Long non-coding RNAs as potential therapeutic targets in non-small cell lung cancer (Review)

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Abstract. Non-small cell lung cancer (NSCLC) is one of the most common malignancies with a high morbidity and mortality rate. Long non-coding RNAs (lncRNAs) have been reported to be closely associated with the occurrence and progression of NSCLC. In addition, lncRNAs have been documented to participate in the development of drug resistance and radiation sensitivity in patients with NSCLC. Due to their extensive functional characterization, high tissue specificity and sex specificity, lncRNAs have been proposed to be novel biomarkers and therapeutic targets for NSCLC. Therefore, in the current review, the functional classification of lncRNAs were presented, whilst the potential roles of lncRNAs in NSCLC were also summarized. Various physiological aspects, including proliferation, invasion and drug resistance, were all discussed. It is anticipated that the present review will provide a perspective on lncRNAs as potential diagnostic molecular biomarkers and therapeutic targets for NSCLC.

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Abbreviations: ATG, autophagy-related; CASC9, candidate tumor susceptibility gene 9; CASC15, cancer susceptibility candidate 15; DSP, desmoplakin; DUSP1, dual specificity phosphatase 1; EMT, epithelial-mesenchymal transition; EZH2, zeste homolog 2; FOXC1, forkhead box C1; HIF-1α, hypoxia-inducible factor 1α; HMGA2, high mobility group AT-Hook 2; HRE, hypoxia response element; H3K27me3, histone methyl transferase EZH2 trimethylates histone H3; IFI44, interferon induced protein 44; KCNQ1OT1, opposite strand/antisense transcript 1; lncRNAs, long non-coding RNAs; UPLA1, lung adenocarcinoma related transcriptional-1; LOY, Y chromosome inlay deletion; LUAD, lung adenocarcinoma; UCA1, lncRNA urothelial carcinoma-associated 1; Linc00301, long intergenic non-coding RNA 00301; Linc01116, long intergenic non-protein coding RNA 1116; Linc01234, long intergenic non-coding RNA 01234; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; MDM4, murine double minute 4; NSCLC, non-small cell lung cancer; PIK3CD-AS2, PIK3CD antisense RNA 2; RING1, really interesting new gene 1; SBRT, stereotactic radiotherapy; SLC16A1-AS1, lncRNA SLC16A1 antisense transcript 1; SOX4, SRY-related HMG box 4 transcription factor; TTTY15, testicle-specific transcription Y-related gene 15; XIST, candidate gene for X-inactivation center; YBX1, Y-box binding protein 1

Key words: lncRNA, NSCLC, therapeutic targets, biomarkers, drug resistance

Contents

1. Introduction

According to the global cancer statistics, the incidence of lung cancer is second only to breast cancer, accounting for >21% of all cancers (1). Non-small cell lung cancer (NSCLC) is the primary pathological subtype of lung cancer, accounting for ~85% of all cases lung cancer (2). In addition, NSCLC can be further sub-divided into lung squamous cell carcinoma, lung adenocarcinoma (LUAD) and large-cell lung cancer (3). Early diagnosis of NSCLC is of importance to both the improved cure rates and superior prognosis (4,5). Although novel targeted drug therapies have made considerable progress, both the overall survival rates and early diagnosis rates of patients remain <20% (6,7). Therefore, it is necessary to discover novel predictive biomarkers and therapeutic targets for NSCLC.

Until recently, long non-coding (lncRNAs) have been considered to be 'junk' material on the genome that serves little purpose. However, as genomic research improves,

roles of lncRNAs were progressively revealed in numerous diseases (8,9). LncRNAs are RNA sequences that consist of >200 nucleotides and serve important roles in transcriptional regulation and epigenetic gene regulation (10). In addition, lncRNAs confer obvious advantages in epigenetic regulation (11). A number of lncRNAs have high tissue expression specificity and are evolutionary conserved (12). Previous pan-cancer transcriptome analysis showed that the expression of lncRNAs were frequently dysregulated and in manner that was specific to multitude of tumors, including lung cancer (13), breast cancer (14), and glioblastoma (8,15-18).

LncRNAs are closely associated with the occurrence and progression of NSCLC, notably by regulating the development of drug resistance and radiation sensitivity in patients with NSCLC. Overexpression of PIK3CD antisense RNA 2 (PIK3CD-AS2) was found to promote NSCLC cell proliferation, apoptosis and progression through the PIK3CD-AS2/Y-box binding protein 1 (YBX1)/p53 signaling axis (19). Elucidating the mechanism of lncRNAs on NSCLC would be beneficial for the development of therapeutic strategies against its tumorigenesis. However, the detailed mechanisms remain to be fully elucidated. The present review therefore summarized the recent progress on lncRNA research and their potential underlying mechanisms revealed in NSCLC, to provide reference for the potential implications of lncRNAs in NSCLC.

