Research progress on long non-coding RNAs in lung cancer (Review)

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Received October 13, 2025; Accepted January 23, 2026

DOI: 10.3892/mmr.2026.13827

Abstract. Lung cancer remains a significant global health challenge, largely due to difficulties in early detection and the lack of effective therapeutic strategies for more advanced-stage disease. Elucidating the molecular mechanisms underlying lung carcinogenesis and identifying reliable biomarkers is of urgent importance. Long non-coding RNAs (lncRNAs), a class of transcripts of >200 nucleotides without protein-coding potential, have recently emerged as key regulators of tumor cell invasion, metastasis, proliferation, apoptosis and angiogenesis. Accumulating evidence suggests that lncRNAs hold notable promise as diagnostic and prognostic biomarkers in lung cancer. However, a comprehensive overview that integrates their mechanistic roles, clinical potential and the technological advances in their detection, while critically addressing the associated challenges, is lacking, to the best of the authors' knowledge. In the present review, a summary of recent advances in the mechanistic roles of lncRNAs during lung cancer progression and their involvement in therapy response and chemoresistance was provided, along with an up-to-date discussion of emerging detection technologies and their implications for clinical translation. The advantages, limitations and challenges of using lncRNAs as diagnostic or prognostic biomarkers in lung cancer are discussed. By synthesizing these aspects, the present review aimed to highlight the novel insights into lncRNAs and outline future research directions, thereby addressing a critical gap in the current literature.

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Key words: lung cancer, long non-coding RNAs, biomarker, treatment, prognosis, exosomal long non-coding RNAs, chemoresistance

Contents

1. Introduction

Lung cancer represents one of the most prevalent malignancies worldwide, with an annual incidence of ~1.2 million new diagnoses (1). Histologically, it is divided into two principal categories: Small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). NSCLC constitutes ~80% of all lung cancer cases and can be further subdivided into several subtypes: Lung adenocarcinoma (LUAD), squamous cell carcinoma and large cell carcinoma. In the early stages, NSCLC is often asymptomatic, leading to delayed detection, allowing the cancer to progress and thus high recurrence rates when treated. Although therapeutic strategies, including radiotherapy, chemotherapy and epidermal growth factor receptor (EGFR)-targeted agents, have improved, the 5-year survival rate for patients with NSCLC remains poor, ranging from 4-17% (2). While several studies have focused on protein-coding genes, the molecular pathways driving lung cancer pathogenesis and metastasis remain incompletely elucidated. Thus, continued exploration of molecular alterations is essential to uncover novel biomarkers and advance therapeutic interventions for this disease.

Long non-coding RNAs (lncRNAs) are RNA molecules of >200 nucleotides in length (3). Due to the absence of a complete open reading frame, lncRNAs have traditionally been considered incapable of encoding proteins (4). Accumulating evidence now indicates that a number of transcripts previously annotated as lncRNAs contain small open reading frames and encode functional micropeptides (5). During transcription, lncRNAs are by-products generated by RNA polymerase II, initially considered as 'junk' fragments (6). In 1991, Borsani *et al* (7) confirmed that the lncRNA XIST is involved in X-chromosome inactivation. Since then, increasing research has demonstrated the critical role of lncRNAs in biological

functions, with abnormal expression often leading to various diseases, particularly malignancies (8). Differential expression of lncRNAs has been observed in cancerous and adjacent non-cancerous tissues, suggesting their involvement in cancer initiation and progression. For example, Li *et al* (9) found that the expression of lncRNA HOXA11-AS was markedly higher in oral squamous cell carcinoma tissue compared to adjacent non-cancerous tissues. Liu *et al* (10) reported that lncRNA H19 is markedly downregulated in nephroblastoma, highlighting its potential role in the development of this cancer.

The multi-faceted roles of lncRNAs in tumorigenesis are increasingly being uncovered. Current evidence indicates their involvement in regulating gene expression through several mechanisms, from epigenetic remodeling to post-transcriptional processing (8,11). Such regulation directly impacts pivotal cellular processes, including cell invasion, metastasis, proliferation, apoptosis and angiogenesis, which define cancer pathogenesis (12). Illustrating their significance, lncRNAs such as HOTAIR, MALAT1, NEAT1 and MEG3 have been characterized as active contributors, either promoting or restraining tumor progression in various contexts (13). A key translational advantage of lncRNAs lies in their detectability in bodily fluids such as plasma and urine, where their expression profiles dynamically reflect disease activity (14). This property positions them as potentially valuable biomarkers for the early detection and prognostic monitoring of lung cancer.

While the roles of lncRNAs in various cancers have been reviewed, a focused, critical evaluation in the context of lung cancer is warranted. This necessity stems from the need to decipher the specific molecular pathogenesis of the world's leading cause of cancer death. Lung cancer's distinct etiology, most notably its strong association with tobacco smoke, drives a unique spectrum of molecular alterations and shapes a correspondingly unique and therapeutically relevant landscape of lncRNA dysregulation (15). This is exemplified by the direct induction of smoke-responsive oncogenic lncRNAs such as smoke and cancer-associated lncRNA 1, which is upregulated by cigarette smoke to mediate reactive oxygen species detoxification and promote cell survival (16). Understanding these etiology-driven lncRNA mechanisms is therefore not merely an academic exercise, but crucial for developing targeted strategies against this uniquely prevalent malignancy. Additionally, the profound clinical challenges in lung cancer, including the high frequency of late-stage diagnosis and the rapid development of resistance to therapy, underscore an urgent and specific need for novel biomarkers and therapeutic targets that lncRNAs may meet (17).

Positioning of this review. While existing reviews have markedly advanced our understanding, a synthesis organized around a dedicated translational framework is still needed. Such a framework should explicitly link mechanistic insights, including therapy resistance, to clinical applications by emphasizing the role of enabling technologies, while also critically evaluating implementation challenges. To precisely define our contribution, this work is positioned through a detailed comparison with five key reviews published between 2019 and 2024.

Compared to the narrative review by Yu *et al* (18), which begins by highlighting the limitations of traditional lung cancer screening methods and then focuses on summarizing dysregulated lncRNAs as promising biomarkers, the present review adopted a fundamentally different translational structure. Rather than organizing content around biomarker discovery per se, the present review structured its narrative as a continuous translational pipeline. This framework begins with molecular mechanisms, extends to clinical applications including therapy response prediction and culminates in a discussion of the technological advances and practical challenges that determine real world clinical implementation. Thus, while both reviews recognize the clinical potential of lncRNAs, the present review provided a more comprehensive roadmap for their translation.

Whereas Hu *et al* (19) focus on lncRNA functions in NSCLC tumorigenesis using a translational 'from bench to bedside' structure, the present review encompassed both NSCLC and SCLC. Beyond broadening the scope, the present review provided a deeper, dedicated analysis of predictive biomarkers for therapy response. Moreover, it included a standalone section on advances in lncRNA detection, a critical dimension absent from the discussion of Hu *et al* (19).

In contrast to the broad overview by Lv *et al* (20), which encompasses all major non-coding RNA types, including miRNAs, lncRNAs and circular RNAs and dedicates significant attention to exosomal ncRNAs in lung cancer, the present review delivered a focused, in-depth synthesis exclusively on lncRNAs across lung cancer. Its core theme is the integrated translational pathway for lncRNAs, rather than the exosome as a functional unit.

While the comprehensive review by Ao *et al* (21) details the roles of lncRNAs as oncogenes or tumor suppressors within NSCLC, exploring mechanistic networks such as the competing endogenous RNA (ceRNA) and tumor microenvironment modulation, the present review extended the discussion by introducing a key translational pillar. A primary distinction is its dedicated section evaluating advances in lncRNA detection. The present review focused specifically on how cutting-edge single-cell and spatial transcriptomics revolutionized discovery and bridge biology with clinical application. This represents a distinct technological dimension that complements their mechanistic and clinical analysis.

Finally, in relation to the foundational overview by Jiang *et al* (22) on regulation patterns and biologic functions, the present review integrated significant subsequent advances, particularly in therapy response and detection methodologies. It employed a more modern translational medicine framework with distinct sections on clinical potential and detection technology and a more comprehensive critical analysis of challenges and future solutions.

