities. Therefore, the promotion of molecular genetic screening for NSCLC is beneficial and necessary. In addition to tissue biopsy, liquid biopsy can also provide molecular typing of patients. Circulating tumor DNA (ctDNA) and circulating tumor cells (CTCs) in plasma can both be targets for liquid biopsy [3], among which the detection technology of peripheral blood ctDNA used to identify EGFR mutations has achieved good clinical results [11]. Compared with tissue biopsy, liquid biopsy has the advantages of safety, non-invasiveness, simplicity, and economy.

Long non-coding RNAs (lncRNAs) are a class of RNA with more than 200 nucleotides without protein-coding potential. A substantial body of research has found a close relationship between lncRNA and cancer. LncRNAs exert biological effects through various pathways, including transcriptional regulation, chromatin modification, nuclear structure regulation, and RNA interference [12]. In addition, lncRNAs are closely associated with the tumor microenvironment and the modulation of cellular signaling pathways [13, 14]. Increasing evidence suggests the association between lncRNAs and the occurrence or progression of NSCLC, including their roles in proliferation, invasion, migration, and drug resistance. Upregulation of H19 leads to upregulation of STAT3 expression through sponging miR-17, thereby promoting the growth, invasion, and migration of NSCLC cells [15]. ANRIL overexpression silences KLF2 and P21 by binding enhancer of zeste homolog 2 (EZH2), ultimately facilitating proliferation and inhibiting apoptosis, ultimately leading to a poor prognosis in NSCLC [16]. Therefore, lncRNAs have potential as biomarkers for NSCLC diagnosis, prognosis and therapy [17–20].

Our study focuses on lncRNAs associated with the efficacy of chemotherapy, targeted therapy, and immunotherapy, investigating their mechanisms of action and impact on prognosis. To ensure the practical significance of the research findings, the aberrant expression of lncRNAs selected in this study is derived from clinical cases or open databases such as the cancer genome atlas (TCGA). Additionally, during the literature screening, we found some studies that identified differentially expressed lncRNAs through RNA-seq screening of sensitive and drug-resistant cell lines. However, these studies were not included in this review. It is worth noting that even with clinical data, most studies still establish drug-resistant cell lines to validate the expression levels of lncRNAs compared to sensitive cell lines. Furthermore, we have categorized and organized these lncRNAs based on their functional mechanisms. We aim to provide new directions for cancer treatment research.

LncRNA biogenesis and localization

Similar to mRNA, the transcription of lncRNA is catalyzed by Pol II and requires processing such as 5'-capping, polyadenylation, and splicing [21]. However, in

terms of post-transcriptional processing, some lncRNAs undergo unique processes. Some transcripts contain tRNA-like structures and A/U-rich sequences at their 3' ends, which are cleaved by RNase P to form a highly stable triple helix, functioning similarly to a poly(A) tail to enhance the stability of the transcript [22, 23]. Well-known lncRNAs that undergo this processing include MALAT1 and NEAT1 [21]. Different post-transcriptional processing results in diverse lncRNA species, including circular RNAs (circRNAs) formed by non-canonical splicing of introns, circular intronic long non-coding RNAs (ciRNAs) that escape classical lariat loop-debranching and degradation after canonical intron splicing, sno-lncRNAs generated by the trimming of tandem Small Nucleolar RNAs (snoRNAs) within a single intron. Besides, there are lncRNAs containing miRNAs within their sequences. These transcripts are cleaved by microprocessor at the 3' end, terminating transcription in a non-polyadenylated manner to produce lnc-pri-miRNA, which is then processed by the microprocessor complex to form miRNAs and lncRNAs. However, the resulting lncRNAs are degraded due to their lack of a poly(A) tail [21].

Compared to mRNA, a larger proportion of lncRNAs are localized in the nucleus. This is partly attributed to the presence of nuclear retention elements (NREs) in some lncRNAs, where a higher content of these sequences correlates with a higher degree of nuclear enrichment of the lncRNA [24]. Known examples of such elements include a 356nt sequence (from 798nt to 1153nt) in MEG3 [25], C-rich sequences in Alu repeats [24], repeating RNA domains (RRDs) in FIRRE [26], C-rich sequences distributed across 21 lncRNAs [27], and a pentameric AGCCC motif in the BORG intergenic lncRNA [28]. Notably, these sequences require binding to specific molecules to mediate the nuclear localization of lncRNAs. For instance, the 356nt sequence in MEG3 binds to U1 snRNP [25], C-rich sequences in Alu bind to hnRNPK [24], and RRDs in FIRRE bind to hnRNPU [26]. Studies have shown that the expression levels of these binding partners vary among different cell types [24], indicating that the nuclear enrichment of lncRNAs also depends on the levels of these binding partners. In addition to NREs, low splicing efficiency and alternative polyadenylation also contribute to the nuclear accumulation of lncRNAs [29]. LncRNAs exhibit weaker splicing signals due to a lower pyrimidine content in their splicing signals, and the distance between the branch point and the 3' splice site is greater in lncRNAs than in mRNAs, both of which contribute to the low splicing efficiency of lncRNAs [30]. Alternative polyadenylation can lead to subcellular localization differences among isoforms of the same gene, such as the nuclear localization of CCAT1-L and the cytoplasmic localization of CCAT1-S, due to the presence of an additional polyadenylation site in CCAT1-L compared to CCAT1-S [31] (Fig. 1).

Apart from biogenesis and localization, lncRNAs also differ from mRNAs in their structure and expression. For instance, lncRNAs tend to have fewer but longer exons, are less evolutionarily conserved, and exhibit greater tissue specificity or differences in expression profiles among different states of the same cell type compared to mRNAs [21, 29].

LncRNAs related with chemotherapy

Chemotherapy is the cornerstone of NSCLC treatment and is applicable to patients at various stages of the disease [32]. Chemotherapy involves the use of cytotoxic drugs to kill or inhibit the growth and spread of NSCLC cells and can be administered intravenously or orally. Chemotherapy can be used as a standalone treatment or in combination with surgery, radiotherapy, or immunotherapy to achieve optimal therapeutic outcomes [32]. Cisplatin (DDP) is one of the most commonly used chemotherapeutic agents for NSCLC in clinical practice. Therefore, we focused on DDP-related lncRNAs in this review to provide insights into the roles of lncRNAs in chemotherapy resistance.

Among existing studies, the number of lncRNAs related to chemotherapy is the highest. Firstly, there are lncRNAs that regulate downstream gene expression through modulation of nuclear translocation. One example is the X inactive-specific transcript (XIST) gene located in the X inactivation center [33],distributed mainly in the cytoplasm, upregulated in patients with NSCLC, and its high expression is correlated with DDP treatment and poor prognosis [34]. XIST combines with SMAD2 and decreases nuclear translocation of SMAD2, in turn inhibiting SMAD2-induced transcription of p53 and NLRP3, ultimately alleviating DDP-mediated pyroptosis and reducing chemosensitivity [34].Another example is urothelial carcinoma associated 1 (UCA1), which is located on human chromosome 19p13.12, with a full length of 1439 bp [35], and its high level is associated with resistance to DDP in patients with NSCLC [36]. In LUAD, overexpressed UCA1 induces NRF2 nuclear translocation and promotes the expression of NRF2 and heme HO-1, therefore activating NRF2/HO-1 pathway inhibiting oxidative stress and apoptosis, and upregulating its downstream protein levels, including catalase and SOD1 [37]. Besides, ENO1 was identified as one of the RNA-binding proteins of UCA1 and UCA1 could elevate the level of excision repair cross-complementing 1 (ERCC1) [38]. ENO1 promotes the progression of LUAD [39], and ERCC1 is correlated with DDP resistance in NSCLC [40].

Furthermore, there are lncRNAs that exert their effects through the competing endogenous RNA (ceRNA)

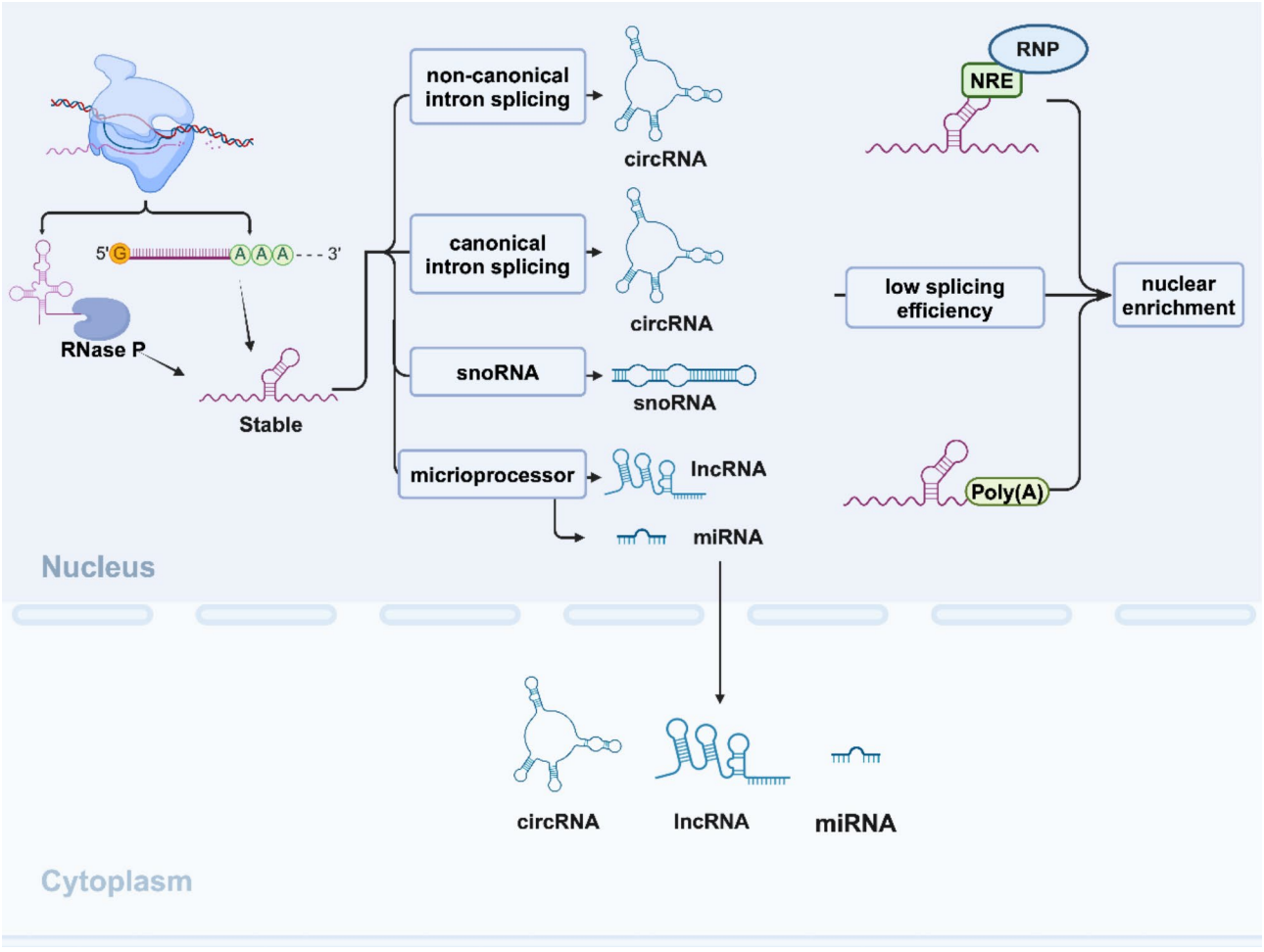

Fig. 1 Mechanisms of lncRNA biogenesis and nuclear localization. Some lncRNAs contain tRNA-like structures at their 3′ ends, which form highly stable triple-helical sequences after RNase P cleavage, thereby increasing stability. Some lncRNAs undergo a series of splicing processes to form special RNAs, including circRNA formed by non-consecutive splicing of introns, circRNA formed by classical intron splicing, sno-lncRNA containing snoRNA components, and lncRNA and miRNA formed by miRNA splicing. Lower splicing efficiency, nuclear retention element, and alternative polyadenylation can all lead to the nuclear localization of lncRNAs. Created in BioRender. Shen, Z. (2024) BioRender.com/v66l891