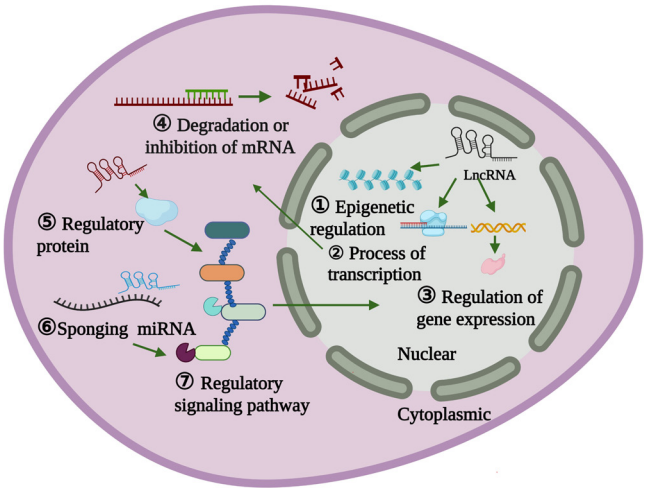

Figure 1. Mechanisms of lncRNAs in nucleus and cytoplasm. In the nucleus, ① lncRNAs regulate chromatin or act as scaffolds to recruit multiple regulatory molecules to gene promoters to activate or suppress gene expression, ② regulate messenger RNA processing by recruiting regulatory molecules to messenger RNA, ③ and bind to numerous chromatin remodelers and regulated histones, thereby promoting or suppressing gene expression, or modifying DNA to suppress gene expression. In cytoplasm, ④ lncRNAs regulate mRNA stability by directly binding to mRNA to form RNA-RNA duplexes, ⑤ interact with proteins to regulate signaling cascades and subsequent changes in gene expression, ⑥ and act as miRNA sponges to competitively bind miRNA regulation, which in turn has an impact on ⑦ signaling pathways. lncRNA, long non-coding RNA; miR, microRNA.

2. Functional classification of lncRNAs

The majority of lncRNAs are similar to mRNAs, in that they are transcribed by RNA polymerase II from the genomic loci in chromatin (20). LncRNAs can be classified according to their positions relative to the encoding genes (8), namely long intergenic RNAs, intron lncRNAs, antisense lncRNAs, bidirectional lncRNAs and enhancer lncRNAs. LncRNAs can be classified into oncogenes and tumor suppressor genes in accordance with whether their expression can promote tumor development. In general, lncRNAs that are overexpressed to promote tumor development are classified as oncogenes, whilst lncRNAs that function in the opposite way manner would be deemed to be tumor suppressor genes (21,22). In addition, lncRNAs can be classified into cis-acting lncRNAs and trans-acting lncRNAs according to whether it serves a cis-regulatory or trans-regulatory role in cancers (23).

LncRNAs show a diverse array of characteristic functions, in addition to having high tissue and sex specificity (24). The functions of lncRNAs are largely reflected by their subcellular localization (Fig. 1). Nuclear lncRNAs typically regulate chromatin organization, transcriptional and post-transcriptional gene expression, where they can also serve as structural scaffolds anchoring nuclear domains to regulate biological processes (25). By contrast, cytoplasmic lncRNAs generally regulate various functions, including mRNA conversion, translation, protein stability, cytokine sponging and cell signaling (26). LncRNAs can interact with different types of biomolecules, which would be of great significance in the proliferation and apoptosis, invasion and migration, epithelial-mesenchymal transition (EMT) and metastasis, in addition to drug resistance of NSCLC cells. Therefore, monitoring changes in lncRNA expression and elucidating its functional mechanisms are likely to have clinical implications for the diagnosis, treatment and prognosis of NSCLC.

3. LncRNAs in NSCLC

Roles of LncRNAs in the proliferation and apoptosis of NSCLC. The occurrence and development of malignancies are frequently accompanied with changes in cell cycle and apoptosis signaling. As summarized in the present review, lncRNAs can regulate the activity of signaling cascades by binding to proteins and affecting their stability. In addition, lncRNAs can serve as a competitive endogenous RNA by interacting with miRNAs to regulate downstream target gene expression. Conversely, miRNAs can regulate the expression of lncRNAs, since certain lncRNAs share structural similarities with certain mRNAs. Several lncRNAs associated with NSCLC proliferation and apoptosis are summarized in this section.

P53 is an important tumor suppressor, that can regulate apoptosis, autophagy and senescence (27). In particular, splice factor YBX1 is a negative p53 regulator that serves an essential role in autophagy in NSCLC (28,29). PIK3CD-AS2 was found to inhibit p53 signaling by binding with YBX1, protecting YBX1 from ubiquitination and degradation (Fig. 2A) (19). In addition, metastasis-associated LUAD transcript 1 (MALAT1) was reported to be associated with a number of cancers (30-33). Murine double minute 4 (MDM4), an essential negative regulator of p53, was frequently found to be overexpressed in cancer cells expressing wild-type p53. As shown in Fig. 2B, overexpression of MALAT1 can upregulate miR-185-5p expression to reduce the expression of MDM4, which inhibited the migration and invasion of NSCLC (34). In another study, MALAT1 was