In conclusion, the present review offered a distinct integrative and translational perspective. It connected fundamental molecular mechanisms with the complete clinical picture, placing particular emphasis on the role of lncRNAs in predicting therapy response. Furthermore, the present review integrated critical discussions on emerging detection technologies and the principal challenges facing clinical translation, weaving them into a unified narrative. This structured approach addresses a recognized need in the literature and aimed to provide a clear roadmap for advancing lncRNA research toward clinical applications across all major forms of lung cancer, including both SCLC and NSCLC.

2. lncRNA mechanisms of action

lncRNAs share key biogenetic features with mRNAs, including synthesis by RNA polymerase II from chromatin-template regions (23). Their classification is primarily grounded in a genomic context and includes long intergenic, intronic, antisense, bidirectional and enhancer-associated lncRNAs (24). Functionally, lncRNAs exhibit a dichotomy in cancer, acting as either oncogenes or tumor suppressors; the former are frequently overexpressed to drive tumorigenesis, while the latter oppose malignant progression and metastasis (25). This dualistic paradigm is clearly illustrated in lung cancer, where disease progression is driven by a dynamic interplay between upregulated oncogenic genes (such as HOTAIR and MALAT1) and downregulated tumor suppressors (such as GAS5 and MEG3). A further functional distinction lies in their range of action: Cis-acting lncRNAs modulate local gene activity, whereas trans-acting types influence targets distantly, reflecting the broad regulatory versatility of these molecules across physiological and pathological states (26).

The functions of lncRNA are largely defined by its subcellular destination (Fig. 1). In the nucleus, these transcripts predominantly govern transcriptional regulation and chromatin architecture. Their strategy often involves recruiting key modifiers, such as transcription factors and epigenetic regulators, to specific genomic sites to alter gene expression (27). For example, the oncogenic lncRNA HOTAIR operates as a modular epigenetic scaffold in the nucleus, recruiting complexes, such as PRC2, to repress histone markers [histone H3 lysine 27 trimethylation (H3K27me3)] and silence tumor suppressor genes (28). This epigenetic reprogramming is associated with the hyperactivation of oncogenic pathways, such as the Wnt/β-catenin pathway (29). A distinct nuclear role entails functioning as molecular scaffolds that provide a structural foundation for nuclear bodies, thereby coordinating extensive regulatory networks (30). Similarly, MALAT1 localizes to nuclear speckles and regulates alternative splicing by interacting with serine/arginine-rich proteins, while also participating in transcriptional activation (31). Shifting to the cytoplasm, the functional focus of lncRNAs transitions to post-transcriptional control. Here, they exert influence over a broad spectrum of events, including mRNA stability, translational efficiency and the dynamics of intracellular signaling pathways, in part through mechanisms such as molecular sponging (32). MALAT1, for example, functions as a classic molecular sponge by sequestering tumor-suppressive miR-145, thereby dysregulating the SOX9 oncogene and enhancing cancer progression, a process that can be targeted by natural compounds such as *Glehnia littoralis* polysaccharides (33). Conversely, the tumor-suppressive lncRNA GAS5 functions as a decoy in the cytoplasm by binding to the glucocorticoid receptor, preventing its transcriptional activation of pro-survival genes and also acts as a ceRNA to modulate pathways, such as mTOR and AKT (34). These mechanisms and associated signaling pathways are summarized in Table I (28,29,31,33-36).

lncRNAs exert their regulatory influence on gene expression via three core mechanistic modes: Chromatin interaction, RNA target binding and modulation of protein activity (37). A single lncRNA frequently operates through multiple such pathways in parallel, forming intricate regulatory circuits. This functional versatility allows them to interface with diverse cellular components, a property of substantial relevance to cancer (38). The frequent downregulation of tumor-suppressive lncRNAs such asGAS5 and MEG3 in advanced lung cancer, often through mechanisms such as promoter hypermethylation, removes essential growth constraints (35). In the case of MEG3, this epigenetic silencing abrogates its critical nuclear function in activating the p53 tumor suppressor pathway, a key mechanism for its growth-inhibitory effects (36). Indeed, numerous studies have linked lncRNA activity to key oncogenic processes, including uncontrolled proliferation, evasion of apoptosis, invasion, metastasis and resistance to therapy (36,39,40). Therefore, a systematic exploration of lncRNA expression and function is essential, both for advancing our fundamental understanding of tumors and for developing novel diagnostics and targeted therapies. Future therapeutic strategies must therefore be dual-pronged, aiming to inhibit oncogenic lncRNAs while devising means to reactivate silenced tumor-suppressive ones.

3. lncRNAs in the development of lung cancer

The onset and progression of lung cancer are both driven by dysregulated gene expression, typically involving the activation of oncogenes and the inhibition of tumor suppressor genes. lncRNAs have been identified as key regulatory factors that influence lung cancer cell proliferation and apoptosis, as well as invasion, metastasis and tumor angiogenesis (Fig. 2).

lncRNAs in lung cancer cell proliferation and apoptosis. How tumor cells achieve uncontrolled proliferation and evade cell death is a central question in cancer research (41). lncRNAs are important regulators of these processes in lung cancer, primarily through acting as ceRNAs to sponge miRNAs, modulating epigenetic states and influencing key metabolic pathways such asglycolysis (42,43). A prevalent mechanism is the presence of ceRNA networks, where lncRNAs sequester specific miRNAs, thereby reducing the expression of the miRNAs' target genes and thus driving oncogenic phenotypes. For example, Tang *et al* (44) demonstrated that lncRNA UCA1 promotes lung cancer cell proliferation and inhibits apoptosis by competitively binding miR-383 to upregulate vascular endothelial growth factor A (VEGFA). Similarly, Liu *et al* (45) demonstrated that lncRNA DARS-AS1 drives tumor progression in lung cancer by enhancing cell proliferation and suppressing apoptotic death. Mechanistically, DARS-AS1 functions by sequestering miR-188-5p, an action that ultimately leads to the elevated expression of the KLF12 protein. This ceRNA mechanism also extends to the regulation of cancer cell metabolism. lncRNA HOXA11-AS promotes proliferation and glycolysis by binding to miR-148b-3p to enhance PKM2 expression (46), while LINC00665 facilitates aerobic glycolysis via a let-7c-5p/HMMR axis (42).

Beyond post-transcriptional regulation, lncRNAs directly influence the cell cycle and epigenetic programming. lnc-TMEM132D-AS1 promotes proliferation and induces M2/G_1 cell cycle arrest by sponging miR-766-5p to upregulate ENTPD1 (39). By contrast, lncRNA SNHG6 employs a different strategy; it recruits EZH2 to the p27 promoter,