network. XIST also exerts its biological function through acting as a ceRNA, including upregulating BAG-1 expression through sponging miR-let-7i in LUAD [41], enhancing autophagy activity by miR-17/autophagy associated gene (ATG) 7 axis [42]. Hua et al. reported that XIST promoted glycolysis and DDP resistance by sponging miR-101-3p, manifested specifically by increased expression of the glycolytic enzymes HK2 and LDH2, as well as enhanced glucose uptake and lactate production [43]. Li et al. reported that UCA1 could sponge miR-495 to upregulate NRF2 expression [36]. HOX antisense intergenic RNA (HOTAIR) is a 2158 nucleotides transcript located on human chromosome 12q13.13 [44]. Overexpressed HOTAIR sponges miR-149-5p to upregulate DCLK1 expression, thereby inducing resistance to DDP [45]. With 751 nt in length, tumor protein 53 target gene 1 (TP53TG1) is enriched in the cytoplasmic fraction [46]. The level of TP53TG1 is downregulated in NSCLC tissues and is related to TNM staging [46]. TP53TG1 positively modulates PTEN expression by acting as a molecular sponge of miR-18a [46]. PTEN exerts its tumor suppressor function through PI3K/AKT pathway and many other pathways [47]. The hyperactivation of the PI3K/AKT pathway is closely associated with the occurrence, metastasis, and drug resistance of NSCLC, and studies have found it to be correlated with other NSCLC-related mutations [48]. Thus, depletion of TP53TG1 leads to loss of PTEN, ultimately inhibiting apoptosis and DDP sensitivity in NSCLC. Small nucleolar RNA host gene (SNHG) 1 is a nuclear-enriched lncRNA localized on chromosome 11q12.3, and its transcript is around 1.2 kb [49]. SNHG1 is overexpressed in DDP-resistant NSCLC tissues [50]. SNHG1 mediates aberrant activation of Wnt/β-catenin signaling by sponging miR-140-5p [50]. Notably, Wnt/β-catenin signaling and its downstream targets including cyclin D1 and c-Myc were

found involved in NSCLC prognosis and progression [51, 52]. SNHG1 also directly targets miR-330-5p to upregulate DCLK1 expression, subsequently inducing the phosphorylation of PI3K and protein kinase B (AKT) and enhancing resistance to DDP [53]. Distal-less homeobox 6 antisense 1 (DLX6-AS1) is located on human chromosome 7q21.3, with a length of 1990 bp, major in the cytoplasm and abundantly expressed in LUSC tissues [54]. Moreover, its overexpression is associated with poor prognosis [54]. H3K4me1 is enriched in the DLX6-AS1 promoter region, inducing DLX6-AS1 expression. Upregulated DLX6-AS1 in turn elevates the level of CELF1 through sponging miR-181-5p/miR-382-5p, and confers secondary DDP resistance [54]. FYVE RhoGEF and PH domain containing 5 antisense 1 (FGD5-AS1) is a 3772 nt lncRNA mapping to chromosome 3 [55], and is upregulated in DDP-resistant LUAD [56]. FGD5-AS1 promotes PD-L1 expression via directly interacting with miR-142, depressing chemosensitivity to DDP [56]. Notably, PD-L1 is one of the key targets of immune checkpoint inhibitors, which suggests FGD5-AS1/miR-142/PD-L1 axis may be involved in immunotherapy for NSCLC [57]. SNHG14 is located on human chromosome 15q11.2, and overexpressed in clinical NSCLC samples [58]. SNHG14 positively regulates the HMGB1 level by sponging miR-34a [58]. SNHG14/miR-34a/HMGB1 axis induces malignant behaviors of NSCLC cells, including invasion and migration, and promotes DDP resistance [58]. Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) is located within human chromosome 11q13, around 7 kb [59], highly expressed in NSCLC tissues and correlated with shorter overall survival [60]. MALAT1 induces p120-ctn expression through directly binding to miR-197-3p, therefore enhancing resistance to DDP in NSCLC [60]. However, unlike common ceRNA networks, MALAT1 elevates miR-197-3p level and decreases p120-catenin level [60]. Moreover, MALAT1 enhances the expression of p300 by sponging miR-1297, which in turn upregulates β-catenin and MDR1 expressions, decreases caspase-3 expression, reduces the apoptotic rate of cells, and inhibits β-catenin nuclear translocation [61]. Notably, overexpression of MDR1 can lead to resistance to DDP [62]. And the regulatory effect of MALAT1/miR-1297/p300 axis can be reversed by Asiatic acid [61].

LncRNAs can also exert their functions by associating with EZH2 or regulating signaling pathways. HOTAIR inhibits p21 expression to increase the percentage of S phase cells and reduce DDP chemosensitivity [63]. According to previous studies, the regulation of p21 by HOTAIR may be induced through EZH2 [64, 65]. On the other hand, MALAT1 upregulates MRP1 and MDR1 levels by phosphorylation of STAT3 [66]. SRY-box transcription factor 2 overlapping transcript (SOX2-OT) is a lncRNA with length of around 3.4 kb which is expressed in both the cytoplasm and the nucleus, mapped to human chromosome 3q26.3 [67], and a correlation exists between its elevated level, poor prognosis, reduced clinical response to DDP treatment, and metastasis in oncology [68]. SOX2-OT upregulates levels of total-AKT, total-Extracellular Signal-Regulated Kinase (ERK) and phosphorylated-AKT, therefore activating the PI3K/AKT pathway [68]. Furthermore, SOX2-OT positively regulates GLI-1 expression, which is also correlated with DDP resistance [68].

We found that lncRNAs can influence the expression of downstream genes, thereby affecting DDP resistance in NSCLC patients (Fig. 2), through both direct and indirect means. Notably, this regulatory mechanism is highly complex, as a single lncRNA may regulate downstream genes through multiple pathways and potentially target multiple downstream genes.

In addition, some lncRNAs that modulate DDP resistance by interacting with miRNAs have been included in Table 1.

In addition to DDP, chemotherapy for NSCLC involves a variety of drugs. Commonly used clinically, these include carboplatin, paclitaxel, pemetrexed, gemcitabine, vinorelbine, and adriamycin. Furthermore, studies have shown that lncRNAs participate in the drug resistance processes of these agents through the ceRNA network. For instance, the MALAT1/miR-1927/p120-catenin axis, mentioned previously, not only affects DDP resistance but also influences resistance to adriamycin and paclitaxel [60]. Additionally, Li et al. found that LINC01296, which is localized in the cytoplasm, is highly expressed in NSCLC tissues and is associated with shorter survival times [85]. LINC01296 promotes the expression of ATG2B by targeting miR-143-3p, thereby facilitating tumor growth and metastasis. Knocking down LINC01296 can effectively increase the sensitivity of NSCLC to paclitaxel [85]. HLA Complex Group 11 (HCG11), located on chromosome 6 and approximately 7 kb in length, is significantly downregulated in NSCLC patients [86]. HCG11 upregulates p21 expression by sponging miR-17-5p. The low expression of HCG11 in drug-resistant cells decreases p21 levels, leading to increased tumor cell proliferation, decreased apoptosis, and reduced sensitivity to gemcitabine [87]. MALAT1 is highly expressed in tissues from gemcitabine-resistant patients, and MALAT1 upregulates PBOV1 levels by sponging miR-27a-5p, thereby promoting gemcitabine resistance [88].

LncRNAs related with targeted therapy

Targeted therapy is not applicable to all cases of NSCLC. Only patients with identified mutations in EGFR, mesenchymal-epithelial transition factor (MET), or BRAF, as well as ALK, ROS1, RET, or NTRK translocations, can

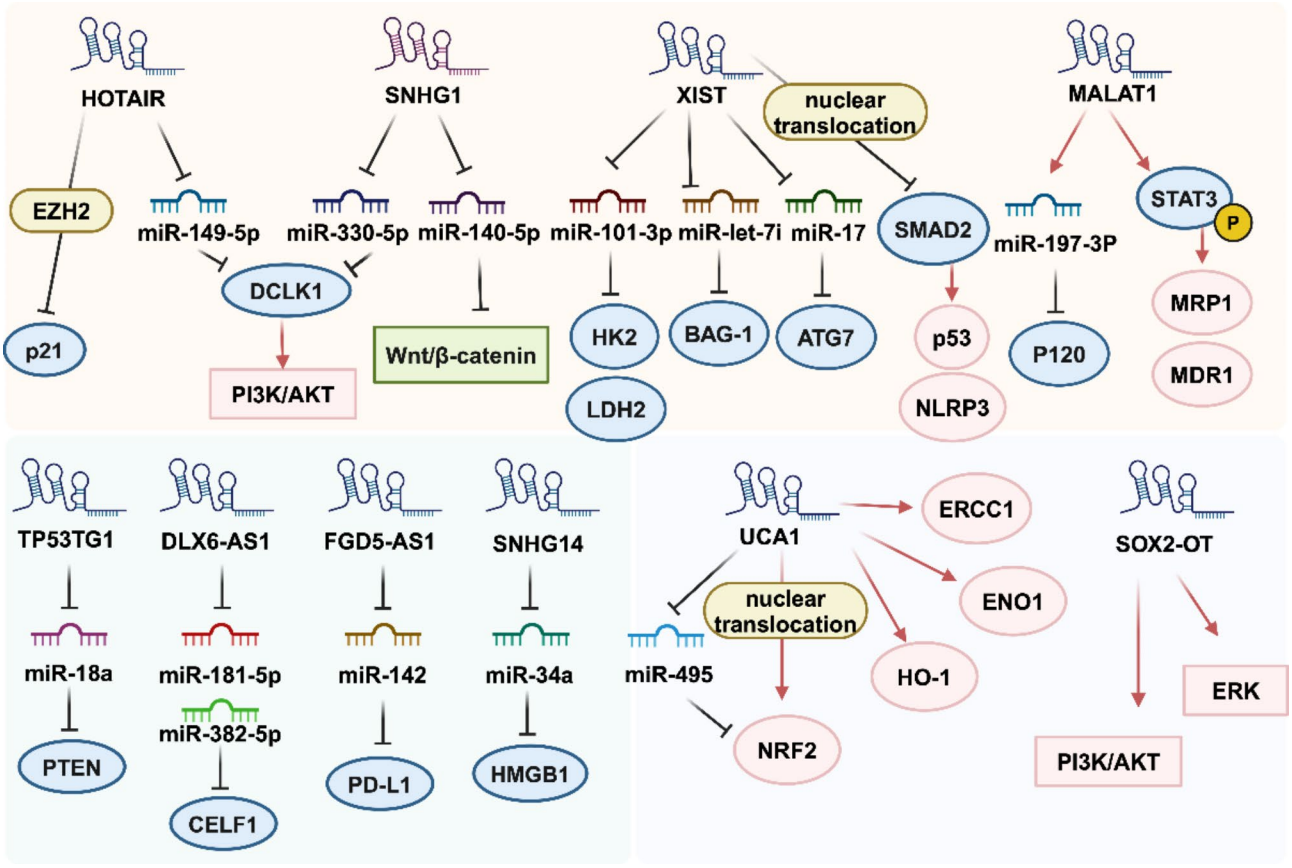

Fig. 2 LncRNAs Related to DDP Resistance. HOTAIR, SNHG1, XIST, MALAT1, TP53TG1, DLX6-AS1, FGD5-AS1, SNHG14 and UCA1 regulate the expression of downstream proteins or affect the stability of downstream proteins through the ceRNA network. HOTAIR, XIST, MALAT1, UCA1 and SOX-OT directly regulate the phosphorylation or expression of downstream proteins, among which HOTAIR exerts its functions through EZH2. Red arrows represent the promotion of expression or increase in stability, while black arrows represent the inhibition of expression or decrease in stability. Created in BioRender. Shen, Z. (2024) BioRender.com/j45y740

receive corresponding targeted drugs [89]. Due to limited targetable mutations in the genetic profile of LUSC, targeted therapy is generally not applicable to this subtype [90]. Among these mutation sites, EGFR mutations including deletions in the exon 19 and L858R substitution in the exon 21 are the most common [89], so we focused on the resistance to EGFR tyrosine kinase inhibitors (EGFR-TKIs) in the present study. EGFR-TKIs are a class of small-molecule inhibitors that specifically target the tyrosine kinase domain of EGFR, thereby blocking the downstream signaling pathways involved in cell proliferation and survival [91, 92]. Currently, EGFR-TKIs used in clinical practice include first-generation (gefitinib and erlotinib), second-generation (afatinib), and third-generation (osimertinib) drugs. The clinical trial and population mortality rates both suggested that EGFR-TKIs improved the prognosis of patients with NSCLC, especially in early-stage treatment [5, 93].