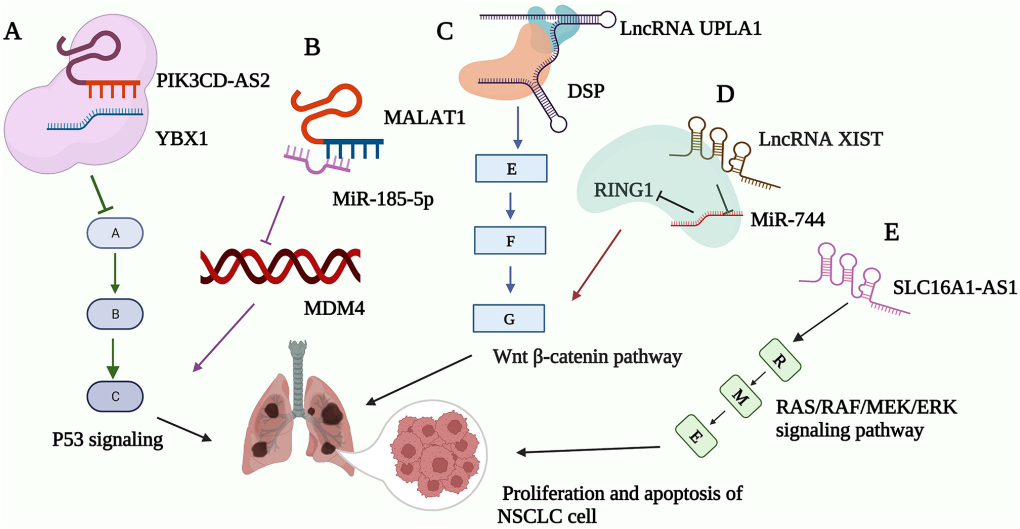

Figure 2. Mechanisms of lncRNAs regulating the proliferation and apoptosis of NSCLC. (A) PIK3CD-AS2 inhibits p53 signaling by binding with p53 negative regulator YBX1. (B) MALAT1 inhibits p53 signaling by upregulating miR-185-5p and reducing the expression of MDM4. (C) UPLA1 facilitates Wnt/β-catenin signaling by binding to DSP. (D) XIST modulates miR-744 by serving as an endogenous competitive RNA, increasing RING1 expression and enhancing the Wnt/β-catenin signaling pathway. (E) SLC16A1-AS1 affects overall survival and progression-free survival in NSCLC by regulating the RAS/RAF/MEK/ERK signaling pathway. lncRNA, long non-coding RNA; NSCLC, non-small cell lung cancer; PIK3CD-AS2, PIK3CD antisense RNA 2; YBX1, Y-box binding protein 1; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; MDM4, murine double minute 4; UPLA1, lung adenocarcinoma related transcriptional-1; DSP, desmoplakin; XIST, candidate gene for X-inactivation center; miR, microRNA; RING1, really interesting new gene 1; lncRNA SLC16A1-AS1, SLC16A1 antisense transcript 1.

demonstrated to promote the proliferation of NSCLC through the MALAT1-FOXP3-GINS1 axis (35). In conclusion, targeting PIK3CD-AS2 and MALAT1 may be a NSCLC treatment strategy for restoring p53 function in tumors.

As a critical component of desmosomal plaque proteins, desmoplakin (DSP) can also serve as a tumor suppressor by inhibiting the Wnt/β-catenin signaling pathway in lung cancer (36). This pathway is central to the tumorigenesis, prognosis and therapeutic resistance of NSCLC (37-41). As revealed in Fig. 2C, upregulation promoting LUAD-associated transcript-1 (UPLA1) was found to be closely associated with cell proliferation, migration and apoptosis in NSCLC cells by regulating the DSP/Wnt/β-catenin pathway (42). LncRNA candidate gene for X-inactivation center (XIST) inhibited the miR-744/really interesting new gene 1 (RING1) pathway whilst activating that of Wnt/β-catenin signaling (Fig. 2D), which inhibited the proliferation of NSCLC cells (43).

The RAS/RAF/MEK/ERK signaling pathway is an extensively studied signaling pathway, particularly in cancer (44,45). Hyperactivation of MAPK signaling has been found to induce the occurrence of cancer (46). As demonstrated in Fig. 2E, lncRNA SLC16A1 antisense transcript 1 (SLC16A1-AS1) affected the overall survival and progression-free survival of patients with NSCLC by regulating the RAS/RAF/MEK pathway (47). SLC16A1-AS1 has also been reported in other cancers (48). In brief, SLC16A1-AS1 can potentially serve a role in regulating the proliferation and apoptosis of NSCLC.

In conclusion, PIK3CD-AS2, MALAT1, UPLA1, XIST and SLC16A1-AS1 can all potentially serve different roles in the cell proliferation, migration and apoptosis of NSCLC cells by intervening in various regulatory pathways. They can be exploited for the treatment of NSCLC. The role and mechanism of lncRNAs in proliferation and apoptosis of NSCLC are listed in Table I.

Roles of lncRNAs in migration, invasion and EMT of NSCLC. Cancer metastasis increases the mortality rate of NSCLC, which requires cell migration and the maintenance of activity by altering the cell arrangement of EMT (82). A large number of lncRNAs have been found to possibly regulate the migration and invasion of NSCLC. Nuclear lncRNAs can not only induce methylation to regulate the transcription of genes and binding of transcription factors to gene promoters (83), but they can also recruit other components to regulate mRNA (84). LncRNAs associated with migration, invasion and EMT of NSCLC are summarized in Table II.