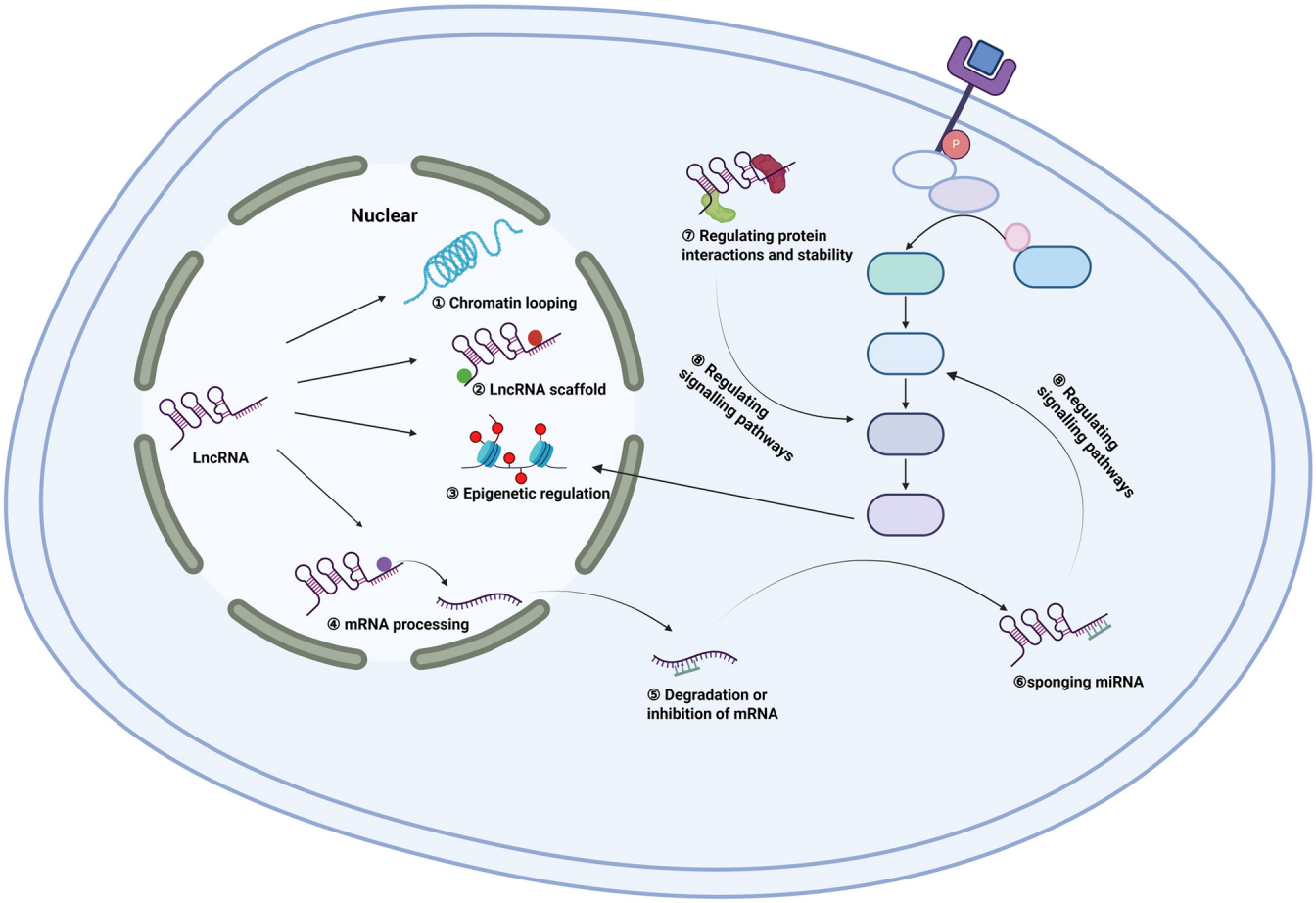

Figure 1. Mechanisms of lncRNA-mediated regulation in the nucleus and cytoplasm. Within the nucleus, lncRNAs facilitate gene regulation through multiple mechanisms. They can promote ① the formation of chromatin loops or ② serve as scaffolding platforms that recruit diverse regulatory complexes to gene promoters, leading to transcriptional activation or repression. This is often achieved by ③ guiding epigenetic modifiers to specific genomic loci, thereby altering DNA or histone methylation patterns. ④ Nuclear lncRNAs can also recruit regulatory molecules to mRNAs to regulate mRNA processing. Following their export to the cytoplasm for translation, mRNAs become targets for miRNAs, which typically repress gene expression by ⑤ inducing mRNA degradation or inhibiting translation. ⑥ Cytoplasmic lncRNAs can counteract this repression by acting as ceRNAs, sequestering miRNAs and consequently derepressing their target mRNAs. Beyond miRNA sponging, cytoplasmic lncRNAs also ⑦ regulate protein-protein interactions and protein stability, thereby modulating signal transduction pathways and the resulting gene expression profiles. ⑧ Similarly, the sequestration of miRNAs by sponging mechanisms serves as a key regulatory layer for signaling cascades by controlling mRNA activity. lncRNA, long non-coding RNAs; miRNAs, microRNAs; ceRNAs, competitive endogenous RNAs.

leading to H3K27me3-mediated epigenetic silencing of this key cell cycle inhibitor, thereby enhancing the G_1/S transition and proliferation (47). In summary, these studies underscore the critical role of lncRNAs in regulating lung cancer cell proliferation, the cell cycle and apoptosis. A summary of these mechanisms is provided in Table II (39,42,44-60).

While *in vitro* models have provided most of the current insights into lncRNA function in lung cancer cell growth and death, the true regulatory landscape within a complex tumor microenvironment (TME) is markedly more complex. This disparity between model systems and physiological reality represents a key challenge that can only be addressed through robust *in vivo* experimentation.

lncRNAs in lung cancer cell invasion and metastasis. Tumor cell invasion and metastasis constitute the primary drivers of cancer recurrence and patient mortality (61), underscoring the critical need to elucidate their underlying mechanisms for therapeutic advancement. Within this paradigm, lncRNAs have been identified as essential regulators. For example, work by Li *et al* (62) illustrated how lncRNA TEX41 promoted lung cancer cell invasion and metastasis by upregulating Runx2 and suppressing the PI3K/AKT signaling pathway. This regulatory influence extended beyond the cancer cells themselves. Notably, components of the TME, such as neutrophil extracellular traps (NETs) formed during infection or inflammation, are increasingly being recognized for their role in facilitating metastatic spread (63). Supporting this, Wang *et al* (64) demonstrated that NETs promoted NSCLC metastasis by inhibiting lncRNA MIR503HG, an action that activated the pro-metastatic NF-κB/NOD-like receptor protein 3 inflammasome pathway.

Central to cancer metastasis is epithelial-mesenchymal transition (EMT), a pivotal reprogramming event that dismantles the epithelial phenotype and confers cells increased migratory and invasive attributes associated with a mesenchymal state (65). As key regulators of this process, the dysregulation of specific lncRNAs has been shown to drive EMT, thereby endowing lung cancer cells with invasive and metastatic capabilities. Pan *et al* (66) reported that lncRNA

Table I. Key lncRNAs in lung cancer, their mechanisms and associated signaling pathways.

First author/s, year	LncRNA	Functional role	Expression	Subcellular localization	Primary mechanisms of action	Associated signaling pathways	(Refs.)
Herrera-Solorio *et al*, 2017; Hakami *et al*, 2024	HOTAIR	Oncogene	Up	Nucleus	Functions as a modular epigenetic scaffold. Recruits PRC2 to deposit the repressive histone mark H3K27me3, leading to silencing of tumor suppressor genes.	Wnt/β-catenin pathway (activated via epigenetic silencing of its inhibitors).	(28,29)
Tripathi *et al*, 2010; Alinejad *et al*, 2025	MALAT1	Oncogene	Up	Nucleus/ Cytoplasm	1. Nucleus: Localizes to nuclear speckles; regulates alternative splicing by interacting with SR proteins and participates in transcriptional activation. 2. Cytoplasm: Acts as a molecular sponge/ ceRNA by sequestering tumor-suppressive miR-145, leading to dysregulation of oncogenes such as SOX9.	miR-145/SOX9 axis and other pathways promoting cancer progression.	(31,33)
Zhou and Chen, 2020	GAS5	Tumor suppressor	Down	Cytoplasm	1. Decoy mechanism: Serves as a decoy RNA by binding to the GR, preventing its transcriptional activation of pro-survival genes. 2. ceRNA mechanism: Functions as a ceRNA to modulate pathways such as mTOR and AKT.	GR pathway, mTOR pathway, AKT pathway.	(34)
Ghafouri-Fard and Taheri, 2019; Lu *et al*, 2013	MEG3	Tumor suppressor	Down	Nucleus	Exerts growth-inhibitory effects primarily by activating the p53 tumor suppressor pathway. Its frequent downregulation is often mediated by promoter hypermethylation.	p53 tumor suppressor pathway.	(35,36)

HOTAIR, HOX antisense intergenic RNA; MALAT1, metastasis-associated lung adenocarcinoma transcript1; GAS5, growth arrest-specific transcript 5; MEG3, maternally expressed gene 3; PRC2, polycomb repressive complex 2; ceRNA, competing endogenous RNA; SOX9, Sex-determining region Y-box 9; GR, glucocorticoid receptor; mTOR, mammalian target of rapamycin.