Among the lncRNAs associated with targeted therapy, the majority still exert their effects through acting as miRNA sponges. Cancer susceptibility candidate 9 (CASC9) is located in a gene desert on human chromosome 8q21.11 [94], overexpressed in patients with NSCLC, and associated with resistance to gefitinib and unfavourable prognosis [95]. Overexpressed CASC9 upregulates FOXO3 expression by sponging miR-195-3p, and in turn, FOXO3 accelerates CASC9 expression by combining with CASC9 promoter, the feedback loop accelerating NSCLC gefitinib resistance [95]. LINC00460 has seven transcripts and is located on human chromosome 13q33.2 [96]. Its level is increased in NSCLC tissues, correlated with resistance to gefitinib and poor prognosis [97]. The distribution of LINC00460 is mainly in the cytoplasm [97]. LINC00460 sponges miR-769-5p to promote EGFR expression, which ultimately enhances resistance to gefitinib in NSCLC [97]. In LUAD, LINC00460 also acts as a ceRNA for miR-149-5p to facilitate IL-6 production, thereby inducing gefitinib resistance [98]. Previous research reported that IL-6 activated JAK/STAT3 or AKT signaling pathway, therefore inducing epithelial-mesenchymal transition (EMT) and low response to EGFR-TKIs [99, 100]. The overexpression of

Table 1 NSCLC vs. Healthy Control/Cisplatin-resistant vs. Cisplatin-sensitive

lncRNA	Chromosomal localization	Subcellular localization	Expression direction	Pathway	Subtype	Prognostic analysis	Xenograft	Study
GAS5	1q25	nucleus	↙	miR-217/LHPP	-	-	√	Yang,2021 [69]
TUG1	22q12.2	nucleus	↙	miR-221/PTEN	-	√	√	Guo,2019 [70]
NORAD	20q11.23	both in the cytoplasm and nucleus	↗	miR-129-1-3p/SOX4	-	√	-	Huang,2020 [71]
TATDN1			↗	miR-451/TRIM66	-	√	√	Wang,2019 [72]
LUCAT1	5q14.3 antisense chain	cytoplasm	↗	miR-514a-3p/ULK1	-	-	√	Shen,2020 [73]
TP73-AS1	1q36	cytosol (predicted)	↗	miR-34a-5p/TRIM29	-	√	-	Luo,2020 [74]
LINC01140	1p22.3	cytoplasm	↙	miR-4742-5p/TACC1	-	-	-	Wang,2022 [75]
PVT1	8q24	cytoplasm	↗	miR-216b/Beclin-1	-	√	√	Chen,2019 [76]
LINC00221		cytoplasm (predicted)	↗	miR-519a/ZBTB5	-	√	-	Tang,2019 [77]
LINC00511		cytoplasm	↗	miR-625/LRRC8E	-	-	-	Liu,2022 [78]
LINC00852		cytoplasm (predicted)	↗	hsa-miR-145-5p/KLF4	-	√	√	Tuo,2021 [79]
FOXD3-AS1	1p31.3	exosome	↗	miR-127-3p/MDM2	-	-	√	Zeng,2020 [80]
FOXD2-AS1	1p33	cytoplasm	↗	miR-185-5p/SIX1	-	-	√	Ge,2019 [81]
MEG3	14q32.3	nucleus	↙	miR-21-5p/SOX7	-	-	√	Wang,2017 [82]
NNT-AS1	5p12	cytoplasm	↗	miR-1236-3p/ATG7	-	-	√	Wang,2020 [83]
LINC00485	12q23.2	cytoplasm	↗	miR-195/CHEK1	LUAD	-	-	Zuo,2019 [84]

prostate cancer-associated transcript (PCAT) 6 results in the upregulation of IFNAR2 expression through sponging miR-326, thereby conferring gefitinib resistance in NSCLC [101]. In LUAD, the down-regulation of SNHG5 expression leads to reduction of CASP1 by means of miR-377 sponging, consequently inducing acquired resistance to gefitinib [102]. Overexpressed RP11-89K21.1 induces upregulation of RHPN2 expression by sponging miR-146a/b-5p, RHPN2 further activating ROCK pathway which promotes cell proliferation and enhancing gefitinib resistance in LUAD [103]. The MALAT1/miR-197-3p/p120 pathway mentioned earlier is also associated with gefitinib resistance [60].

Aside from the aforementioned investigations, the subsequent lncRNAs have been implicated in resistance to EGFR-TKIs in NSCLC as follows. CASC9 represses DUSP1 expression through recruiting EZH2 to the promoter region of DUSP1 and induces H3K27 trimethylation, ultimately activating ERK signaling pathway to drive NSCLC cell proliferation, invasion, migration and contributing to acquired resistance to gefitinib in NSCLC [104]. SOX2-OT can influence erlotinib resistance by regulating the PI3K/AKT and ERK signaling pathway [68]. SNHG17 is located on human chromosome 20, with a full length of 1186 bp [105], mainly distributed in the nucleus and elevated in gefitinib-resistant LUAD [106]. Overexpressed METTL3 increases the m6A modification of SNHG17 and enhances the stability of SNHG17 [106]. In turn, SNHG17 recruits EZH2 to the large tumor suppressor kinase 2 (LATS2) promoter and EZH2 inhibits LATS2 expression through H3K27 trimethylation, therefore decreasing E-cadherin expression, upregulating N-cadherin, Vimentin and Snail levels, promoting LUAD EMT and resistance to gefitinib [106]. Transcribed from an intergenic region of human chromosome 7, LINC01510 is upregulated in NSCLC tissues and associated with poor prognosis [91]. The level of LINC01510 is regulated by KMT5C that is low-expressed in NSCLC [92]. KMT5C induces H4K20 trimethylation modification present within the gene body of LINC01510 to inhibit the expression of LINC01510 [92]. Moreover, LINC01510 is a positive transcriptional regulator of MET [92]. Thus, loss of KMT5C increases LINC01510 and MET levels, consequently conferring erlotinib resistance [92]. Other than erlotinib, MET overexpression is a leading factor to acquired resistance to Osimertinib [107].

In summary, the above studies have elucidated how various lncRNAs are involved in the development and progression of EGFR-TKI resistance in NSCLC through the regulation of different molecular pathways (Fig. 3). Some lncRNAs, such as CASC9, LINC00460, and PCAT6, sponge miRNA inhibitors to upregulate the expression of oncogenes (e.g., FOXO3, EGFR, IFNAR2), thereby promoting tumor cell proliferation, survival, and the acquisition of EGFR-TKI resistance. Other lncRNAs, like SNHG17, recruit the EZH2 methyltransferase to suppress the expression of tumor suppressor genes (e.g., LATS2), inducing the EMT process and

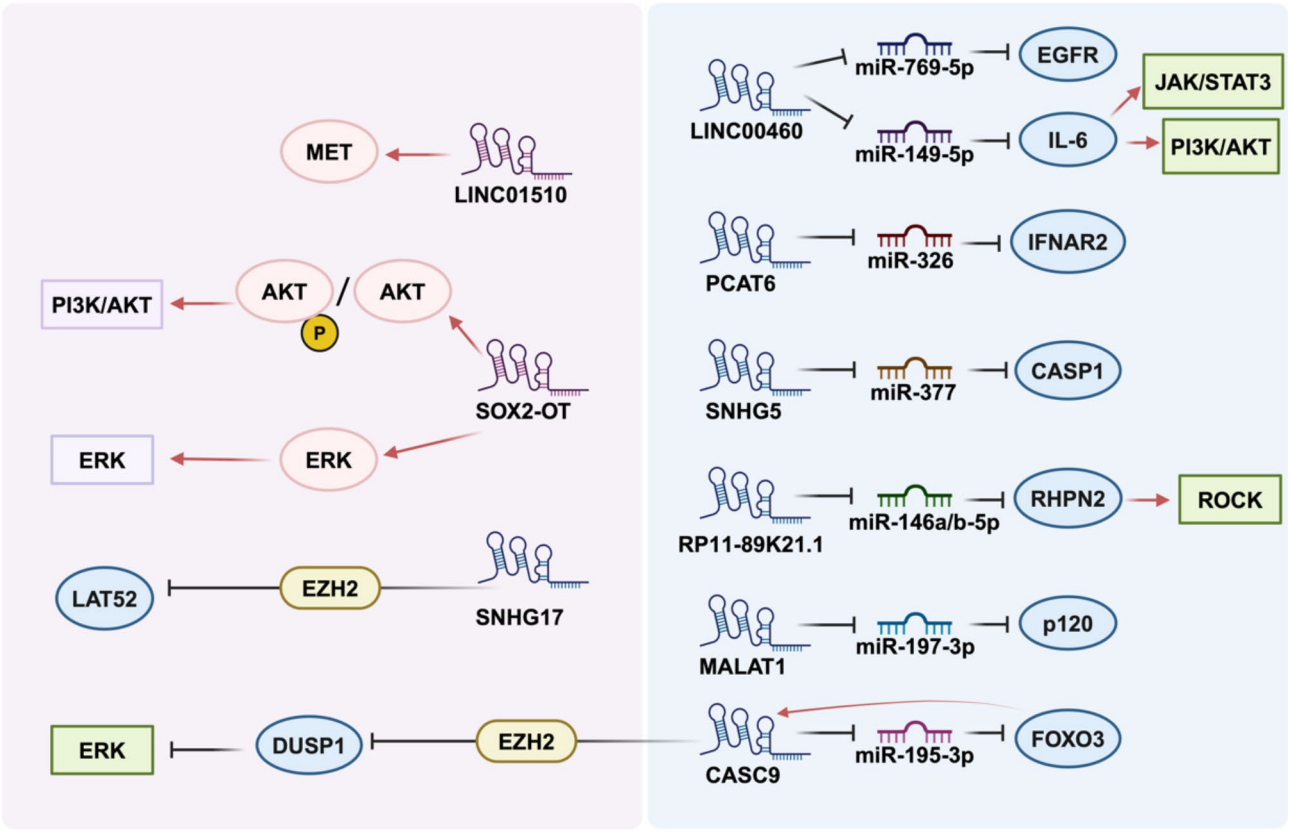

Fig. 3 LncRNAs Related to EGFR-TKIs Resistance. LINC00460, PCAT6, SNHG5, RP11-89K21.1, MALAT1, and CASC9 regulate the expression of downstream proteins or affect the stability of downstream proteins through the ceRNA network. LINC01510, SNHG17, SOX2-OT, and CASC9 directly regulate the expression of downstream proteins, among which SNHG17 and CASC9 exert their functions through EZH2. Red arrows represent the promotion of expression or increase in stability, while black arrows represent the inhibition of expression or decrease in stability. Created in BioRender. Shen, Z. (2024) BioRender.com/r42n471

ultimately leading to EGFR-TKI drug resistance. Additionally, lncRNAs such as RP11-89K21.1 and LINC01510 promote EGFR-TKI resistance through the activation of the ROCK and MET pathways, respectively. These findings provide new insights into the molecular mechanisms underlying EGFR-TKI resistance in NSCLC and lay the foundation for developing novel lncRNA-targeted therapeutic strategies. However, as research on lncRNAs in the field of targeted therapy for NSCLC is relatively new, only a few lncRNAs and their mechanisms of action are currently known. Future studies are needed to comprehensively elucidate the regulatory networks and specific functions of lncRNAs in this process.

In addition to EGFR mutations, clinically utilized targets also include ALK (crizotinib, alectinib, ceritinib, brigatinib, lorlatinib, ensartinib) and ROS1 (crizotinib, entrectinib), among others. However, there are relatively few studies on the resistance of lncRNAs to these drugs. Yang et al. reported that silencing HOTAIR can reduce the phosphorylation of the kinase ULK1, which is crucial in autophagy, inhibit the viability of NSCLC cells, and promote apoptosis, thereby enhancing the sensitivity of NSCLC cells to crizotinib [108].

LncRNAs related with radiotherapy

Radiotherapy plays a vital role in the treatment of NSCLC. For early-stage NSCLC patients who are not suitable for surgery, radiotherapy is their optimal treatment option, while for cases with metastases, a combination of chemotherapy or immunotherapy is generally adopted [109]. Over the past two decades, significant breakthroughs have been achieved in radiotherapy, including stereotactic ablative body radiotherapy and intensity-modulated radiotherapy, which reducing radiation toxicity to normal tissues while ensuring treatment efficacy.

Certain lncRNAs directly regulate downstream gene expression, thereby affecting radiosensitivity. Located on human chromosome 8q24 [110], PCAT1 is overexpressed in NSCLC tissues and associated with poor prognosis [111]. PCAT1 upregulates SOX2 expression by directly binding to SOX2 promoter, while SOX2 suppresses cyclic GMP-AMP synthase (cGAS) expression

by binding to cGAS promoter [111]. Thus, PCAT1 overexpression inhibits the activation of cGAS/stimulator of interferon genes (STING) pathway. In vivo experiments showed that PCAT1 downregulation promotes radiosensitivity in NSCLC, while SOX2 overexpression attenuates CD8+T-cell-mediated anti-tumor immune response [111]. The cGAS/STING pathway promotes the IFN-I production [112], which induces CD8+T cell-mediated anti-tumor immune response [113]. DNA damage caused by radiation therapy can activate the cGAS/STING pathway, which is one of the important anti-tumor effects of radiation therapy [114]. PCAT1 Overexpression inhibits the activation of cGAS/STING pathway, and thus reduces the radiosensitivity of NSCLC. Upregulation of IFN-β in NSCLC cells caused by SOX2 silencing also confirmed the mechanism [111]. Besides, SOX2 silencing also led to increased dsDNA accumulation [111], which suggests its function of maintaining DNA stability. Colorectal neoplasia differentially expressed (CRNDE) induce H3K27me3 modification and suppress p21 expression through recruitment EZH2 to p21 promoter, therefore inhibiting G1 phase arrest, apoptosis and increasing radioresistance in LUAD [115].