Elevated expression of the transcription factor c-Myc has been frequently observed in human cancers, which is also associated with increased tumor invasion and adverse clinical outcomes (94,95). C-Myc promotes tumor cell proliferation by amplifying the output of the existing gene expression program (96). A previous study identified a novel oncogenic axis involving long intergenic non-coding RNA 01234 (linc01234), RNA-binding protein heterogeneous nuclear ribonucleoprotein A2/B1, miR-106b-5p, downregulating cryptochrome 2 and c-Myc (89). The upregulation of linc01234 in NSCLC was positively associated with poorer prognosis. In addition, linc01234 was found to facilitate the migration and invasion of NSCLC cells through different pathway in cytoplasm and nucleus (90). Specifically, linc01234 inhibited cell migration functioning as a competing endogenous RNA for miR-340-5p and miR-27b-3p in the cytoplasm. In the nucleus, linc01234 can interact with RNA-binding proteins lysine-specific demethylase 1 and enhancer of zeste homolog 2 (EZH2), which led to histone modification and the transcriptional suppression of B-cell translocation gene 2, an anti-proliferative gene. Linc01123 also promoted proliferation and aerobic glycolysis in NSCLC cell through the miR-199a-5p/c-Myc axis, whilst inhibiting the malignancy

Table I. Role and mechanism of lncRNAs in proliferation and apoptosis of NSCLC.

First author, year	LncRNA	Upregulation or downregulation	Mechanism	Function in NSCLC	(Refs.)
Zheng X., 2020	PIK3CD-AS2	Upregulation	PIK3CD-AS2/YBX1/p53 signaling axis	Cell proliferation, apoptosis, progression	(19)
Wang D., 2020	MALAT1	Upregulation	MiR-185-5p/MDM4 axis	Proliferation, apoptosis, migration	(34)
Li M., 2021			MALAT1-FOXP3-GINS1 axis	Proliferation	(35)
Han X., 2020	UPLA1	Upregulation	DSP/Wnt/β-catenin	Migration, invasion, proliferation, cell cycle, TNM	(42)
Wang J., 2019	XIST	Upregulation	MiR-744/RING1 Wnt/β-catenin	Proliferation, migration and invasion	(43)
Liu H. Y., 2020	SLC16A1-AS1	Downregulation	RAS/proto-oncogene serine/RAF/MEK/ERK	Survival, proliferation, cell cycle, apoptosis	(47)
Zang X., 2020	UFC1	Upregulation	UFC1/EZH2/PTEN/PI3K/Akt signaling pathway	Proliferation, migration and invasion	(49)
Yang Z., 2020	Linc00525	Upregulation	MiR-338-3p/IRS2 axis	Proliferation, migration and invasion	(50)
Fang P., 2021			EZH2/RBMS2/p21	Cell proliferation and cell cycle progression	(51)
Yang M., 2019	MiR4435-2HG	Upregulation	MiR4435-2HG/TGF-β1 axis	Migration and proliferation	(52)
Xu F., 2021	LncRNA AC020978	Upregulation	MDH2/AKT signaling pathway	Metastasis and progression	(53)
Cai Y., 2020	AZIN1-AS1	Upregulation	MiR-513b-5p/DUSP11	Proliferation, migration	(54)
Wu S., 2021	LncRNA LEISA	Upregulation	STAT3 and IL-6	Progression and prognosis	(55)
Wang R. Q., 2021	Lnc-GAN1	Downregulation	MiR-26a-5p/PTEN	Proliferation, colony formation, and cell cycle progression and induces apoptosis	(56)
Li C., 2020	KTN1-AS1	Upregulation	KTN1-AS1miR-130a-5p/PDPK1	Proliferation, apoptosis, poor prognosis	(57)
Liu C., 2020			MiR-23b/DEPDC1 axis	Colony formation and migration ability	(58)
Zhu Y., 2020	Linc00467	Upregulation	Akt signaling pathway	Cell growth and metastasis, and poor prognosis	(59)
Yang J., 2019			Wnt/beta-catenin signaling pathway	Proliferation migration	(60)
Chang Y., and Yang, 2019			MiR-4779 and miR-7978	Cell proliferation, apoptosis, and stemness	(61)
Xue F., 2021			miR-125a-3p/sirtuin 6 axis/ERK1/2 signaling pathway	Cisplatin resistance	(62)
Yin H., 2021	LncRNA RMRP	Upregulation	TGFBR1/SMAD2/SMAD3 pathway	Proliferation and progression	(63)
Sun C. C., 2021	Linc00301	Upregulation	FOXC1/Linc00301/EZH2/EAF2/pVHL/HIF1α FOXC1/Linc00301/miR-1276/HIF1α	Proliferation, apoptosis, migration, invasion	(64)
Shi L., 2021	LncRNA KIMAT1	Upregulation	KRAS signaling	Cell survival, growth and invasion	(65)
La Montagna M., 2021			KRAS/KIMAT1/LDHB/AMPKα axis	Growth and migration	(66)
Shi J., 2021	BBOX1-AS1	Upregulation	MiR-27a-5p/MELK and FAK signaling pathway	Proliferation, migration, invasion and epithelial-mesenchymal transition	(67)
Ni J., 2021	LncRNA-SOX2OT	Upregulation	MiRNA-194-5p/RAC1 signaling axis	Invasion and migration, bone metastasis	(68)
Lv X., 2021	Linc00662	Upregulation	MiR-320d/E2F1 axis	Proliferation, invasion, and migration, apoptosis, cell cycle arrest	(69)
Liu S., 2022	LncRNA CBR3-AS1	Upregulation	CBR3-AS1/miR-409-3p/SOD1 axis	Proliferation, invasion, and migration	(70)
Wang C., 2021	CTD-2245E15.3	Upregulation	ACC1, PC	Cell-cycle arrest and induction of apoptosis	(71)
Wang S., 2020	MALAT1	Upregulation	MiR-613/COMD8 axis	Proliferation, glycolysis, apoptosis, tumor growth	(72)

Table I. Continued.