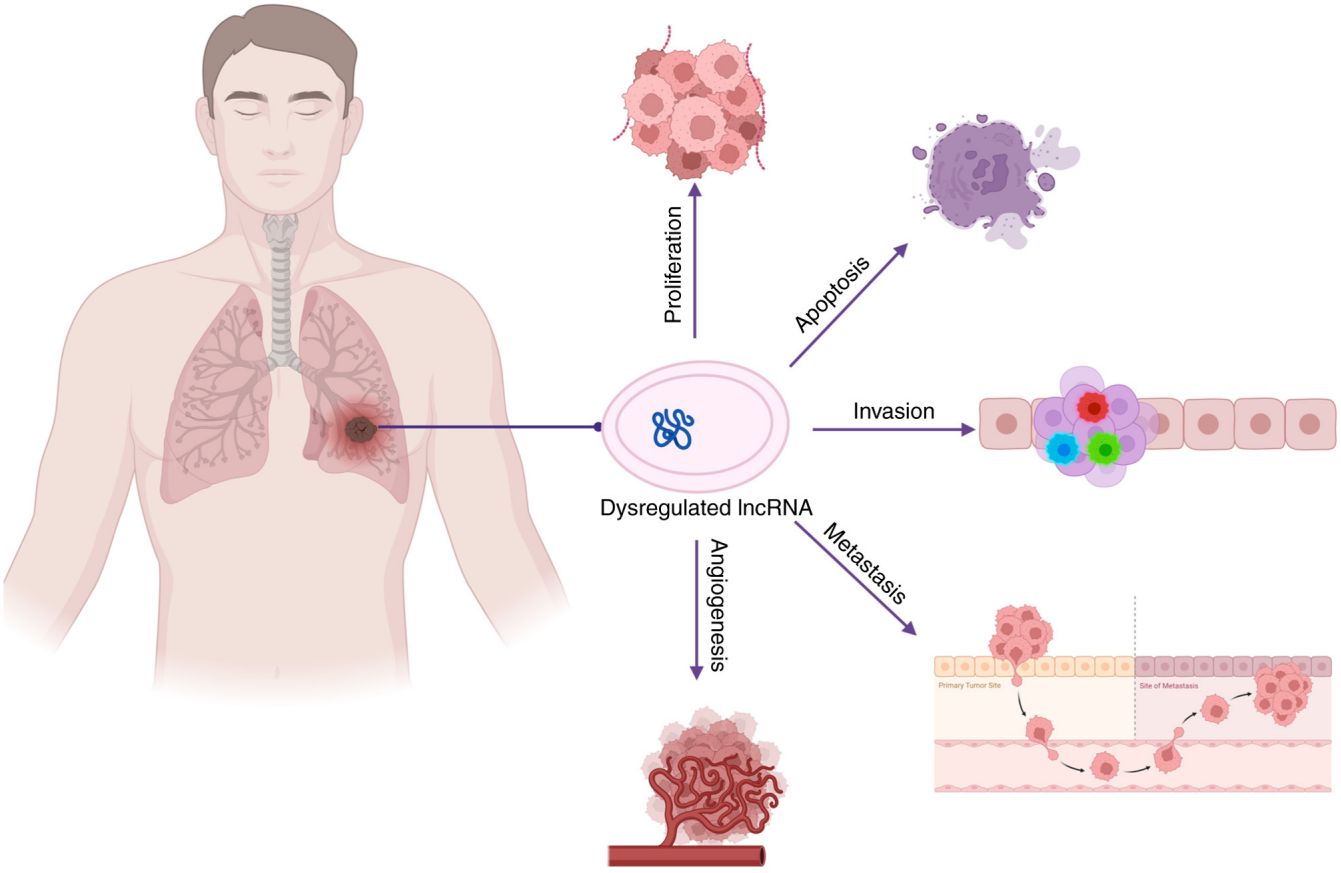

Figure 2. lncRNAs participate in the regulation of cell proliferation, apoptosis, invasion, metastasis and angiogenesis in lung cancer. lncRNA, long non-coding RNAs.

JPX promoted lung cancer cell invasion and metastasis by competitively binding miR-33a-5p to upregulate Twist1, thereby activating the Wnt/β-catenin signaling pathway, thereby inducing EMT. Additionally, Zhong *et al* (67) found that lncRNA AFAP1-AS1 induced EMT and accelerated the migration and invasion of lung cancer cells by interacting with SNIP1 to upregulate c-Myc. The specific mechanism involves AFAP1-AS1 binding to SNIP1, which acts as a molecular guide to mediate the SNIP1-c-Myc interaction. This interaction likely masks the ubiquitination site of c-Myc, thereby inhibiting its ubiquitination and proteasomal degradation, leading to the accumulation of stabilized c-Myc protein. The elevated c-Myc protein, as a transcription factor, subsequently upregulates the transcription of key EMT master regulators, including ZEB1, ZEB2 and SNAIL. The increased expression of these factors drives the EMT program, characterized by the loss of epithelial markers, such as E-cadherin and the gain of mesenchymal markers. This reprogramming confers enhanced migratory and invasive properties to lung cancer cells, ultimately promoting metastasis (67).

In summary, invasion and metastasis are multi-step malignant processes and lncRNAs may act as key regulatory factors in these processes. Developing blockers targeting lncRNAs could potentially reduce lung cancer metastasis, thus improving patient prognosis. A summary of lncRNAs associated with lung cancer migration, invasion, metastasis and EMT is provided in Table III (40,62,64,66-74).

lncRNA in lung cancer angiogenesis. Angiogenesis is the formation of new blood vessels from preexisting vessels to provide a nutrient supply that supports tumor cell growth. Tumor-induced angiogenesis is characterized by high permeability, irregular blood vessel formation, vascular infiltration and immature blood vessels (75). Generally, tumor angiogenesis is a complex process regulated by various angiogenic factors and signaling pathways, such as VEGF and the angiopoietin (Ang)/Tie2 signaling pathway (76). VEGF is the primary regulator of endothelial cell proliferation, directly facilitating tumor growth and metastasis (77). Chen *et al* (78) found that lncRNA LINC00173.v1 acts as a molecular sponge for miR-511-5p, thereby enhancing VEGFA expression. VEGFA, in turn, directly acts on endothelial cells to promote angiogenesis, accelerating the progression of lung squamous cell carcinoma. Additionally, Hou *et al* (79) demonstrated that in NSCLC, lncRNA EPIC1 stimulates endothelial cell proliferation via the Ang2/Tie2 pathway, leading to angiogenesis and the formation of vascular channels.

The pro-angiogenic functions of lncRNAs establish them as key facilitators of tumor progression, directly orchestrating the shift from a localized lesion to widespread metastatic disease.

4. Clinical potential of lncRNAs

As our understanding of the pathogenic roles of lncRNAs in lung cancer increases, their translational prospects have

Table II. Role and mechanism of lncRNAs in proliferation and apoptosis of lung cancer.

First author/s, year	LncRNA	Expression	Molecular mechanism	Function in lung cancer	(Refs.)
Wang *et al*, 2023	TMEM132D-AS1	Up	miR-766-5p/ENTPD1	Cell cycle/proliferation/apoptosis	(39)
Li *et al*, 2024	LINC00665	Up	Let-7c-5p/HMMR	Proliferation/glycolysis	(42)
Tang *et al*, 2023	UCA1	Up	miR-383/VEGFA	Proliferation/apoptosis	(44)
Liu *et al*, 2021	DARS-AS1	Up	miR-188-5p/KLF12	Proliferation/apoptosis	(45)
Chen *et al*, 2023	HOXA11-AS	Up	miR-148b-3p/PKM2	Proliferation/glycolysis	(46)
Wang *et al*, 2022	SNHG6	Up	EZH2/p27	Cell cycle/proliferation	(47)
Zheng *et al*, 2020	PIK3CD-AS2	Up	YBX1/p53	Proliferation/apoptosis	(48)
Li *et al*, 2021	MALAT1	Up	FOXP3/GINS1	Proliferation	(49)
Han *et al*, 2020	UPLA1	Up	DSP/Wnt/β-catenin	Cell cycle/proliferation	(50)
Jin *et al*, 2020	FTX	Down	miR-200a-3p/FOXA2	Proliferation	(51)
Cao *et al*, 2020	MBNL1-AS1	Down	miR-135a-5p/LOXL4	Cell cycle/proliferation/apoptosis	(52)
Yang *et al*, 2023	LINC02159	Up	ALYREF/YAP1	Cell cycle/proliferation/apoptosis	(53)
Zhu *et al*, 2022	MNX1-AS1	Up	MNX1-AS1/IGF2BP	Cell cycle/proliferation	(54)
Min *et al*, 2024	MIR100HG	Up	miR-5590-3p/DCBLD2	Proliferation	(55)
Hong *et al*, 2024	MACC1-AS1	Up	miR-579-3p/NOTCH1	Proliferation/apoptosis	(56)
Ma *et al*, 2024	HAR1A	Down	MYC/HSP90β	Proliferation/apoptosis	(57)
Zhai *et al*, 2025	SLC7A11AR	Up	miR-150-5p/SLC7A11	Proliferation	(58)
Ke *et al*, 2025	LINC00323	Up	LINC00323/AKAP1	Proliferation	(59)
Wang *et al*, 2021	GAN1	Down	miR-26a-5p/PTEN	Proliferation/apoptosis	(60)