Furthermore, the most abundant lncRNAs still exert their function as ceRNAs. With 91 kb in full length, KCNQ1 opposite strand/antisense transcript 1 (KCNQ1OT1) is localized on chromosome 11p15.5 [116]. KCNQ1OT1 is upregulated in LUAD samples, and associated with poor response to concurrent chemoradiotherapy and poor prognosis. KCNQ1OT1 upregulates autophagy-related (ATG) 5 and ATG12 expression by sponging miR-372-3p [117]. ATG5 and ATG12 are essential in autophagosome formation [118], and autophagy leads to therapeutic resistance [119]. In this way, KCNQ1OT1 overexpression promotes autophagy and confers radioresistance in LUAD. Except for the miR-372-3p/ATG5/ATG12 axis, in LUSC, upregulated KCNQ1OT1 also targets the miR-491-5p/TPX2/RNF2 axis, and enhances resistance to radiotherapy [120]. Cytoskeleton regulator (CYTOR), also known as LINC00152, is an 828-bp lncRNA mapped to chromosome 2p11.2. CYTOR is overexpressed in NSCLC tissues, and associated with resistance to radiotherapy and poor prognosis [121]. CYTOR upregulates PTMA expression as miR-206 sponge, and reduces NSCLC radiosensitivity [121]. Another study found CYTOR also targeted miR-195 to reduce NSCLC radiosensitivity. Overexpressed CYTOR upregulates miR-195 targets expression, including CARM1, YAP, GDPD5 and WNT3A [122]. Therefore, variations in CYTOR levels can impact multiple pathways, and these downstream targets were proved to induce progression and radioresistance in other cancers [123–126]. Overexpressed hepatocyte nuclear factor 1 α antisense RNA 1 (HNF1A-AS1) upregulates MAP2K4 expression via sponging miR-92a-3p, and MAP2K4 induces phosphorylation of JNK, and that confers radioresistance in NSCLC [127]. In LUAD, overexpressed LINC00461 upregulates HOXA10 expression by sponging miR-195, therefore inducing proliferation, migration and radioresistance [128]. Overexpressed SBF2 antisense RNA 1 (SBF2-AS1) upregulates MBNL3 through sponging miR-302a, and down-regulation of SBF2-AS1 or up-regulation of miR-302a could reduce the radioresistance of NSCLC cells, but the function of MBNL3 was not defined in the study [129]. Overexpressed protein tyrosine phosphatase, receptor type G antisense RNA 1 (PTPRG-AS1) upregulates TCF4 expression via sponging miR-200c-3p, therefore reducing the radiosensitivity in NSCLC [130]. Overexpressed forkhead box D1 antisense RNA 1 (FOXD1-AS1) upregulates PUM1 expression as miR-4801 sponge, therefore promoting radioresistance in LUSC [131].

Overall, these studies have revealed multiple mechanisms by which lncRNAs modulate radiosensitivity in NSCLC, including regulating gene expression, inducing EMT, promoting autophagy, and impacting various signaling pathways such as cGAS/STING, PI3K/AKT, JNK, and Wnt/β-catenin (Fig. 4). Some lncRNAs, like PCAT1 and CRNDE, directly regulate the expression of key genes involved in DNA damage response and cell cycle control, while others, such as KCNQ1OT1 and CYTOR, function as ceRNAs to modulate the expression of autophagy-related and radioresistance-associated genes. These findings have expanded our understanding of the regulatory roles of lncRNAs in radiotherapy resistance and provided potential therapeutic targets for improving the efficacy of radiotherapy in NSCLC treatment. However, given the complexity and diversity of lncRNA functions, further investigations are warranted to unravel their intricate regulatory networks and identify clinically relevant lncRNAs as potential biomarkers or therapeutic targets. Moreover, studies on the resistance mechanisms associated with the combination of radiotherapy and other treatment modalities (such as chemotherapy, targeted therapy, and immunotherapy) may provide new insights for enhancing the overall treatment efficacy in NSCLC.

RNA therapy to reduce treatment resistance

Treatment resistance is a pivotal factor contributing to poor prognosis in NSCLC patients, and RNA therapy can address this issue to a certain extent. RNA therapy inhibits tumor progression and drug resistance by targeted delivery of small RNAs to tumor tissues and suppressing specific mRNA expression, encompassing antisense oligonucleotides (ASOs), miRNAs, and short interfering RNAs (siRNAs). This delivery process relies on nanoparticle matrices, which link small RNAs to nanoparticles through electrostatic attachment or covalent conjugation,

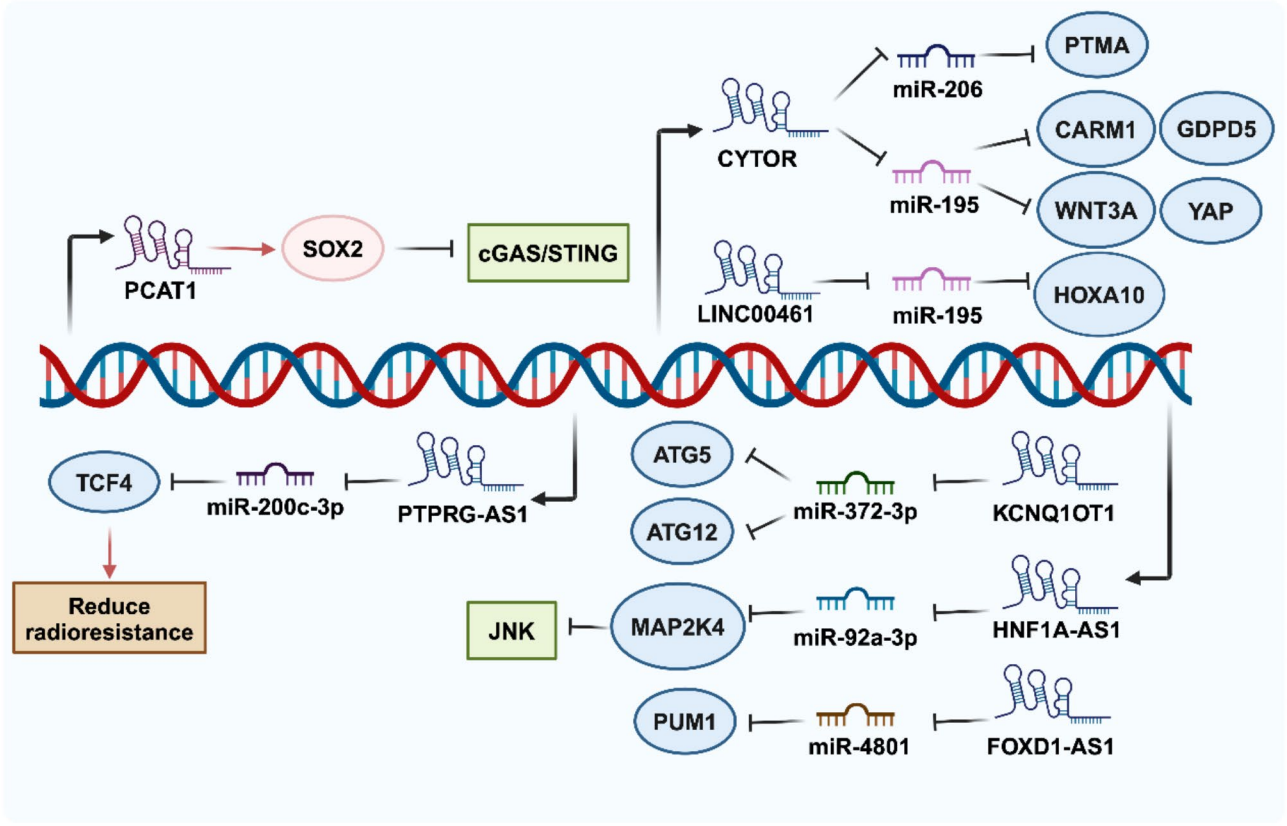

Fig. 4 LncRNAs Related to Radiotherapy. CYTOR, LINC00461, KCNQ1OT1, HNF1A-AS1, FOXD1-AS1, PTPRG-AS1 regulate the expression of downstream proteins or affect the stability of downstream proteins through the ceRNA network. PCAT1 directly regulate the expression of the downstream protein. Red arrows represent the promotion of expression, while black arrows represent the inhibition of expression or decrease in stability. Created in BioRender. Shen, Z. (2024) BioRender.com/x86i614

and can attach this complex to drug molecules [132]. Furthermore, nanoparticles protect small RNAs from degradation in vivo [132], an effect that can also be achieved through different chemical modifications, such as the introduction of fluoro, amino, or O-methyl groups at the 2' position of the ribose [133]. Currently, several studies have employed RNA therapy to improve resistance to chemotherapy, targeted therapy, and radiotherapy in NSCLC.

Nascimento et al. used chitosan nanoparticles to deliver mitotic arrest deficient-2 (Mad2) siRNA, finding a significant reduction in DDP resistance [134]. Additionally, Nascimento et al. conjugated the aforementioned complex with a 12-amino acid peptide targeting EGFR, which is often overexpressed in NSCLC tissues, thereby enhancing delivery efficiency [135]. Mattheolabakis et al. synthesized nanoparticles by conjugating hyaluronic acid (HA) with poly(ethyleneimine) or poly(ethylene glycol) for the delivery of survivin-siRNA, discovering a substantial decrease in the IC value of DDP [136]. To further overcome DDP resistance, Mattheolabakis et al. combined Pt(IV) with various lipid molecules to form platinum derivatives, among which CDDP-C8, combined with octanoic anhydride, exhibited the best efficacy, and HA-survivin-siRNA similarly significantly enhanced the efficacy of CDDP-C8 [136]. Chen et al. found that LINC00173.v1 is overexpressed in LUSC and promotes tumorigenesis and metastasis through the ceRNA network. They constructed ASOs targeting LINC00173.v1 and found that this molecule could increase DDP sensitivity in tumor cells and mice [137]. The aforementioned miR-let-7i is suppressed in DDP-resistant patients, and in fact, decreased expression of other miR-let-7 family members is also correlated with drug resistance. Reduced miR-let-7b expression leads to paclitaxel and gemcitabine resistance [138], decreased expression of the miR-let-7 family results in gefitinib resistance [139], lower miR-let-7a levels are associated with reduced radiosensitivity [140], and transfection with the miR-let-7 family can reverse drug resistance [138, 139]. Furthermore, Esposito et al. combined miR-let-7 g with an aptamer (GL21.T) targeting Axl, enabling in vivo targeted delivery to tumor tissues expressing Axl [141]. Cortez et al. used lipid nanoparticles to deliver miR-200 C, enhancing mouse sensitivity to radiotherapy. However, it should be noted that this method had poor targeting efficiency, with

increased miR-200 C levels observed in multiple tissues, including the liver and brain [142].

Beyond the aforementioned methods of delivering a single RNA at a time, studies have also achieved the simultaneous delivery of two RNAs. Ganesh et al. constructed an HA-based nanosystem to co-deliver survivin-siRNA and Bcl-2-siRNA, reversing DDP resistance [143]. Ganesh et al. demonstrated that this HA nanosystem can target CD44, which is highly expressed in lung cancer tissues, thereby achieving targeted delivery and cellular internalization of siRNA [144]. Taratula et al. used mesoporous silicon nanoparticles to deliver MRP1-siRNA and Bcl-2-siRNA, and conjugated this complex with LHRH to improve targeting efficiency. The authors found that this system could enhance sensitivity to DDP and doxorubicin. Notably, inhalation administration resulted in more concentrated drug delivery to lung tissues compared to intravenous injection [145].

Despite the crucial roles of lncRNAs in the initiation, growth, metastasis, and drug resistance of NSCLC, there are currently no studies on RNA therapy targeting or utilizing lncRNAs. We believe this is primarily due to the much larger molecular weight of lncRNAs compared to the aforementioned ASOs, miRNAs, and siRNAs, making it difficult for them to bind to nanoparticles for delivery and cellular internalization. Additionally, individual lncRNAs encompass multiple downstream targets, meaning that using lncRNA for therapy may cause unpredictable side effects and make it challenging to target specific genes.

Conclusions

Through literature review, we have found that the aberrant expression of multiple lncRNAs is associated with poor treatment outcomes in NSCLC patients (Fig. 5). The aberrant expression of the lncRNAs investigated in these studies is not only observed between treatment-resistant and non-resistant groups but also between tumor and tumor-adjacent tissues, as well as between diagnosed patients and the normal population.