First author, year	LncRNA	Upregulation or downregulation	Mechanism	Function in NSCLC	(Refs.)
Jin D., 2019			MALAT1-miR-1914-3p-YAP axis	Drug resistance and metastasis	(73)
Jin S., 2020	FTX	Downregulation	FTX/miR-200a-3p/FOXA2	Proliferation and metastasis	(74)
Sun J., 2021	CASC15	Upregulation	HIF-1α/CASC15/SOX4/β-catenin pathway	Migration and growth	(75)
Fan H., 2021	SNHG18	Upregulation	MiR-211-5p/BRD4 axis	Growth and metastasis	(76)
Chen J., 2020	Linc00173.v1	Upregulation	MiR-511-5p/VEGFA	Proliferation, migration and the tumorigenesis	(77)
Xiao L., 2020	LOC389641	Upregulation	EGFR, MET and STAT3 proteins	Colony formation, proliferation, invasion, autophagy and apoptosis	(78)
Cao G., 2020	MBNL1-AS1	Downregulation	MiR-135a-5p/LOXL4	Proliferation, cell cycle, migration and invasion, apoptosis	(79)
Hua Q., 2020	AC020978	Upregulation	PKM2/HIF-1α axis	Proliferation and glycolytic metabolism	(80)
Chen Q., 2020	LncRNA SBF2-AS1	Upregulation	MiR-338-3p/ADAM17 axis	Growth and metastatic phenotypes	(81)

lncRNA, long non-coding RNA; NSCLC, non-small cell lung cancer; miR, microRNA; PIK3CD-AS2, PIK3CD antisense RNA 2; EZH2, zeste homolog 2; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; MDM4, murine double minute 4; PIK3CD-AS2, PIK3CD antisense RNA; UPLA1, lung adenocarcinoma related transcriptional-1; HIF-1α, hypoxia-inducible factor 1α.

Table II. Roles and mechanisms of lncRNAs in migration, invasion and EMT of NSCLC.

First author, year	LncRNA	Upregulation or Downregulation	Mechanism	Function in NSCLC	(Refs.)
Guo Z., 2021	Lnc CRYBG3	Upregulation	Bub3 protein	Tumorigenesis and metastasis	(85)
Tian B., 2020	Linc01426	Upregulation	Hsa-miR-30b3p AZGP1	Proliferation, migration, invasion, wound healing	(86)
Liu X., 2021			USP22/SHH protein	Proliferation, migration, EMT	(87)
Jia D., 2021	Linc02678	Upregulation	EZH2, H3K27me3 and CDKN1B	Proliferation and progression, migration, invasion and EMT	(88)
Chen Z., 2020	Linc01234	Upregulation	HNRNPA2B1/miR-106b-5p/CRY2/c-Myc	Migration, invasion	(89)
Chen Z., 2020			EZH2, LSD1 and BTG2	Metastasis and shorter survival	(90)
Zheng F., 2020	HOTAIR	Upregulation	HOTAIR/miR-34a-5p/E-cadherin/vimentin/snail	Migration, invasion, EMT	(91)
Hua Q., 2019	Linc01123	Upregulation	MiR-199a-5p/c-Myc	Proliferation and aerobic glycolysis	(92)
Zhang M., 2020			MiR-449b-5p/NOTCH1	Cell growth, migration, EMT	(93)

lncRNA, long non-coding RNA; NSCLC, non-small cell lung cancer; EMT, epithelial-mesenchymal transition; miR, microRNA; EZH2, zeste homolog 2.