UCA1, urothelial cancer associated 1; VEGFA, vascular endothelial growth factor A; DARS-AS1, aspartyl-tRNA synthetase anti-sense 1; KLF12, Krüppel-like factor 12; HOXA11-AS, homeobox A11 antisense; PKM2, pyruvate kinase M2; HMMR, hyaluronan-mediated mobility receptor; TMEM132D-AS1, ENTPD1, ectonucleoside triphosphate diphosphohydrolase-1; SNHG6, small nucleolar RNA host gene 6; EZH2, enhancer of zeste homolog 2; YBX1, Y-box binding protein 1; MALAT1, metastasis-associated lung adenocarcinoma transcript1; FOXP3, forkhead box protein 3; GINS1, GINS complex subunit 1; UPLA1, upregulation promoting LUAD-associated transcript-1; DSP, desmoplakin; FTX, five prime to Xist; FOXA2, forkhead box A2; MBNL1-AS1, muscleblind like splicing regulator 1 antisense RNA 1; LOXL4, lysyl oxidase-like 4; ALYREF, Aly/REF export factor; YAP1, Yes-associated protein 1; MNX1-AS1, motor neuron and pancreas homeobox 1-antisense RNA1; IGF2BP, insulin-like growth factor 2 mRNA-binding proteins; DCBLD2, discoidin, CUB and LCCL domain containing 2; NOTCH1, neurogenic locus notch homolog protein 1; HAR1A, highly accelerated region 1 A; HSP90β, heatshock protein 90β; SLC7A11, solute carrier family 7 member 11; SLC7A11AR, SLC7A11 associated lncRNA; AKAP1, A-kinase anchoring protein 1; PTEN, phosphatase and tensin homolog.

become increasingly compelling. Their specific expression across different disease contexts provides a foundation for novel approaches in early detection, treatment monitoring and outcome prediction. This section addressed the advances in applying lncRNAs as diagnostic biomarkers, therapeutic targets and prognostic tools, tracing their development from bench research to clinical utility.

lncRNAs as diagnostic biomarkers for lung cancer. The ongoing challenge of early lung cancer diagnosis, primarily due to a lack of reliable biomarkers, continues to negatively impact patient survival, even as imaging technologies advance (1). This reality highlights the critical need for diagnostic methods that are not only effective but also economical and minimally invasive. Here, lncRNAs offer considerable promise. They are notable for their high specificity, stability in body fluids such as serum and saliva and suitability for quantitative analysis, making them strong candidates as diagnostic biomarkers (12).

However, a critical assessment from the perspective of non-invasive diagnosis reveals several challenges. While lncRNAs demonstrate good stability in circulation, their typically low abundance in body fluids poses significant technical challenges for the reliability of detection and analytical sensitivity, potentially limiting their clinical utility in real-world settings (80). However, the performance of individual lncRNAs varies. A comparative analyses of key diagnostic metrics across different studies, such as area under the curve (AUC), sensitivity and specificity, are summarized in the present review, revealing the potential and limitations of various lncRNA candidates (Table IV) (81-93). HOTAIR, for example, is dysregulated across numerous types of cancer yet shows a sensitivity of only 52.3% in NSCLC detection, despite an 86.9% specificity, which is insufficient for a standalone diagnosis (81). This characteristically low sensitivity is particularly problematic for non-invasive early detection, as it can lead to unacceptably high false-negative rates in screening scenarios, potentially missing early-stage cancer when intervention would be most beneficial.

A more productive approach involves combining several biomarkers. One study found that the exosomal lncRNA GAS5 is downregulated in NSCLC. When GAS5 was used in conjunction with the conventional marker CEA, the combined AUC reached 0.929, outperforming either marker alone and demonstrating a significant boost in positive diagnosis

Table III. Roles and mechanisms of lncRNAs in migration, invasion, metastasis and EMT of lung cancer.

First author/s, year	LncRNA	Expression	Molecular mechanism	Function in lung cancer	(Refs.)
Wang *et al*, 2025	RP11-297P16.4	Up	miR-145-5p/MMP-2/9	Migration/invasion	(40)
Li *et al*, 2023	TEX41	Up	Runx2/PI3K/AKT	Migration/invasion/metastasis/autophagy	(62)
Wang *et al*, 2022	MIR503HG	Up	NF-κB/NLRP3	Metastasis	(64)
Pan *et al*, 2020	JPX	Up	miR-33a-5p/Twist1	Metastasis/invasion/EMT	(66)
Zhong *et al*, 2021	AFAP1-AS1	Up	SNIP1/c-Myc	Metastasis/invasion/EMT	(67)
Nie *et al*, 2022	DUBR	Down	c-Myc/DUBR/ZBTB11	Migration/invasion	(68)
Chen *et al*, 2025	MSTO2P	Up	Wnt/β-catenin	Migration/invasion	(69)
Ma *et al*, 2025	SPAT	Down	SF1/KITLG	Metastasis/migration	(70)
Chen *et al*, 2025	EP300-AS1	Down	PTBP1/PRMT5	Metastasis/migration/invasion	(71)
Xu *et al*, 2025	LINC00472-ORF	Down	HDAC2/SP1	Migration	(72)
Wu *et al*, 2025	TMEM99	Up	TMEM99-FUBP3-p21/IGF2BP2	Migration/invasion/autophagy	(73)
Fang *et al*, 2025	LUCAT1	Up	ALYREF/TTYH3	Migration/invasion/EMT/metastasis	(74)

TEX41, testis expressed 41; Runx2, runt-related transcription factor 2; MIR503HG, MIR503 host gene; NLRP3, NOD-like receptor protein 3; JPX, XIST activator; Twist1, twist-related protein 1; AFAP1-AS1, actin filament associated protein 1 antisense RNA 1; SNIP1, smad nuclear interacting protein 1; DUBR, dppa2 upstream binding RNA; ZBTB11, zinc finger, and BTB domain containing 11; MSTO2P, MISATO family member 2; SPAT, splice associated transcript; SF1, splicing factor 1; KITLG, KIT proto-oncogene ligand; MMP-2/9, matrix metalloproteinase 2/9; PTBP1, polypyrimidine tract binding protein 1; PRMT5, protein arginine methyltransferase 5; LINC00472-ORF, a 15-aa tumor-suppressive polypeptide; HDAC2, histone deacetylase 2; SP1, specific protein 1; FUBP3, far upstream element-binding protein 3; p21, Cyclin-dependent kinase inhibitor 1A; IGF2BP2, insulin-like growth factor 2 mRNA-binding protein 2; LUCAT1, lung cancer-related transcript 1; ALYREF, Aly/REF export factor; TTYH3, Tweety homolog 3; TMEM9, transmembrane protein 9.

rates (82). Notably, combining lncRNAs themselves can also yield improvements. Serum levels of XIST and HIF1A-AS1 are elevated in NSCLC. Their combined use achieved an AUC of 0.931, which was higher than that of XIST (AUC=0.834) or HIF1A-AS1 (AUC=0.876) used independently (83). A systematic comparison of the diagnostic performance between single and combined biomarkers is provided in Table IV (81-93). A clear pattern emerged; all combined biomarker panels demonstrated a consistent increase in AUC values to >0.9, with synchronous optimization of both sensitivity and specificity, markedly outperforming any single biomarker. This comparison provides compelling evidence of the substantial value in incorporating lncRNAs into combined diagnostic strategies. While these combination strategies show improved performance, they also increase the complexity and potential cost of non-invasive tests, which are important considerations for developing economically viable liquid biopsy platforms suitable for widespread clinical implementation.