There are various pathways through which lncRNAs regulate treatment resistance, including ceRNA networks, regulation of protein nuclear translocation, recruitment of EZH2 to regulate gene expression, and direct regulation of protein expression and phosphorylation. CeRNA networks account for the majority, where lncRNAs in cells form complexes by binding to miRNAs, thereby blocking the binding of miRNAs to their target mRNAs, enabling these target mRNAs to escape miRNA-mediated degradation or inhibition mechanisms. The second most common pathway is through the recruitment of EZH2 to regulate gene expression,

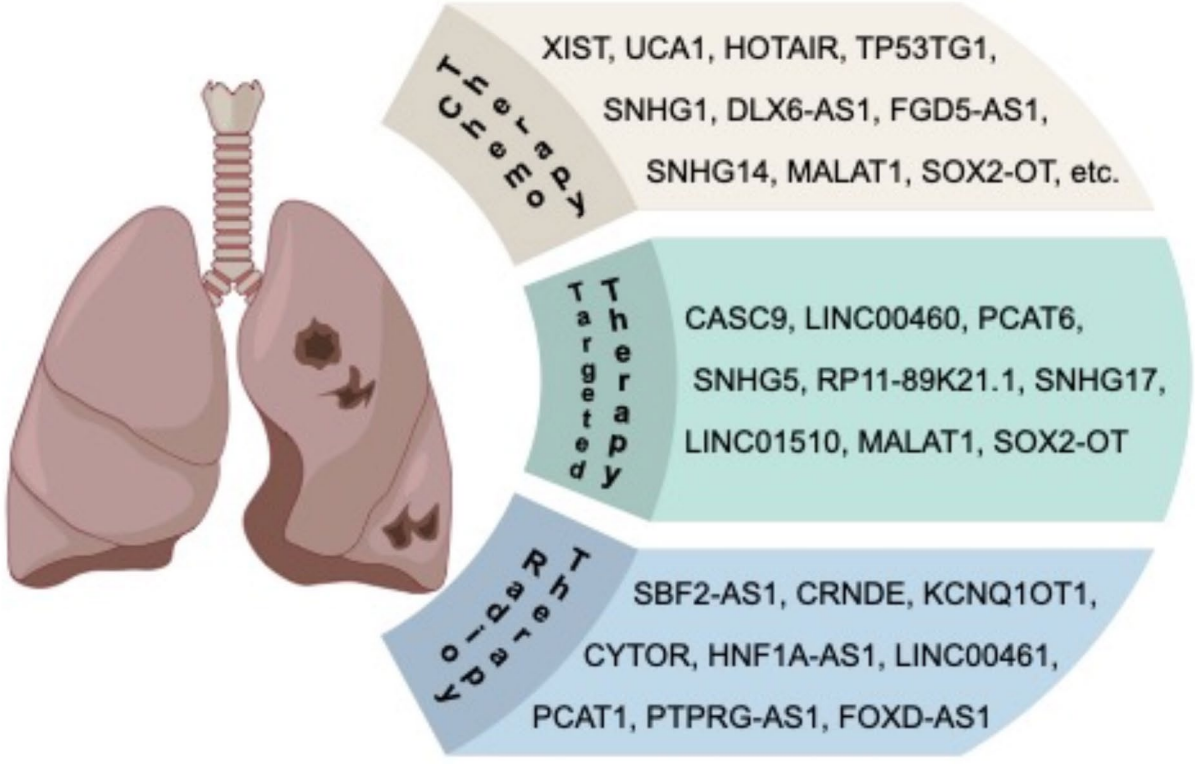

Fig. 5 LncRNAs related to the therapeutic effect of NSCLC. XIST, UCA1, HOTAIR, TP53TG1, SNHG1, DLX6-AS1, FGD5-AS1, SNHG14, MALAT1, and SOX2-OT are associated with chemotherapy. CASC9, LINC00460, PCAT6, SNHG5, RP11-89K21.1, SNHG17, LINC01510, MALAT1, and SOX2-OT are associated with targeted therapy. SBF2-AS1, CRNDE, KCNQ1OT1, CYTOR, HNF1A-AS1, LINC00461, PCAT1, PTPRG-AS1, and FOXD-AS1 are related to radiotherapy

where lncRNAs recruit EZH2 to the promoter sequence of specific genes, inhibiting gene expression through methylation at specific sites [63, 65, 104, 106, 115]. It is noteworthy that lncRNAs are involved in multiple signaling pathways when modulating therapeutic resistance (Fig. 6).

When analyzing the potential biological effects of lncRNAs, subcellular localization is a good initial indicator [12]. For example, lncRNAs localized in the cytoplasm are likely to be involved in ceRNA networks, while lncRNAs localized in the nucleus may interact with specific chromosomal regions. We found that many studies followed this research approach and had significant similarities in subsequent functional experiments. The most common functional experiments include using CCK-8 assays to measure cell viability and proliferation after drug or radiation treatment, clone formation assays, flow cytometry to measure cell apoptosis, and detection

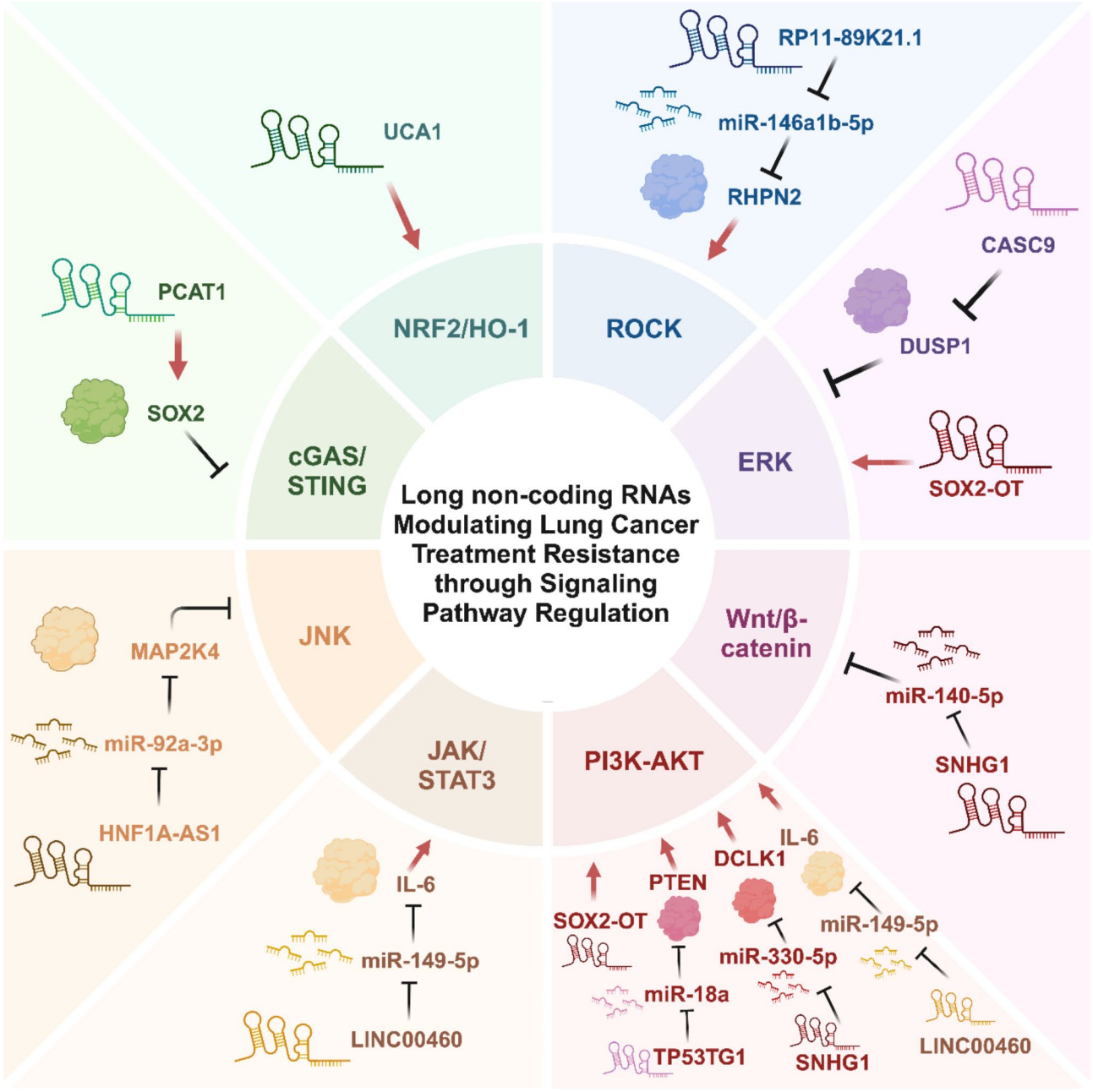

Fig. 6 LncRNAs Influence Therapeutic Resistance in NSCLC by Regulating Signaling Pathways. Specifically, RP11-89K21.1 regulates the ROCK pathway, CASC9 and SOX2-OT regulate the ERK pathway, SNHG1 regulates the Wnt/β-catenin pathway, LINC00460, SNHG1, TP53TG1, and SOX2-OT regulate the PI3K-AKT pathway, LINC00460 also regulates the JAK/STAT3 pathway, HNF1A-AS1 regulates the JNK pathway, PCAT1 regulates the cGAS/STING pathway, and UCA1 regulates the NRF2/HO-1 pathway. Created in BioRender. Shen, Z. (2024) BioRender.com/e72m039

of specific signaling pathway protein phosphorylation levels. In clone formation assays, crystal violet staining or Edu staining can be used, and we believe that these two methods are equivalent in terms of conclusions. Due to the similarity in experimental design, most of the conclusions obtained are consistent.

Experimental evidence has demonstrated the significant role of lncRNAs in reducing the effectiveness of NSCLC treatment, indicating their potential as therapeutic targets. However, we did not find any literature studying the specific proportion of aberrant expression of lncRNAs in NSCLC patients, which is a prerequisite for the development and application of targeted lncRNA therapies. In addition, lncRNAs also have the potential to serve as biomarkers for diagnosis, efficacy, and prognosis. However, due to the abundance of lncRNAs that affect treatment outcomes, screening and weighting of the aforementioned lncRNAs are expected to be necessary for clinical applications.

Although current research on the therapeutic effects of lncRNA regulation is relatively comprehensive, there is still limited research on the upstream regulation of lncRNA. According to the selected articles in this study, regulation at the lncRNA level includes transcriptional and post-transcriptional modifications. Transcriptional regulation involves H3K4me1 modification in the promoter region [54] and its binding with FOXO3 [95], as well as KMT5C-mediated H4K20me3 modification upstream of the gene [92]. Post-transcriptional modification includes METTL3-mediated m6A modification of SNHG17, which increases the stability of lncRNA [106]. Notably, RNA m6A modification requires coordination between methyltransferases, m6A binding proteins, and demethylases. METTL3 belongs to the methyltransferase, while the roles of the other two factors in regulating drug-resistant lncRNA levels await further investigation.

In summary, various lncRNAs have a significant impact on the therapeutic effects of NSCLC, and the current research on their downstream mechanisms is relatively detailed. Therefore, we believe that future research should focus more on the upstream regulatory mechanisms and the proportion of specific lncRNA aberrant expression in patients, in order to fully tap into their potential as therapeutic targets or clinical biomarkers.

While the current studies have unraveled the involvement of various lncRNAs in regulating radiotherapy resistance in NSCLC, several aspects warrant further investigation to fully elucidate their clinical significance and underlying regulatory mechanisms. Firstly, large-scale case-control studies are needed to evaluate the expression levels of these lncRNAs across different stages, pathological subtypes of NSCLC, and their associations with disease prognosis and radiotherapy efficacy. Such analyses would shed light on the potential of these lncRNAs as early diagnostic biomarkers or predictors of radiosensitivity, paving the way for the development of lncRNA-based diagnostic kits or targeted therapeutics. most existing studies have focused on the downstream mechanisms of lncRNAs, while their upstream regulatory networks remain largely unexplored. Future efforts should elucidate the molecular events influencing lncRNA transcription, processing, and stability, such as transcription factors, chromatin remodeling, RNA-binding proteins, and RNA methylation modifications. Unraveling these regulatory networks may unveil novel strategies for precise modulation of lncRNA levels. As NSCLC patients often receive multimodal treatments including chemotherapy, targeted therapy, and immunotherapy, it is imperative to investigate the interplay between lncRNAs and resistance mechanisms associated with these diverse therapeutic modalities. Exploring lncRNA expression profiles and mechanisms under different treatment regimens could provide valuable insights for enhancing the overall treatment efficacy.

Furthermore, most studies have treated lncRNAs as individual regulators, but the complex phenomenon of treatment resistance is unlikely to be explained by a single lncRNA. Adopting a systems biology approach by integrating expression and regulatory data of multiple lncRNAs and protein-coding genes could unveil cooperative networks and elucidate the underlying molecular mechanisms contributing to resistance.Lastly, current research heavily relies on known lncRNAs, but a myriad of potential regulatory lncRNAs may remain undiscovered in tumors. Novel bioinformatics pipelines, coupled with multi-omics data (e.g., RNA-seq, DNA methylation arrays), could enable the identification of lncRNAs specifically expressed in tumor or resistant tissues, providing new targets for functional characterization.

In conclusion, while significant progress has been made in understanding the roles of lncRNAs in NSCLC radiotherapy resistance, vast unexplored territories remain, necessitating interdisciplinary collaborations and systems biology approaches. Innovative discoveries in this field are anticipated to unveil the clinical implications and intricate regulatory networks of lncRNAs, ultimately contributing to improved therapeutic strategies for NSCLC.