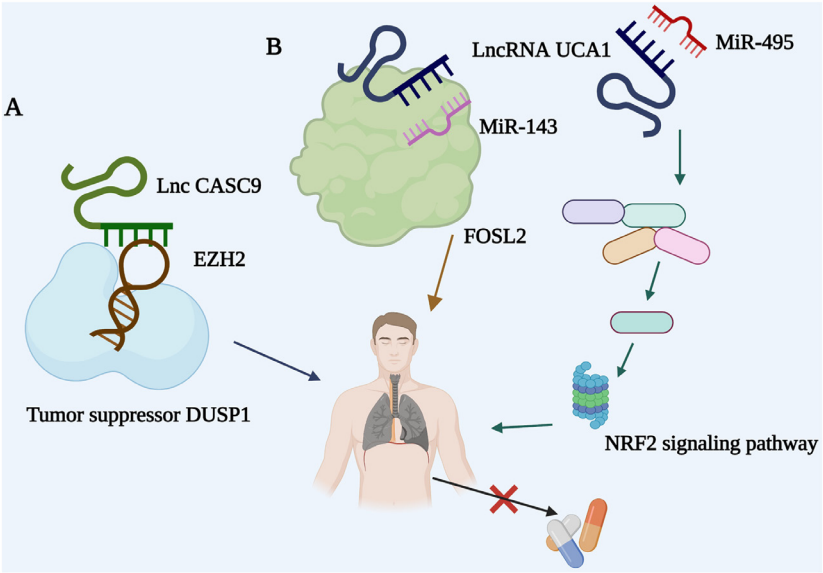

Figure 3. Mechanisms of CASC9 and lncRNA UCA1 in drug resistance in NSCLC. (A) CASC9 suppresses the tumor suppressor DUSP1 by recruiting histone methyltransferase EZH2 and increasing the resistance to gefitinib. (B) LncRNA UCA1 acts as an endogenous competitive RNA that can bind with miR-143 to regulate the expression of FOSL2. In addition, lncRNA UCA1 increases resistance to cisplatin through the UCA1/miR-495/NRF2 signaling pathway. CASC9, candidate tumor susceptibility gene 9; lncRNA, long non-coding RNA; UCA1, lncRNA urothelial carcinoma-associated; NSCLC, non-small cell lung cancer; DUSP1, dual specificity phosphatase 1; miR, microRNA; EZH2, zeste homolog 2.

of LUAD through the miR-449b-5p/NOTCH1 axis (93). This suggests that linc01234 and linc01123 can be used as potential biomarkers and therapeutic targets for NSCLC.

Apart from c-Myc, lncRNAs have also been found to regulate to activity of SRY-related HMG box 4 transcription factor (SOX4), which is a master regulator of EMT. It can promote tumorigenesis by endowing cells with migratory and invasive properties, stemness and resistance to apoptosis (97,98). Cancer susceptibility candidate (CASC) 15 is a hypoxia-sensitive lncRNA that appears to be important for NSCLC cell migration and proliferation (75). CASC15 is transcriptionally activated by hypoxia signaling in NSCLC cells, in a process that is dependent hypoxia-inducible factor 1α (HIF-1α) and hypoxia response elements (HREs). CASC15 served an essential role in the development and progression of NSCLC through the HIF-1α/CASC15/SOX4/β-catenin pathway. Accordingly, inhibiting the HIF-1α/CASC15/SOX4/β-catenin axis may be a novel therapeutic strategy for treating patients with NSCLC. The expression of long intergenic non-coding RNA 00301 (linc00301) was found to be upregulated in NSCLC and associated with prognosis (99). The linc00301 carcinogenic mechanism was found to involve the forkhead box C1 (FOXC1)/linc00301/EZH2/EAF2/pVHL/HIF1α and FOXC1/linc00301/miR-1276/HIF1α pathways, which offered novel ideas and potential therapeutic targets.

In conclusion, linc01234, linc01123 and CASC15 are potential therapeutic targets for improving NSCLC by inhibiting migration, invasion and EMT. Additional mechanistic studies have shown the signaling pathways that are involved downstream of c-Myc and SOX4. In addition, as shown in Table II, lncCRYBG3, linc01426 and HOTAIR were also found to be associated with migration, invasion and EMT in NSCLC. Research on the relationship between lncRNAs and NSCLC progression provided insight into the treatment of NSCLC.

LncRNAs in drug resistance of NSCLC. NSCLC is not susceptible to immunotherapy or chemotherapy, which reduces its overall survival (100,101). In addition to recruiting epigenetic regulatory complexes, lncRNAs can also act as sponges of miRNAs after gene transcription to regulate downstream signal transduction cascades (102). LncRNAs have been documented to exert an impact on therapeutic resistance of NSCLC by regulating gene transcription (103). LncRNAs were found to be associated with drug sensitivity in the treatment of NSCLC, such as cisplatin and EGFR-tyrosine kinase inhibitors gefitinib and afatinib (Table III).

Histone methyl transferase EZH2 trimethylates histone H3 (H3K27me3) at lysine 27 kept enzymatic activity in cancer cells. The effect of candidate tumor susceptibility gene 9 (CASC9) on the sensitivity of NSCLC was associated with EZH2 and dual specificity phosphatase 1 (DUSP1), reducing the sensitivity of NSCLC to gefitinib (105). Ectopic expression of DUSP1 was found to reduce NSCLC resistance to gefitinib, suggesting that the CASC9/EZH2/DUSP1 axis can be a target for overcoming EGFR resistance in NSCLC (Fig. 3A). In addition, linc00525 was found to act on NSCLC through H3K27me3, rendering it another potential therapeutic target for LUAD (51). Therefore, since both CASC9 and linc00525 had an impact on drug resistance in NSCLC, they may provide novel targets for drug resistance therapy in NSCLC.

LncRNAs can regulate drug sensitivity in NSCLC through different pathways. Exosome-derived lncRNA urothelial carcinoma-associated 1 (UCA1) was found to be overexpressed in gefitinib-resistant NSCLC cells. In Fig. 3B, lncRNA UCA1 functioned as an endogenous competitive RNA that can bind miR-143 to regulate the expression of FOSL2 (119). Overexpression of lncRNA UCA1 contributed to the development of resistance to cisplatin through the UCA1/miR-495/NRF2 signaling pathway (108) In addition, lncRNA UCA1 induced resistance to gefitinib by epigenetically silencing CDKN1A in NSCLC (109).

Table III. Roles and mechanisms of lncRNAs in clinical efficacy of NSCLC.