Research has indicated that exosomes are selectively packaged with distinct lncRNA profiles in malignant tissues, facilitating their role in cell-to-cell communication and tumor progression (94-96). Exosomal lncRNAs are crucial for studying tumor biology as they participate in various processes such as cell proliferation, invasion, metastasis, angiogenesis, drug resistance and immune-suppressive microenvironments (97,98). For example, Shi *et al* (97) found that lncRNA Mir100hg is upregulated in lung cancer stem cells and can be delivered via exosomes to target miR-15a-5p and miR-31-5p, thereby increasing glycolytic activity and enhancing the metastatic potential of lung cancer cells. Therefore, lncRNA Mir100hg may serve as a diagnostic biomarker for lung cancer. Similarly, Mao *et al* (98) demonstrated that exosomal lncRNA FOXD3-AS1 derived from lung cancer cells upregulated the expression of ELAV-like RNA-binding protein 1 and activated the PI3K/Akt pathway to promote lung cancer progression, thus making lncRNA FOXD3-AS1 another potential diagnostic biomarker for lung cancer. Despite this strong biological rationale, the technical challenges in consistently isolating and characterizing tumor-derived exosomes from blood samples remain substantial. The current lack of standardized protocols for exosome isolation and lncRNA quantification represents a major bottleneck in translating these findings into clinically applicable non-invasive tests (99).

lncRNAs show promising diagnostic efficiency as non-invasive biomarkers for lung cancer, yet their clinical translation requires addressing key limitations. Current evidence is constrained by insufficient sample sizes, unclear mechanisms of dysregulation, technical challenges in reliably isolating tumor-derived exosomes from bodily fluids and a lack of comprehensive specificity analysis across cancer types (21). Future work should prioritize large-scale multicenter validation using standardized liquid biopsy protocols, mechanistic studies of lncRNA secretion and function in biofluids and direct comparisons of leading lncRNA candidates across a range of populations. Ultimately, transforming lncRNAs into clinically viable non-invasive diagnostic tools will depend on

Table IV. LncRNAs as diagnostic markers in lung cancer.

First author/s, year	Biomarker	Expression	Sample	Method	AUC	Sensitivity, %	Specificity, %	(Refs.)
Yao *et al*, 2022	HOTAIR	Up	Tissue	RT-qPCR	0.801	52.3	86.9	(81)
Li *et al*, 2019	GAS5	Down	Serum exosome	RT-qPCR	0.857	85.94	70.00	(82)
Li *et al*, 2019	CEA	UP	Serum	RT-qPCR	0.758	57.81	87.50	(82)
Li *et al*, 2019	GAS5+CEA	NA	NA	NA	0.929	89.06	90.00	(82)
Tantai *et al*, 2015	XIST	UP	Serum	RT-qPCR	0.834	NR	NR	(83)
Tantai *et al*, 2015	HIF1A-AS1	UP	Serum	RT-qPCR	0.876	NR	NR	(83)
Tantai *et al*, 2015	XIST+HIF1A-AS1	NA	NA	NA	0.931	NR	NR	(83)
Min *et al*, 2022	RP5-977B1	Up	Serum	RT-qPCR	0.8899	82.86	84.93	(84)
He *et al*, 2022	HEIH	Up	Peripheral blood	RT-qPCR	0.860	72.86	95.71	(85)
Wang *et al*, 2022	LINC00313	Up	Serum	RT-qPCR	0.916	78.91	90.63	(86)
Yang *et al*, 2020	LINC00173	Up	Serum	RT-qPCR	0.809	62.96	89.01	(87)
Zhang *et al*, 2019	DLX6-AS1	Up	Serum	RT-qPCR	0.806	77.5	85.9	(88)
Li *et al*, 2025	MIR99AHG	Down	Serum	RT-qPCR	0.908	85.71	92.38	(89)
Zang *et al*, 2020	UFC1	Up	Serum exosome	RT-qPCR	0.794	73.3	74.1	(90)
Mohamed *et al*, 2022	RP11-510M2.10	Down	Serum exosome	RT-qPCR	0.918	95	90	(91)
Wang *et al*, 2022	LUCAT1	Up	Serum exosome	RT-qPCR	0.852	84.45	77.38	(92)
Teng *et al*, 2019	SOX2-OT	Up	Serum exosome	RT-qPCR	0.815	76	73.17	(93)

HOTAIR, HOX antisense intergenic RNA; GAS5, growth arrest-specific transcript 5; CEA, carcinoembryonic antigen; XIST, X inactive-specific transcript; HIF1A-AS1, hypoxia inducible factor 1α-antisense RNA 1; HEIH, hepatocellular carcinoma upregulated EZH2-associated lncRNA; DLX6-AS1, distal-less homeobox 6 antisense 1; MIR99AHG, mir-99a-let-7c cluster host gene; LUCAT1, lung cancer associated transcript 1; SOX2-OT, SOX2 overlapping transcript; RT-qPCR, reverse transcription-quantitative PCR; AUC, area under the curve.

developing robust, cost-effective detection methods and rigorously demonstrating their analytical and clinical validity in real-world settings.

Application of lncRNAs in lung cancer treatment. Currently, surgery, thoracic radiotherapy, chemotherapy and targeted therapies are commonly used either alone or in combination to treat patients with lung cancer (100). However, resistance to chemotherapy and targeted therapies requires exploration of novel therapeutic approaches (2). Since lncRNAs play crucial roles in various aspects of lung cancer development and regulate key signaling pathways, they represent promising therapeutic targets. Moreover, several lncRNAs are associated with enhanced chemotherapy resistance, suggesting that targeting these lncRNAs may potentially restore cancer cell sensitivity to chemotherapy drugs (101,102).

There are several strategies for targeting lncRNAs in cancer treatment, including RNA interference (RNAi)-based gene silencing, antisense oligonucleotide (ASO)-based therapies, small-molecule regulators that modulate lncRNA-protein interactions and the delivery of tumor-suppressive lncRNAs (36,103-105). It has been shown that HOTAIR-siRNA, loaded into sodium alginate microspheres, can markedly inhibit the proliferation, migration and invasion of lung cancer cells (103). Further study in a PC9/GR cell xenograft model in male BALB/c nude mice confirmed that intratumoral injection of si-HOTAIR suppresses tumor growth *in vivo* (103). This anti-tumor effect is attributed to its ability to alleviate acquired resistance to EGFR-tyrosine kinase inhibitors (TKIs) by regulating the Hedgehog-Gli1 signaling pathway (103). Furthermore, HOTAIR siRNA-mediated knockdown increases the sensitivity of lung cancer cells to cisplatin treatment (106). However, RNAi may cause off-target effects and nuclear RNA targeting poses challenges, as several lncRNAs function within the cell nucleus in lung cancer. By contrast, ASOs offer advantages due to their high affinity, relatively low off-target effects and reduced toxicity (107). A study demonstrated that, in the mice model of experimental lung metastasis established via intravenous injection of A549 cells, treatment with MALAT1 ASO resulted in smaller lung tumor nodules compared to control (105). Additionally, Gong *et al* (104) developed a MALAT1-specific ASO and nuclear-targeted TAT peptide co-functionalized Au nanoparticles, called ASO-Au-TAT nanoparticles. These nanoparticles exhibited high biocompatibility and markedly reduced the formation of metastatic lung tumor nodules in an experimental lung metastasis model established by intravenous injection of A549 cells in mice. This suggests that MALAT1-ASO can inhibit lung cancer metastasis and may serve as a reliable therapeutic approach for managing lung cancer. Targeting the interaction between lncRNAs and proteins may be an effective strategy to reduce off-target effects and enhance targeting specificity. Several lncRNAs promote tumorigenesis in lung cancer through interactions with the epigenetic regulator EZH2 or by modulating EZH2 activity. Researchers have developed high-throughput screening methods to identify small molecule inhibitors that target specific lncRNA-EZH2 interactions (108). lncRNA MEG3, a well-known tumor suppressor, inhibits lung cancer cell migration and invasion and is downregulated in lung cancer tissues (109). Overexpression of lncRNA MEG3 exerts

potent antitumor effects in lung cancer. *In vivo*, ectopic expression of MEG3 markedly suppressed the growth of SPC-A1 cell-derived xenograft tumors in female athymic BALB/c nude mice. This was associated with reduced proliferation and induced apoptosis of NSCLC cells *in vitro* (36). These findings indicate that delivering tumor-suppressive lncRNAs, such as MEG3, represents a promising therapeutic strategy for lung cancer. However, delivering tumor-suppressive lncRNAs as a clinical treatment still requires further research.

Predictive lncRNAs for therapeutic response in lung cancer. Beyond their potential as direct therapeutic targets, lncRNAs are increasingly recognized for their value as predictive biomarkers. This application focuses on forecasting an individual patient's likelihood of responding to a specific, established therapy, such as chemotherapy, targeted agents, or immunotherapy, thereby guiding personalized treatment decisions and avoiding ineffective treatments and associated toxicity (110).

To date, this predictive potential has been substantiated across all major therapeutic modalities for lung cancer. In the realm of targeted therapy, reduced lncRNA H19 expression promotes acquired resistance to EGFR-TKIs such as erlotinib in EGFR-mutant lung cancers by activating the PKM2/AKT signaling axis (111). The observation that AKT inhibition restores erlotinib sensitivity in resistant models further supports the functional importance of this pathway (111). In clinical cohorts of EGFR-mutant lung cancer patients receiving EGFR-TKIs, lower H19 levels are associated with markedly shorter progression-free survival, indicating its utility as a predictive biomarker for this specific patient population (111).