Abbreviations

NSCLC	Non-small cell lung cancer
LUAD	Lung adenocarcinoma
LUSC	Lung squamous cell carcinoma
EGFR	Epidermal growth factor receptor
ARMS	Amplification refractory mutation system
FISH	Fluorescence in situ hybridization

LncRNA	Long non-coding RNA
EZH2	Enhancer of zeste homlog 2
DDP	Cisplatin
XIST	X inactive-specific transcript
UCA1	Urothelial carcinoma associated 1
ERCC1	Excision repair cross-complementing 1
ceRNA	Competing endogenous RNA
ATG	Autophagy associated gene
HOTAIR	HOX antisense intergenic RNA
TP53TG1	Tumor protein 53 target gene 1
SNHG	Small nucleolar RNA host gene
AKT	Protein kinase B
DLX6-AS1	Distal-less homeobox 6 antisense 1
FGD5-AS1	FYVE RhoGEF and PH domain containing 5 antisense 1
MALAT1	Metastasis-associated lung adenocarcinoma transcript 1
SOX2-OT	SRY-box transcription factor 2 overlapping transcript
ERK	Extracellular signal-regulated kinase
HCG11	HLA Complex Group 11
MET	Mesenchymal-epithelial transition factor
EGFR-TKI	EGFR tyrosine kinase inhibitor
CASC9	Cancer susceptibility candidate 9
EMT	Epithelial-mesenchymal transition
PCAT	Prostate cancer-associated transcript
LATS2	Large tumor suppressor kinase 2
cGAS	Cyclic GMP-AMP synthase
STING	Stimulator of interferon genes
CRNDE	Colorectal neoplasia differentially expressed
KCNQ1OT1	KCNQ1 opposite strand/antisense transcript 1
CYTOR	Cytoskeleton regulator
HNF1A-AS1	Hepatocyte nuclear factor 1 α antisense RNA 1
SBF2-AS1	SBF2 antisense RNA 1
PTPRG-AS1	Protein tyrosine phosphatase, receptor type G antisense RNA 1
FOXD1-AS1	Forkhead box D1 antisense RNA 1
ASO	Antisense oligonucleotide
siRNA	Short interfering RNA
Mad2	Mitotic arrest deficient-2
HA	Hyaluronic acid

Acknowledgements
We would like to thank the Lam Chung Nin Foundation for Systems Biomedicine for their kindly support.

Author contributions
Conceptualization and design: YY. Writing of first draft: XG. Figures and tables: XG and ZS. Final editing of text: ZS and YY.All authors reviewed the manuscript.

Funding
This study was supported by grants including the National Key Research and Development Program of China (2021YFA1300601); National Natural Science Foundation of China (grant 82030081); the Lam Chung Nin Foundation for Systems Biomedicine.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent for participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 29 May 2024 / Accepted: 29 October 2024
Published online: 09 November 2024

References

1. Siegel RL, Miller KD, Wagle NS, Jemal A, Cancer statistics. 2023. CA: a cancer journal for clinicians. 2023;73(1):17–48.
2. Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. Cancer J Clin. 2024;74(1):12–49.
3. Chen P, Liu Y, Wen Y, Zhou C. Non-small cell lung cancer in China. Cancer Commun (London England). 2022;42(10):937–70.
4. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2021. Cancer J Clin. 2021;71(1):7–33.
5. Howlader N, Forjaz G, Mooradian MJ, Meza R, Kong CY, Cronin KA, et al. The effect of advances in lung-Cancer treatment on Population Mortality. N Engl J Med. 2020;383(7):640–9.
6. Miller M, Hanna N. Advances in systemic therapy for non-small cell lung cancer. BMJ (Clinical Res ed). 2021;375:n2363.
7. Preoperative chemotherapy for. Non-small-cell lung cancer: a systematic review and meta-analysis of individual participant data. Lancet (London England). 2014;383(9928):1561–71.
8. Li W, Lyu Y, Wang S, Zhou X, Ma J, Xu C, et al. Trends in Molecular Testing of Lung Cancer in Mainland People's Republic of China over the Decade 2010 to 2019. JTO Clin Res Rep. 2021;2(4):100163.
9. [Current status of postoperative. Pathological diagnosis of lung cancer in China: a multicenter big data study]. Zhonghua Bing Li Xue Za Zhi = Chin J Pathol. 2021;50(8):882–90.
10. Cheng Y, Wang Y, Zhao J, Liu Y, Gao H, Ma K, et al. Real-world EGFR testing in patients with stage IIIB/IV non-small-cell lung cancer in North China: a multicenter, non-interventional study. Thorac cancer. 2018;9(11):1461–9.
11. Li Y, Xu H, Su S, Ye J, Chen J, Jin X, et al. Clinical validation of a highly sensitive assay to detect EGFR mutations in plasma cell-free DNA from patients with advanced lung adenocarcinoma. PLoS ONE. 2017;12(8):e0183331.
12. Hombach S, Kretz M. Non-coding RNAs: classification, Biology and Functioning. Adv Exp Med Biol. 2016;937:3–17.
13. Botti G, Scognamiglio G, Aquino G, Liguori G, Cantile M, LncRNA. HOTAIR Tumor Microenvironment: What Role? Int J Mol Sci. 2019;20(9).
14. Peng WX, Koirala P, Mo YY. LncRNA-mediated regulation of cell signaling in cancer. Oncogene. 2017;36(41):5661–7.
15. Huang Z, Lei W, Hu HB, Zhang H, Zhu Y. H19 promotes non-small-cell lung cancer (NSCLC) development through STAT3 signaling via sponging miR-17. J Cell Physiol. 2018;233(10):6768–76.
16. Nie FQ, Sun M, Yang JS, Xie M, Xu TP, Xia R, et al. Long noncoding RNA ANRIL promotes non-small cell lung cancer cell proliferation and inhibits apoptosis by silencing KLF2 and P21 expression. Mol Cancer Ther. 2015;14(1):268–77.
17. Lu T, Wang Y, Chen D, Liu J, Jiao W. Potential clinical application of lncRNAs in non-small cell lung cancer. OncoTargets Therapy. 2018;11:8045–52.
18. Yao X, Wang T, Sun MY, Yuming Y, Guixin D, Liu J. Diagnostic value of lncRNA HOTAIR as a biomarker for detecting and staging of non-small cell lung cancer. Biomarkers: biochemical indicators of exposure, response, and susceptibility to chemicals. 2022;27(6):526–33.
19. Wang M, Ma X, Zhu C, Guo L, Li Q, Liu M, et al. The prognostic value of long non coding RNAs in non small cell lung cancer: a meta-analysis. Oncotarget. 2016;7(49):81292–304.
20. Ricciuti B, Mencaroni C, Paglialunga L, Paciullo F, Crinò L, Chiari R, et al. Long noncoding RNAs: new insights into non-small cell lung cancer biology, diagnosis and therapy. Med Oncol (Northwood Lond Engl). 2016;33(2):18.
21. Quinn JJ, Chang HY. Unique features of long non-coding RNA biogenesis and function. Nat Rev Genet. 2016;17(1):47–62.
22. Wilusz JE, Freier SM, Spector DL. 3' end processing of a long nuclear-retained noncoding RNA yields a tRNA-like cytoplasmic RNA. Cell. 2008;135(5):919–32.
23. Wilusz JE, JnBaptiste CK, Lu LY, Kuhn CD, Joshua-Tor L, Sharp PA. A triple helix stabilizes the 3' ends of long noncoding RNAs that lack poly(A) tails. Genes Dev. 2012;26(21):2392–407.
24. Lubelsky Y, Ulitsky I. Sequences enriched in Alu repeats drive nuclear localization of long RNAs in human cells. Nature. 2018;555(7694):107–11.
25. Azam S, Hou S, Zhu B, Wang W, Hao T, Bu X, et al. Nuclear retention element recruits U1 snRNP components to restrain spliced lncRNAs in the nucleus. RNA Biol. 2019;16(8):1001–9.
26. Hacisuleyman E, Shukla CJ, Weiner CL, Rinn JL. Function and evolution of local repeats in the firre locus. Nat Commun. 2016;7:11021.
27. Shukla CJ, McCorkindale AL, Gerhardinger C, Korthauer KD, Cabili MN, Shechner DM et al. High-throughput identification of RNA nuclear enrichment sequences. EMBO J. 2018;37(6).