First author, year	LncRNA	Upregulation or Downregulation	Mechanism	Function in NSCLC	(Refs.)
Brownmiller T., 2020	Linc-SPRY3	Downregulation	IGF2BP3	Radio-sensitivity	(24)
Huang J., 2020	LncRNA SNHG15	Upregulation	MiR-451/MDR-1	Gefitinib resistance	(104)
Chen Z., 2020	CASC9	Upregulation	CASC9/EZH2/DUSP1	Gefitinib resistance	(105)
Bing Z., 2021			CASC9/miR-195-5p/FOXO3	Gefitinib resistance	(106)
Li Z., 2019	UCA1	Upregulation	MiR-143/FOSL2	Gefitinib resistance	(107)
Li C., 2019	Linc01116	Upregulation	MiRNA-495/NRF2 pathway	Cisplatin resistance	(108)
Xu T., 2020			EZH2/CDKN1A	Proliferation and apoptosis	(109)
Wang H., 2020			IFI44	Gefitinib resistance	(110)
Fu J., 2020	FGD5-AS1	Upregulation	MiR-140-5p/WEE1 axis	Cisplatin resistance, progress	(111)
He H., 2020	KCNQ1OT1	Upregulation	MiR-372-3p/ATG5/ATG12	Radio-sensitivity	(112)
Dong Z., 2019			MiR-27b-3p/HSP90AA1 axis	Proliferation, migration, invasion	(113)
Shu D., 2020	BLACAT1	Upregulation	STAT3	Afatinib resistance	(114)
Ju Z. S., 2020			Cyclin D1	Cisplatin resistance	(115)
Zeng Z., 2020	FOXD3-AS1	Upregulation	MiR-127-3p/MDM2 axis	Cisplatin resistance	(116)
Yang D., 2021	Linc00665	Upregulation	Linc00665-EZH2-CDKN1C axis	Cisplatin resistance	(117)
Yu Z., 2020	SBF2-AS1	Upregulation	MBNL3	Radio-sensitivity and apoptosis	(118)

lncRNA, long non-coding RNA; NSCLC, non-small cell lung cancer; miR, microRNA; EZH2, zeste homolog 2; CASC9, candidate tumor susceptibility gene 9; UCA1, lncRNA urothelial carcinoma-associated; DUSP1, dual specificity phosphatase 1; KCNQ1OT1, opposite strand/antisense transcript 1; IFI44, interferon induced protein 44.

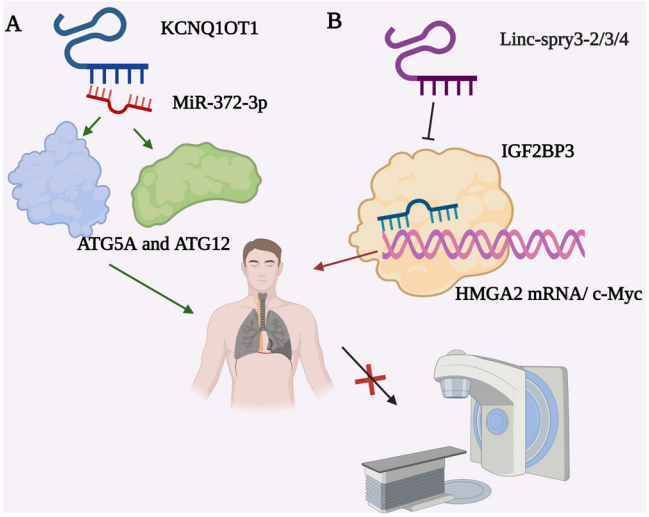

Figure 4. Mechanisms of KCNQ1OT1 and linc-spry3-2/3/4 in radio-sensitivity in NSCLC. (A) KCNQ1OT1 antagonizes SBRT by inducing ATG5 and ATG12-dependent autophagy by sponging miR-372-3p. (B) The binding of linc-spry3-2/3/4 to IGF2BP3 affects the half-life of certain mRNAs, including the anti-apoptotic HMGA2 mRNA and the oncogenic c-Myc mRNA. KCNQ1OT1, opposite strand/antisense transcript 1; NSCLC, non-small cell lung cancer; SBRT, stereotactic radiotherapy; ATG, autophagy-related; miR, microRNA; HMGA2, high mobility group AT-Hook 2.

Therefore, lncRNA UCA1 provides another insight into the regulatory mechanisms of gefitinib-resistant and cisplatin resistance in patients with NSCLC.

A previous study identified the biological function and mechanism of long intergenic non-protein coding RNA 1116 (linc01116) in the drug resistance of cancer cells (110). Linc01116 facilitated gefitinib resistance in NSCLC cells by affecting interferon-induced protein 44 (IFI44) expression. IFI44 was involved in the IFN/STAT1 pathway which could mediate resistance and radiotherapy in the tumor microenvironment (120,121). Linc01116 was also associated with cisplatin resistance in LUAD (122). Increasing the expression of linc01116 was found to be associated with poorer outcomes in patients with LUAD (123). Conversely, downregulation of linc01116 expression inhibited cell proliferation and blocked the cell cycle inhibition of EMT (124). In addition, linc01116 could regulate iron-metabolism and AKT signaling in LUAD (125,126). In conclusion, linc01116 may be a valuable prognostic biomarker and target to improve drug sensitivity for patients with NSCLC.