During chemotherapy, lncRNA UCA1 is frequently upregulated in NSCLC and promotes resistance to platinum-based drugs. Clinically, elevated UCA1 levels in tumor tissues or serum are associated with poor response to platinum-doublet chemotherapy and worse clinical outcomes, positioning it as a potential predictive marker for chemosensitivity (112,113). Similarly, lncRNA XIST drives cisplatin resistance through mechanisms such as modulating glycolysis and inhibiting programmed cell death. Its high expression is associated with poor chemotherapy response in patients and has been validated as a predictive biomarker in preclinical models (114,115). Furthermore, lncRNA HCG11 has been shown to suppress gemcitabine resistance in NSCLC by acting as a ceRNA for miR-17-5p and upregulating p21 expression. Its tumor-suppressive role and ability to modulate chemosensitivity highlight its potential as a predictive biomarker for responses to gemcitabine-based chemotherapy (116).

The predictive role of lncRNAs is also prominently exemplified in the context of immunotherapy, where they can directly modulate the expression of immune checkpoint molecules. Two compelling examples highlight distinct mechanistic layers of this regulation. First, lncRNA LINC02418 functions as a post-translational negative regulator of PD-L1. It promotes the ubiquitination and proteasomal degradation of PD-L1 protein by enhancing its interaction with the E3 ligase Trim21. Consequently, higher LINC02418 expression is associated with lower PD-L1 protein levels, increased CD8+ T cell infiltration and predicts more favorable clinical outcomes in NSCLC patients receiving anti-PD-1/PD-L1 therapy (117). By contrast, lncRNA NKX2-1-AS1 operates at the transcriptional level to suppress PD-L1. It interacts with the transcription factor NKX2-1, interfering with its binding to the CD274 (PD-L1) promoter, thereby repressing PD-L1 gene transcription. Loss of NKX2-1-AS1 may thus contribute to an immune-evasive phenotype characterized by elevated PD-L1 expression, positioning it as a potential biomarker for identifying tumors reliant on the PD-1/PD-L1 axis (118).

These examples underscore a critical translational avenue: the profiling of specific lncRNAs could enable pretreatment stratification of patients into probable responders and non-responders. By integrating such predictive lncRNA signatures with existing clinicopathological and genetic data, a more precise and effective personalized treatment strategy can be envisioned. However, the clinical implementation of lncRNA-based predictive models requires rigorous validation in large, prospective multicenter cohorts and standardization of detection methods in accessible biospecimens such asplasma or serum.

lncRNAs as prognostic biomarkers for lung cancer. Beyond predicting the likelihood of response to specific therapies, lncRNAs also hold significant value in forecasting the long-term outcomes of lung cancer patients. The prognosis of patients with lung cancer is closely associated with the tumor node metastasis (TNM) staging system (119). Due to the presence of drug resistance, the overall survival rate for patients with lung cancer remains low. Currently, there is no accurate method to assess the prognosis of lung cancer. Studies have shown that lncRNAs can serve as predictive biomarkers for TNM staging, suggesting their potential as prognostic markers for lung cancer. For example, Wang *et al* (120) performed bioinformatics analysis and experimental validation, discovering that a novel lncRNA, AC079630.4, was markedly downregulated in lung cancer tissues. Low expression of lncRNA AC079630.4 was associated with later-stage disease and a worse prognosis compared to those with high expression, indicating that it could serve as a potential prognostic marker for lung cancer. Similarly, Chen *et al* (121) found that lncRNA AC099850.3 was markedly upregulated in LUAD. Through Cox multivariate regression analysis, it was demonstrated that lncRNA AC099850.3 was an independent prognostic factor associated with overall survival (OS), disease-free survival and progression-free survival in patients with LUAD. Liu *et al* (122) discovered that lncRNA KTN1-AS1 promoted the proliferation, migration, invasion and EMT of NSCLC cells while inhibiting apoptosis. The expression of KTN1-AS1 is associated with TNM stage, histological grade and lymph node metastasis, with high KTN1-AS1 expression correlating with reduced OS in patients with NSCLC. Furthermore, Song *et al* (123) used Cox regression and LASSO regression analysis to identify five lncRNAs associated with LUAD prognosis. Among them, GSEC, FAM83A-AS1, AL606489.1 and AC010980.2 were identified as potential risk factors, whereas AL034397.3 was a potential protective factor.

These findings indicate that lncRNAs can serve as prognostic markers and their expression levels in tumors may be used to assess patients' clinicopathological features and OS.

5. Advances in lncRNA detection

Since the 1970s, DNA sequencing has evolved from first-generation technologies to third-generation sequencing, making significant contributions to the unraveling of the human genome sequence (124). When applied to lncRNA research, these advanced technologies have proven particularly powerful. For example, Qi *et al* (125) identified a novel lncRNA, LNC11649, in NSCLC using PacBio third-generation sequencing technology. This molecule was shown to promote cytoplasmic MSI1 distribution by interacting with MSI1, thereby activating the Akt signaling pathway to regulate NSCLC cell proliferation and migration. These findings not only reveal a novel molecular mechanism in NSCLC progression but also highlight the potential of LNC11649 as a diagnostic biomarker, given its specific role in promoting oncogenic signaling pathways.

Similarly, single-cell sequencing has become indispensable for dissecting the roles of lncRNAs within the complex TME, as it can reveal gene expression patterns and lncRNA regulatory networks at the cellular level, which is crucial for understanding tumor heterogeneity (126). The power of single-cell resolution is exemplified by several recent studies leading to the discovery of functionally distinct lncRNAs in LUAD. For instance, mining of the single-cell RNA-seq dataset CancerSEA identified LINC00847, a lncRNA whose expression is associated with immune cell infiltration and PD-L1 regulation and lncRNA PCBP1-AS1, a metastasis suppressor whose expression is negatively associated with metastatic states in single-cell data, these molecules may serve as potential therapeutic targets for LUAD (127,128). Direct analysis of LUAD single-cell RNA-seq data enabled the construction of a prognostic gene signature, from which SFTA3 was prioritized as a key component. Its clinical relevance was validated by prognostic association in independent cohorts and its tumor-suppressive function was confirmed through in functional investigations showing that knockdown promoted proliferation and migration while overexpression inhibited these phenotypes. Its diagnostic potential was further indicated by markedly decreased serum levels in LUAD patients (129). Importantly, these single-cell-derived hypotheses often require spatial validation. A prime example is the study of LINC01116: Initial single-cell analysis re-localized its expression from tumor cells to lymphatic endothelial cells, a finding that was critically validated at spatial resolution by RNA-FISH, thereby solidifying its role in tumor lymphangiogenesis (130). This case highlights a growing paradigm in which high-resolution single-cell findings provide compelling hypotheses for subsequent spatial validation.

To overcome the limitation of single-cell sequencing, which loses spatial information, spatial transcriptomics provides precise localization data. The integration of these two methods is key to fully understanding cellular heterogeneity and spatial organization (131). This powerful combination has directly accelerated lncRNA discovery. Zhu *et al* (132) Combined single-cell RNA sequencing with spatial transcriptomics in LUAD; the authors' work not only identified the specific subpopulations of cancer cells and the TME but also mapped their spatial topography and interactions. This multi-faceted analysis provided a window into the molecular and cellular dynamics driving the progression from *in situ* to invasive adenocarcinoma. Such spatial and molecular characterization of lncRNAs enhances their potential as diagnostic biomarkers by linking their expression to specific tumor regions and progression stages. Lin *et al* (96) employed single-cell RNA sequencing and spatial transcriptomics to identify lncCRLA, a chemotherapy resistance-associated lncRNA in LUAD. This lncRNA was shown to be highly expressed in LUAD and demonstrated prognostic potential for predicting disease progression and evolution. The discovery of lncCRLA underscored the clinical relevance of lncRNAs as biomarkers for both diagnosis and prediction of treatment response in lung cancer.

Furthermore, to support such integrative analyses, resources such as the updated LnCeCell 2.0 database have been developed, which combines single-cell and spatial transcriptomics data and provides tools for investigating lncRNA-related ceRNA networks with high resolution, thereby improving our understanding of regulatory mechanisms in complex ecosystems (133). These resources markedly facilitate the identification and validation of lncRNAs as diagnostic biomarkers by enabling comprehensive analysis of their expression and functional networks across different cellular and spatial contexts.