28. Zhang B, Gunawardane L, Niazi F, Jahanbani F, Chen X, Valadkhan S. A novel RNA motif mediates the strict nuclear localization of a long noncoding RNA. Mol Cell Biol. 2014;34(12):2318–29.
29. Statello L, Guo CJ, Chen LL, Huarte M. Gene regulation by long non-coding RNAs and its biological functions. Nat Rev Mol Cell Biol. 2021;22(2):96–118.
30. Melé M, Mattioli K, Mallard W, Shechner DM, Gerhardinger C, Rinn JL. Chromatin environment, transcriptional regulation, and splicing distinguish lincRNAs and mRNAs. Genome Res. 2017;27(1):27–37.
31. Xiang JF, Yin QF, Chen T, Zhang Y, Zhang XO, Wu Z, et al. Human colorectal cancer-specific CCAT1-L lncRNA regulates long-range chromatin interactions at the MYC locus. Cell Res. 2014;24(5):513–31.
32. Pirker R. Chemotherapy remains a cornerstone in the treatment of nonsmall cell lung cancer. Curr Opin Oncol. 2020;32(1):63–7.
33. Brown CJ, Ballabio A, Rupert JL, Lafreniere RG, Grompe M, Tonlorenzi R, et al. A gene from the region of the human X inactivation centre is expressed exclusively from the inactive X chromosome. Nature. 1991;349(6304):38–44.
34. Xu X, Zhou X, Chen Z, Gao C, Zhao L, Cui Y. Silencing of lncRNA XIST inhibits non-small cell lung cancer growth and promotes chemosensitivity to cisplatin. Aging. 2020;12(6):4711–26.
35. Wang XS, Zhang Z, Wang HC, Cai JL, Xu QW, Li MQ, et al. Rapid identification of UCA1 as a very sensitive and specific unique marker for human bladder carcinoma. Clin cancer Research: Official J Am Association Cancer Res. 2006;12(16):4851–8.
36. Li C, Fan K, Qu Y, Zhai W, Huang A, Sun X, et al. Deregulation of UCA1 expression may be involved in the development of chemoresistance to cisplatin in the treatment of non-small-cell lung cancer via regulating the signaling pathway of microRNA-495/NRF2. J Cell Physiol. 2020;235(4):3721–30.
37. Shi W, Ling L, Li C, Wu R, Zhang M, Shao F, et al. LncRNA UCA1 promoted cisplatin resistance in lung adenocarcinoma with HO1 targets NRF2/HO1 pathway. J Cancer Res Clin Oncol. 2023;149(3):1295–311.
38. Fu J, Pan J, Yang X, Zhang Y, Shao F, Chen J, et al. Mechanistic study of lncRNA UCA1 promoting growth and cisplatin resistance in lung adenocarcinoma. Cancer Cell Int. 2021;21(1):505.
39. Zhou J, Zhang S, Chen Z, He Z, Xu Y, Li Z. CircRNA-ENO1 promoted glycolysis and tumor progression in lung adenocarcinoma through upregulating its host gene ENO1. Cell Death Dis. 2019;10(12):885.
40. Planchard D, Olaussen KA, Soria JC. [ERCC1 and lung cancer]. Rev Mal Respir. 2010;27(4):387–94.
41. Sun J, Pan LM, Chen LB, Wang Y. LncRNA XIST promotes human lung adenocarcinoma cells to cisplatin resistance via let-7i/BAG-1 axis. Cell Cycle (Georgetown Tex). 2017;16(21):2100–7.
42. Sun W, Zu Y, Fu X, Deng Y. Knockdown of lncRNA-XIST enhances the chemosensitivity of NSCLC cells via suppression of autophagy. Oncol Rep. 2017;38(6):3347–54.
43. Hua G, Zeng ZL, Shi YT, Chen W, He LF, Zhao GF. LncRNA XIST contributes to Cisplatin Resistance of Lung Cancer cells by promoting Cellular Glycolysis through Sponging miR-101-3p. Pharmacology. 2021;106(9–10):498–508.
44. Rinn JL, Kertesz M, Wang JK, Squazzo SL, Xu X, Brugmann SA, et al. Functional demarcation of active and silent chromatin domains in human HOX loci by noncoding RNAs. Cell. 2007;129(7):1311–23.
45. Zhan Y, Abuduwaili K, Wang X, Shen Y, Nuerlan S, Liu C. Knockdown of long non-coding RNA HOTAIR suppresses Cisplatin Resistance, Cell Proliferation, Migration and Invasion of DDP-Resistant NSCLC cells by targeting miR-149-5p/Doublecortin-Like kinase 1 Axis. Cancer Manage Res. 2020;12:7725–37.
46. Xiao H, Liu Y, Liang P, Wang B, Tan H, Zhang Y, et al. TP53TG1 enhances cisplatin sensitivity of non-small cell lung cancer cells through regulating miR-18a/PTEN axis. Cell Bioscience. 2018;8:23.
47. Salmena L, Carracedo A, Pandolfi PP. Tenets of PTEN tumor suppression. Cell. 2008;133(3):403–14.
48. Tan AC. Targeting the PI3K/Akt/mTOR pathway in non-small cell lung cancer (NSCLC). Thorac cancer. 2020;11(3):511–8.
49. Sun Y, Wei G, Luo H, Wu W, Skogerbø G, Luo J, et al. The long noncoding RNA SNHG1 promotes tumor growth through regulating transcription of both local and distal genes. Oncogene. 2017;36(49):6774–83.
50. Shi SL, Zhang ZH. Long non-coding RNA SNHG1 contributes to cisplatin resistance in non-small cell lung cancer by regulating miR-140-5p/Wnt/β-catenin pathway. Neoplasma. 2019;66(5):756–65.
51. Xu X, Sun PL, Li JZ, Jheon S, Lee CT, Chung JH. Aberrant Wnt1/β-catenin expression is an independent poor prognostic marker of non-small cell lung cancer after surgery. J Thorac Oncology: Official Publication Int Association Study Lung Cancer. 2011;6(4):716–24.
52. Wang Y, Bai W, Wang M, Yu T, Zhang W, Long Non-Coding RNA, Brain Cytoplasmic. RNA 1 acts as an Oncogene and regulates cell proliferation and metastasis in Non-small Cell Lung Cancer. J Nanosci Nanotechnol. 2019;19(4):1978–85.
53. Ge P, Cao L, Zheng M, Yao Y, Wang W, Chen X. LncRNA SNHG1 contributes to the cisplatin resistance and progression of NSCLC via miR-330-5p/DCLK1 axis. Exp Mol Pathol. 2021;120:104633.
54. Zhao X, Wang J, Zhu R, Zhang J, Zhang Y. DLX6-AS1 activated by H3K4me1 enhanced secondary cisplatin resistance of lung squamous cell carcinoma through modulating miR-181a-5p/miR-382-5p/CELF1 axis. Sci Rep. 2021;11(1):21014.
55. He N, Xiang L, Chen L, Tong H, Wang K, Zhao J, et al. The role of long non-coding RNA FGD5-AS1 in cancer. Bioengineered. 2022;13(4):11026–41.
56. Zhu F, Niu R, Shao X, Shao X. FGD5–AS1 promotes cisplatin resistance of human lung adenocarcinoma cell via the miR–142–5p/PD–L1 axis. Int J Mol Med. 2021;47(2):523–32.
57. Sunshine J, Taube JM. PD-1/PD-L1 inhibitors. Curr Opin Pharmacol. 2015;23:32–8.
58. Jiao P, Hou J, Yao M, Wu J, Ren G. SNHG14 silencing suppresses the progression and promotes cisplatin sensitivity in non-small cell lung cancer. Biomed Pharmacotherapy = Biomedecine Pharmacotherapie. 2019;117:109164.
59. Zhang X, Hamblin MH, Yin KJ. The long noncoding RNA Malat1: its physiological and pathophysiological functions. RNA Biol. 2017;14(12):1705–14.
60. Yang T, Li H, Chen T, Ren H, Shi P, Chen M. LncRNA MALAT1 Depressed Chemo-Sensitivity of NSCLC cells through directly functioning on miR-197-3p/p120 catenin Axis. Mol Cells. 2019;42(3):270–83.
61. Cheng Q, Zhang S, Zhong B, Chen Z, Peng F. Asiatic acid re-sensitizes multidrug-resistant A549/DDP cells to cisplatin by down regulating long non-coding RNA metastasis associated lung adenocarcinoma transcript 1/β-catenin signaling. Bioengineered. 2022;13(5):12972–84.
62. Wang Y, Wang Y, Qin Z, Cai S, Yu L, Hu H, et al. The role of non-coding RNAs in ABC transporters regulation and their clinical implications of multidrug resistance in cancer. Expert Opin Drug Metab Toxicol. 2021;17(3):291–306.
63. Liu Z, Sun M, Lu K, Liu J, Zhang M, Wu W, et al. The long noncoding RNA HOTAIR contributes to cisplatin resistance of human lung adenocarcinoma cells via downregualtion of p21(WAF1/CIP1) expression. PLoS ONE. 2013;8(10):e77293.
64. Kaneko S, Li G, Son J, Xu CF, Margueron R, Neubert TA, et al. Phosphorylation of the PRC2 component Ezh2 is cell cycle-regulated and up-regulates its binding to ncRNA. Genes Dev. 2010;24(23):2615–20.
65. Chen J, Li J, Han Q, Sun Z, Wang J, Wang S, et al. Enhancer of zeste homolog 2 is overexpressed and contributes to epigenetic inactivation of p21 and phosphatase and tensin homolog in B-cell acute lymphoblastic leukemia. Experimental Biology Med (Maywood NJ). 2012;237(9):1110–6.
66. Fang Z, Chen W, Yuan Z, Liu X, Jiang H. LncRNA-MALAT1 contributes to the cisplatin-resistance of lung cancer by upregulating MRP1 and MDR1 via STAT3 activation. Volume 101. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie; 2018. pp. 536–42.
67. Shahryari A, Jazi MS, Samaei NM, Mowla SJ. Long non-coding RNA SOX2OT: expression signature, splicing patterns, and emerging roles in pluripotency and tumorigenesis. Front Genet. 2015;6:196.
68. Herrera-Solorio AM, Peralta-Arrieta I, Armas López L, Hernández-Cigala N, Mendoza Milla C, Ortiz Quintero B, et al. LncRNA SOX2-OT regulates AKT/ERK and SOX2/GLI-1 expression, hinders therapy, and worsens clinical prognosis in malignant lung diseases. Mol Oncol. 2021;15(4):1110–29.
69. Yang X, Meng L, Zhong Y, Hu F, Wang L, Wang M. The long intergenic non-coding RNA GAS5 reduces cisplatin-resistance in non-small cell lung cancer through the miR-217/LHPP axis. Aging. 2021;13(2):2864–84.
70. Guo S, Zhang L, Zhang Y, Wu Z, He D, Li X, et al. Long non-coding RNA TUG1 enhances chemosensitivity in non-small cell lung cancer by impairing microRNA-221-dependent PTEN inhibition. Aging. 2019;11(18):7553–69.
71. Huang Q, Xing S, Peng A, Yu Z. NORAD accelerates chemo-resistance of non-small-cell lung cancer via targeting at miR-129-1-3p/SOX4 axis. Biosci Rep. 2020;40(1).
72. Wang L, Shang X, Feng Q. LncRNA TATDN1 contributes to the cisplatin resistance of non-small cell lung cancer through TATDN1/miR-451/TRIM66 axis. Cancer Biol Ther. 2019;20(3):261–71.
73. Shen Q, Xu Z, Xu S. Long non–coding RNA LUCAT1 contributes to cisplatin resistance by regulating the miR–514a–3p/ULK1 axis in human non–small cell lung cancer. Int J Oncol. 2020;57(4):967–79.
74. Luo S, Shen M, Chen H, Li W, Chen C. Long non–coding RNA TP73–AS1 accelerates the progression and cisplatin resistance of non–small cell lung