In conclusion, the relationship between lncRNAs and drug resistance in NSCLC was partially elucidated, which represented a promising approach for predicting the chemotherapy response of NSCLC. Studies on CASC9, lncRNA UCA1 and linc01116 in drug resistance provided an insight into strategies for improving therapeutic resistance in patients with NSCLC.

LncRNAs in radio-sensitivity of NSCLC. Radiotherapy serves an irreplaceable role in improving local lesions and overall survival of patients with NSCLC (127,128). As understanding into the interaction between radiotherapy and cancer deepens, accumulating studies have combined radiotherapy with novel drugs for NSCLC treatment, such as immunotherapy and DNA damage response inhibitors (129-131). LncRNAs could influence radio-sensitivity by regulating the DNA damage response, stagnation of autophagy, apoptosis and cell cycle progression (132,133). The relationship between lncRNAs and NSCLC radio-sensitivity are listed in Table III.

Knockdown of KCNQ1 opposite strand/antisense transcript 1 (KCNQ1OT1) was found to improve the resistance of LUAD to paclitaxel. KCNQ1OT1 promoted cell proliferation, migration and invasion by regulating the miR-129-5p/JAG1 axis (134). As shown in Fig. 4A, KCNQ1OT1 affected cell proliferation, autophagy and apoptosis by regulating the miR-204-5p/autophagy-related (ATG) 3 axis (135). Higher expression levels of KCNQ1OT1 were found to be associated with autophagy and decreased sensitivity to radiation therapy (112). KCNQ1OT1 induced stereotactic radiotherapy resistance in LUAD by stimulating miR-372-3p to induce ATG5 and ATG12 dependent autophagy. This suggested that KCNQ1OT1 is a potential target for enhancing the anti-tumor effect of radiotherapy.

Human Y chromosome deletion and rearrangement were shown to be associated with the occurrence and development of certain malignancies (136); however, on the possible association between NSCLC and lncRNAs on Y chromosome has not been reported. Long chain non-coding testicle-specific transcription Y-related gene 15 (TTTY15) was previously found to be was associated with the progression of NSCLC (137). LncRNAs in Y chromosome DYZ1 regulated the radiation response. Linc-spry3-2/3/4 transcripts were found to inhibit tumor growth, where their Y chromosome inlay deletion (LOY) may lead to radiation resistance in NSCLC cells (24). Further study revealed that lncRNAs interfered with the stabilization of high mobility group AT-Hook 2 (HMGA2) and c-Myc to reduce radio-sensitivity, by binding to IGF2BP3 (Fig. 4B). It revealed a negative correlation between the linc-SPRY3-2/3/4 or LOY and overall survival. In summary, these findings suggested that linc-spry3-2/3/4 is a promising marker of radiotherapy in patients with NSCLC.

In brief, KCNQ1OT1, TTTY15, and linc-spry3-2/3/4 were associated with radio-sensitivity of NSCLC. As the understanding into the mechanism of interaction between lncRNAs and radiotherapy deepens, lncRNAs may prove to be a potential strategy enhancing the antitumor effects of radiotherapy in patients.

4. Summary and discussion

The incidence of NSCLC has remained high, which is coupled with the 5-year survival rate remaining low. Pathological staging is particularly necessary for designating the treatment of NSCLC (138,139). Therefore, in addition to the current traditional imaging and pathological examination techniques, it is necessary to identify novel characteristic diagnostic biomarkers of NSCLC. LncRNAs can be classified according to the location, function, mechanisms or its roles in the tumors. LncRNAs are involved in proliferation and apoptosis, migration, invasion and EMT, development of drug resistance and radiation sensitivity in NSCLC. Therefore, they have the potential to serve as molecular diagnostic biomarkers, therapeutic targets and prognostic indicators for NSCLC. This is because they have a wide array of characteristic functions, high tissue and sex specificity.

Nevertheless, the application of lncRNAs in clinical therapies patients still had several challenges. Although lncRNAs are promising as an innovative tool, certain lncRNAs lack specificity. It is therefore crucial to identify the most specific lncRNAs associated with tumor staging. In addition, although evidence has been accumulating about the utility of lncRNAs, the structure and functional information on these lncRNAs remain to be fully elucidated, which impedes the application of lncRNAs for clinical diagnosis and treatment. In spite of lncRNAs having high tissue specificity and evolutionary conservation, the conservation among the various species is unsatisfactory. Accordingly, rigorous preclinical studies were required prior to the application of lncRNAs for NSCLC treatment.

LncRNAs have shown obvious advantages for the diagnosis and staging of cancer (140,141). Furthermore, the concept of developing RNA as a novel therapeutic tool has been widely discussed since the discovery of antisense RNA, direct RNA-protein interactions, functional non-coding RNA and RNA-guided gene editing (142). Overall, with further in-depth research and understanding of lncRNAs, it may provide original ideas and insights for the diagnosis and treatment of NSCLC. The development of novel diagnostic and targeted therapy strategies based on lncRNAs would bring an innovative paradigm for research and that may become an effective strategy for cancer treatment in the future.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

PYT conceived the idea and participated in preparing the figures and tables of the manuscript. DJS participated in the preparation and proofreading of the manuscript. WX, LXC and HL supervised the project and guided the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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