cancer by upregulating the expression of TRIM29 via competitively targeting microRNA–34a–5p. Mol Med Rep. 2020;22(5):3822–32.
75. Wang Y, Li M, Zhang L, Chen Y, Ha M. LINC01140 inhibits nonsmall cell lung cancer progression and cisplatin resistance through the miR-4742-5p/TACC1 axis. J Biochem Mol Toxicol. 2022;36(7):e23048.
76. Chen L, Han X, Hu Z, Chen L. The PVT1/miR-216b/Beclin-1 regulates cisplatin sensitivity of NSCLC cells via modulating autophagy and apoptosis. Cancer Chemother Pharmacol. 2019;83(5):921–31.
77. Tang H, Han X, Li M, Li T, Hao Y. Linc00221 modulates cisplatin resistance in non-small-cell lung cancer via sponging miR-519a. Biochimie. 2019;162:134–43.
78. Liu B, Zhou F, Liu H, Wang Y, Wang J, Ren F, et al. Knockdown of LINC00511 decreased cisplatin resistance in non-small cell lung cancer by elevating miR-625 level to suppress the expression of leucine rich repeat containing eight volume-regulated anion channel subunit E. Hum Exp Toxicol. 2022;41:9603271221089000.
79. Tuo Z, Liang L, Zhou R. LINC00852 is associated with poor prognosis in non-small cell lung cancer patients and its inhibition suppresses cancer cell proliferation and chemoresistance via the hsa-miR-145-5p/KLF4 axis. J Gene Med. 2021;23(12):e3384.
80. Zeng Z, Zhao G, Zhu H, Nie L, He L, Liu J, et al. LncRNA FOXD3-AS1 promoted chemo-resistance of NSCLC cells via directly acting on miR-127-3p/MDM2 axis. Cancer Cell Int. 2020;20:350.
81. Ge P, Cao L, Yao YJ, Jing RJ, Wang W, Li HJ. lncRNA FOXD2-AS1 confers cisplatin resistance of non-small-cell lung cancer via regulation of miR185-5p-SIX1 axis. OncoTargets Therapy. 2019;12:6105–17.
82. Wang P, Chen D, Ma H, Li Y. LncRNA MEG3 enhances cisplatin sensitivity in non-small cell lung cancer by regulating miR-21-5p/SOX7 axis. OncoTargets Therapy. 2017;10:5137–49.
83. Wang H, Guo M, Ding D, Yang F, Chen Z. Long non-coding RNA NNT-AS1 contributes to Cisplatin Resistance via miR-1236-3p/ATG7 Axis in Lung Cancer cells. OncoTargets Therapy. 2020;13:3641–52.
84. Zuo W, Zhang W, Xu F, Zhou J, Bai W. Long non-coding RNA LINC00485 acts as a microRNA-195 sponge to regulate the chemotherapy sensitivity of lung adenocarcinoma cells to cisplatin by regulating CHEK1. Cancer Cell Int. 2019;19:240.
85. Li Y, Zhang H, Guo J, Li W, Wang X, Zhang C et al. Downregulation of LINC01296 suppresses non-small-cell lung cancer via targeting miR-143-3p/ATG2B. Acta Biochimica Et Biophysica Sinica. 2021;53(12):1681–90.
86. Wang G, Liu L, Zhang J, Huang C, Chen Y, Bai W, et al. LncRNA HCG11 suppresses cell proliferation and promotes apoptosis via sponging mir-224-3p in Non-small-cell Lung Cancer cells. OncoTargets Therapy. 2020;13:6553–63.
87. Xu Y, Tan X, Yang Q, Fang Z, Chen W. LncRNA HCG11 enhances the chemosensitivity of non-small cell lung cancer cells to Gemcitabine via miR-17-5p/p21 axis. Expert Rev Anticancer Ther. 2024;24(1–2):81–93.
88. Chen W, Tan X, Yang Q, Fang Z, Xu Y. MALAT1 enhances gemcitabine resistance in non-small cell lung cancer cells by directly affecting miR-27a-5p/PBOV1 axis. Cell Signal. 2022;94:110326.
89. Imyanitov EN, Iyevleva AG, Levchenko EV. Molecular testing and targeted therapy for non-small cell lung cancer: current status and perspectives. Crit Rev Oncol/Hematol. 2021;157:103194.
90. Friedlaender A, Banna G, Malapelle U, Pisapia P, Addeo A. Next generation sequencing and genetic alterations in squamous cell lung carcinoma: where are we today? Front Oncol. 2019;9:166.
91. Li J, Wei L. Increased expression of LINC01510 predicts poor prognosis and promotes malignant progression in human non-small cell lung cancer. Biomed Pharmacotherapy = Biomedecine Pharmacotherapie. 2019;109:519–29.
92. Pal AS, Agredo A, Lanman NA, Son J, Sohal IS, Bains M, et al. Loss of KMT5C promotes EGFR Inhibitor Resistance in NSCLC via LINC01510-Mediated Upregulation of MET. Cancer Res. 2022;82(8):1534–47.
93. Rosell R, Carcereny E, Gervais R, Vergnenegre A, Massuti B, Felip E, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol. 2012;13(3):239–46.
94. Wu Y, Hu L, Liang Y, Li J, Wang K, Chen X, et al. Up-regulation of lncRNA CASC9 promotes esophageal squamous cell carcinoma growth by negatively regulating PDCD4 expression through EZH2. Mol Cancer. 2017;16(1):150.
95. Bing Z, Han J, Zheng Z, Liang N. FOXO3-induced oncogenic lncRNA CASC9 enhances gefitinib resistance of non-small-cell lung cancer through feedback loop. Life Sci. 2021;287:120012.
96. Jiang Y, Cao W, Wu K, Qin X, Wang X, Li Y, et al. LncRNA LINC00460 promotes EMT in head and neck squamous cell carcinoma by facilitating peroxiredoxin-1 into the nucleus. J Experimental Clin cancer Research: CR. 2019;38(1):365.
97. Ma G, Zhu J, Liu F, Yang Y. Long noncoding RNA LINC00460 promotes the Gefitinib Resistance of Nonsmall Cell Lung Cancer through epidermal growth factor receptor by sponging miR-769-5p. DNA Cell Biol. 2019;38(2):176–83.
98. Nakano Y, Isobe K, Kobayashi H, Kaburaki K, Isshiki T, Sakamoto S, et al. Clinical importance of long non–coding RNA LINC00460 expression in EGFR–mutant lung adenocarcinoma. Int J Oncol. 2020;56(1):243–57.
99. Shibue T, Weinberg RA. EMT, CSCs, and drug resistance: the mechanistic link and clinical implications. Nat Reviews Clin Oncol. 2017;14(10):611–29.
100. Yadav A, Kumar B, Datta J, Teknos TN, Kumar P. IL-6 promotes head and neck tumor metastasis by inducing epithelial-mesenchymal transition via the JAK-STAT3-SNAIL signaling pathway. Mol cancer Research: MCR. 2011;9(12):1658–67.
101. Zheng Y, Guo Z, Li Y. Long non-coding RNA prostate cancer-associated transcript 6 inhibited gefitinib sensitivity of non-small cell lung cancer by serving as a competing endogenous RNA of miR-326 to up-regulate interferon-alpha receptor 2. Bioengineered. 2022;13(2):3785–96.
102. Wang Z, Pan L, Yu H, Wang Y. The long non-coding RNA SNHG5 regulates gefitinib resistance in lung adenocarcinoma cells by targetting miR-377/CASP1 axis. Biosci Rep. 2018;38(4).
103. Chen H, Shen D, Zhu F, Ou Q, Cheng L, Zhu Y. Long noncoding RNA RP11-89K21.1 interacts with miR-146a/b-5p to promote proliferation and Gefitinib Resistance through regulating RHPN2 and RhoA/ROCK pathway in Lung Adenocarcinoma. Cancer Biother Radiopharm. 2023;38(5):282–92.
104. Chen Z, Chen Q, Cheng Z, Gu J, Feng W, Lei T, et al. Long non-coding RNA CASC9 promotes gefitinib resistance in NSCLC by epigenetic repression of DUSP1. Cell Death Dis. 2020;11(10):858.
105. Ma Z, Gu S, Song M, Yan C, Hui B, Ji H, et al. Long non-coding RNA SNHG17 is an unfavourable prognostic factor and promotes cell proliferation by epigenetically silencing P57 in colorectal cancer. Mol Biosyst. 2017;13(11):2350–61.
106. Zhang H, Wang SQ, Wang L, Lin H, Zhu JB, Chen R, et al. m6A methyltransferase METTL3-induced lncRNA SNHG17 promotes lung adenocarcinoma gefitinib resistance by epigenetically repressing LATS2 expression. Cell Death Dis. 2022;13(7):657.
107. Zalaquett Z, Catherine Rita Hachem M, Kassis Y, Hachem S, Eid R, Raphael Kourie H, et al. Acquired resistance mechanisms to osimertinib: the constant battle. Cancer Treat Rev. 2023;116:102557.
108. Yang Y, Jiang C, Yang Y, Guo L, Huang J, Liu X et al. Silencing of LncRNA-HOTAIR decreases drug resistance of Non-small Cell Lung Cancer cells by inactivating autophagy via suppressing the phosphorylation of ULK1. Biochemical and biophysical research communications. 2018;497(4):1003–10.
109. Brown S, Banfill K, Aznar MC, Whitehurst P, Faivre Finn C. The evolving role of radiotherapy in non-small cell lung cancer. Br J Radiol. 2019;92(1104):20190524.
110. Prensner JR, Chen W, Han S, Iyer MK, Cao Q, Kothari V, et al. The long noncoding RNA PCAT-1 promotes prostate cancer cell proliferation through cMyc. Neoplasia (New York NY). 2014;16(11):900–8.
111. Gao Y, Zhang N, Zeng Z, Wu Q, Jiang X, Li S, et al. LncRNA PCAT1 activates SOX2 and suppresses radioimmune responses via regulating cGAS/STING signalling in non-small cell lung cancer. Clin Translational Med. 2022;12(4):e792.
112. Wang Y, Luo J, Alu A, Han X, Wei Y, Wei X. cGAS-STING pathway in cancer biotherapy. Mol Cancer. 2020;19(1):136.
113. Fuertes MB, Kacha AK, Kline J, Woo SR, Kranz DM, Murphy KM, et al. Host type I IFN signals are required for antitumor CD8 + T cell responses through CD8{alpha}+ dendritic cells. J Exp Med. 2011;208(10):2005–16.
114. Storozynsky Q, Hitt MM. The Impact of Radiation-Induced DNA Damage on cGAS-STING-Mediated Immune Responses to Cancer. International journal of molecular sciences. 2020;21(22).
115. Zhang M, Gao C, Yang Y, Li G, Dong J, Ai Y, et al. Long noncoding RNA CRNDE/PRC2 participated in the Radiotherapy Resistance of Human Lung Adenocarcinoma through Targeting p21 expression. Oncol Res. 2018;26(8):1245–55.
116. Kanduri C. Kcnq1ot1: a chromatin regulatory RNA. Semin Cell Dev Biol. 2011;22(4):343–50.
117. He H, Song X, Yang Z, Mao Y, Zhang K, Wang Y, et al. Upregulation of KCNQ1OT1 promotes resistance to stereotactic body radiotherapy in lung adenocarcinoma by inducing ATG5/ATG12-mediated autophagy via miR-372-3p. Cell Death Dis. 2020;11(10):883.

118. Romanov J, Walczak M, Ibiricu I, Schüchner S, Ogris E, Kraft C, et al. Mechanism and functions of membrane binding by the Atg5-Atg12/Atg16 complex during autophagosome formation. EMBO J. 2012;31(22):4304–17.
119. Levy JMM, Towers CG, Thorburn A. Targeting autophagy in cancer. Nat Rev Cancer. 2017;17(9):528–42.
120. Liu J, Jiang M, Guan J, Wang Y, Yu W, Hu Y, et al. LncRNA KCNQ1OT1 enhances the radioresistance of lung squamous cell carcinoma by targeting the miR-491-5p/TPX2-RNF2 axis. J Thorac Disease. 2022;14(10):4081–95.
121. Jiang G, Yu H, Li Z, Zhang F. lncRNA cytoskeleton regulator reduces non–small cell lung cancer radiosensitivity by downregulating miRNA–206 and activating prothymosin α. Int J Oncol. 2021;59(5).
122. Zhang J, Li W. Long noncoding RNA CYTOR sponges miR-195 to modulate proliferation, migration, invasion and radiosensitivity in nonsmall cell lung cancer cells. Biosci Rep. 2018;38(6).
123. Zheng L, Chen J, Zhou Z, He Z. miR-195 enhances the radiosensitivity of colorectal cancer cells by suppressing CARM1. OncoTargets Therapy. 2017;10:1027–38.
124. Yu S, Jing L, Yin XR, Wang MC, Chen YM, Guo Y, et al. MiR-195 suppresses the metastasis and epithelial-mesenchymal transition of hepatocellular carcinoma by inhibiting YAP. Oncotarget. 2017;8(59):99757–71.
125. Feng C, Zhang L, Sun Y, Li X, Zhan L, Lou Y, et al. GDPD5, a target of miR-195-5p, is associated with metastasis and chemoresistance in colorectal cancer. Volume 101. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie; 2018. pp. 945–52.
126. Li B, Wang S, Wang S. MiR-195 suppresses colon cancer proliferation and metastasis by targeting WNT3A. Molecular genetics and genomics. MGG. 2018;293(5):1245–53.
127. Wang Z, Liu L, Du Y, Mi Y, Wang L. The HNF1A-AS1/miR-92a-3p axis affects the radiosensitivity of non-small cell lung cancer by competitively regulating the JNK pathway. Cell Biol Toxicol. 2021;37(5):715–29.
128. Hou J, Wang Y, Zhang H, Hu Y, Xin X, Li X. Silencing of LINC00461 enhances radiosensitivity of lung adenocarcinoma cells by down-regulating HOXA10 via microRNA-195. J Cell Mol Med. 2020;24(5):2879–90.
129. Yu Z, Wang G, Zhang C, Liu Y, Chen W, Wang H, et al. LncRNA SBF2-AS1 affects the radiosensitivity of non-small cell lung cancer via modulating microRNA-302a/MBNL3 axis. Cell Cycle (Georgetown Tex). 2020;19(3):300–16.
130. Ma Q, Niu R, Huang W, Da L, Tang Y, Jiang D, et al. Long noncoding RNA PTPRG antisense RNA 1 reduces radiosensitivity of Nonsmall Cell Lung Cancer cells Via regulating MiR-200c-3p/TCF4. Technol Cancer Res Treat. 2020;19:1533033820942615.
131. He X, Zhang J, Lu C, Yan W. Knockdown of lncRNA FOXD1-AS1 promotes the radiosensitivity of lung squamous cell carcinoma cells by regulating the miR-4801/PUM1 axis. J Radiation Res Appl Sci. 2023;16(2):100548.
132. Kumar V, Yadavilli S, Kannan R. A review on RNAi therapy for NSCLC: opportunities and challenges. Wiley Interdisciplinary Reviews Nanomed Nanobiotechnol. 2021;13(2):e1677.
133. Ciccone G, Ibba ML, Coppola G, Catuogno S, Esposito CL. The small RNA Landscape in NSCLC: current therapeutic applications and progresses. Int J Mol Sci. 2023;24(7).
134. Nascimento AV, Singh A, Bousbaa H, Ferreira D, Sarmento B, Amiji MM. Overcoming cisplatin resistance in non-small cell lung cancer with Mad2 silencing siRNA delivered systemically using EGFR-targeted chitosan nanoparticles. Acta Biomater. 2017;47:71–80.
135. Nascimento AV, Gattacceca F, Singh A, Bousbaa H, Ferreira D, Sarmento B, et al. Biodistribution and pharmacokinetics of Mad2 siRNA-loaded EGFR-targeted chitosan nanoparticles in cisplatin sensitive and resistant lung cancer models. Nanomed (London England). 2016;11(7):767–81.
136. Mattheolabakis G, Ling D, Ahmad G, Amiji M. Enhanced Anti-tumor Efficacy of Lipid-Modified Platinum Derivatives in combination with survivin silencing siRNA in resistant Non-small Cell Lung Cancer. Pharm Res. 2016;33(12):2943–53.
137. Chen J, Liu A, Wang Z, Wang B, Chai X, Lu W, et al. LINC00173.v1 promotes angiogenesis and progression of lung squamous cell carcinoma by sponging mir-511-5p to regulate VEGFA expression. Mol Cancer. 2020;19(1):98.
138. Dai X, Jiang Y, Tan C. Let-7 sensitizes KRAS Mutant Tumor cells to Chemotherapy. PLoS ONE. 2015;10(5):e0126653.
139. Yin J, Hu W, Pan L, Fu W, Dai L, Jiang Z, et al. let–7 and miR–17 promote self–renewal and drive gefitinib resistance in non–small cell lung cancer. Oncol Rep. 2019;42(2):495–508.
140. Liu JK, Liu HF, Ding Y, Gao GD. Predictive value of microRNA let-7a expression for efficacy and prognosis of radiotherapy in patients with lung cancer brain metastasis: a case-control study. Medicine. 2018;97(44):e12847.
141. Esposito CL, Cerchia L, Catuogno S, De Vita G, Dassie JP, Santamaria G, et al. Multifunctional aptamer-miRNA conjugates for targeted cancer therapy. Mol Therapy: J Am Soc Gene Therapy. 2014;22(6):1151–63.
142. Cortez MA, Valdecanas D, Zhang X, Zhan Y, Bhardwaj V, Calin GA, et al. Therapeutic delivery of miR-200c enhances radiosensitivity in lung cancer. Mol Therapy: J Am Soc Gene Therapy. 2014;22(8):1494–503.
143. Ganesh S, Iyer AK, Weiler J, Morrissey DV, Amiji MM. Combination of siRNA-directed gene silencing with cisplatin reverses Drug Resistance in Human Non-small Cell Lung Cancer. Mol Therapy Nucleic Acids. 2013;2(7):e110.
144. Ganesh S, Iyer AK, Morrissey DV, Amiji MM. Hyaluronic acid based self-assembling nanosystems for CD44 target mediated siRNA delivery to solid tumors. Biomaterials. 2013;34(13):3489–502.
145. Taratula O, Garbuzenko OB, Chen AM, Minko T. Innovative strategy for treatment of lung cancer: targeted nanotechnology-based inhalation co-delivery of anticancer drugs and siRNA. J Drug Target. 2011;19(10):900–14.

Publisher's note