6. Challenges and future perspectives

Although evidence supports the potential of lncRNAs as diagnostic, prognostic and therapeutic tools for lung cancer, numerous limitations remain for their clinical translation, particularly in diagnostics. For example, translating exosomal lncRNA biomarkers into reliable clinical assays faces significant hurdles, including their low abundance in biofluids, technical challenges in isolation and detection and a critical lack of standardization (134). To overcome this, future work must focus on standardizing isolation protocols, developing more sensitive detection technologies (such as digital PCR and next-generation sequencing) and establishing uniform validation criteria for exosomal lncRNAs to ensure their reliability as clinical biomarkers (135). Additionally, while nucleic acid-based therapies (such as ASOs and siRNAs) targeting lncRNAs hold therapeutic promise, their development faces challenges, including off-target effects, which could confound the functional validation of these lncRNAs as diagnostic targets (21). Furthermore, unlike proteins, the three-dimensional structures of several lncRNAs remain largely unknown and the absence of conserved domains complicates the design of small-molecule inhibitors and, more broadly, the understanding of their precise mechanisms of action (136). The mechanisms and regulatory networks of a number of lncRNAs in lung cancer remain poorly understood, hindering the identification of highly specific and reliable diagnostic or prognostic biomarkers. Although certain lncRNAs, such as MALAT1, are conserved, most lack cross-species conservation, hindering validation in animal models and preclinical studies, which are crucial steps for both therapeutic and biomarker development (137,138).

A significant obstacle for therapeutic applications is the difficulty in the pulmonary delivery of nucleic acid-based agents such assiRNA and ASO (139,140). Physical barriers

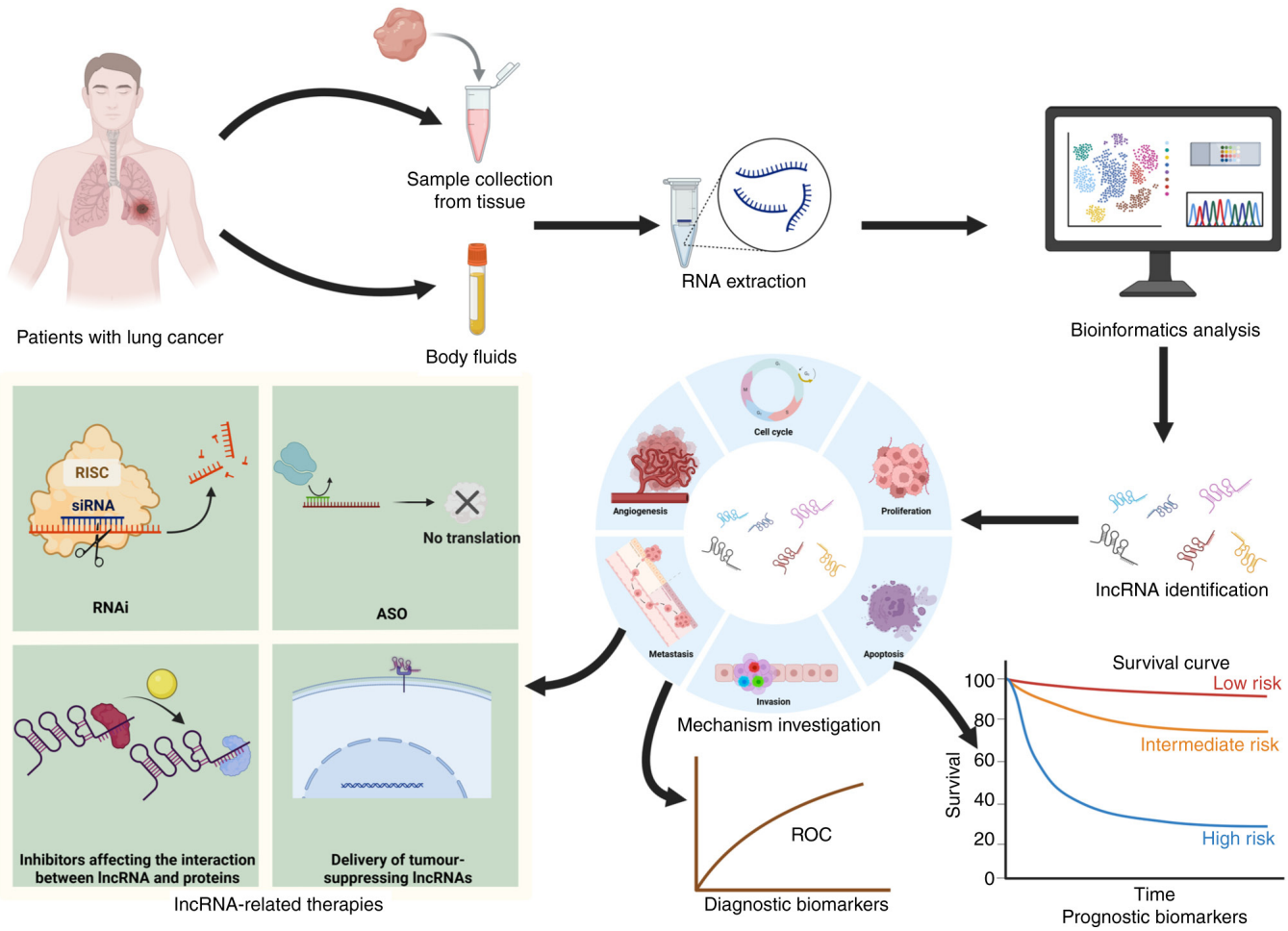

Figure 3. The complete process of lncRNAs in lung cancer research. RNA extraction was carried out from tissues or body fluids of lung cancer patients. Bioinformatics analysis was conducted using single-molecule sequencing technology to identify differential lncRNA molecules and conduct *in vitro* and *in vivo* studies to further clarify the potential mechanisms by which these lncRNAs are involved in the progression of lung cancer. The considerable diagnostic and prognostic potential of lncRNAs is undergoing extensive validation in large clinical cohorts, while simultaneously driving the development of novel therapeutic strategies for lung cancer patients. lncRNA, long non-coding RNAs; RISC, RNA-induced silencing complex; siRNA, short interfering RNA; RNAi, RNA interference; ASO, antisense oligonucleotide.

such as mucosa and cilia, along with immune clearance mechanisms, complicate initial delivery (141). To overcome these drug delivery hurdles, potential solutions include the development of advanced nanoparticle-based delivery systems (such as lipid nanoparticles and polymeric nanoparticles) and novel approaches such as CRISPR-based genome editing tools that can directly target lncRNA genes, though these strategies require further optimization for lung-specific delivery and improved safety profiles (142,143). Zeng *et al* (142) discovered that LINC02178 is a carcinogen for LUAD and accordingly developed a nanoparticle small interfering RNA delivery system (NPs/2178) targeting this gene. The NPs/2178 gene delivery system markedly promoted LUAD apoptosis and inhibited tumor growth, representing a promising gene therapy strategy. Wang *et al* (143) confirmed that lncRNA FAM83H-AS1 is a carcinogen for LUAD and targeted FAM83H-AS1 based on the CRISPR interference method to inhibit the progression of LUAD. Therefore, further optimization of *in vivo* lung drug delivery techniques is necessary to accurately evaluate the therapeutic efficacy of lncRNA-based therapies in lung cancer.

Looking ahead, research should focus on three key areas. First, multi-omics integrative analyses, including studies on lncRNA-protein interaction networks (144) and joint epigenomics-transcriptomics analyses (145). Such integrated approaches can help bridge the current knowledge gaps by comprehensively mapping lncRNA regulatory circuits and identifying novel, clinically relevant lncRNA targets. Second, high-throughput approaches can be used to analyze in greater detail the molecular mechanisms of cross-regulation between redox and epigenetic systems *in vitro* and *in vivo*, elucidating regulatory mechanisms and providing guidance for clinical treatment (146). Third, targeted drug delivery systems for lung cancer treatment need to be developed. For example, Tian *et al* (147) found that intravenous injection of exosome-targeted doxorubicin, a chemotherapy drug, specifically delivered it to tumor tissues in nude mice, inhibiting tumor growth with minimal toxicity. These platforms can be leveraged not only for the targeted delivery of lncRNA therapeutics but also for the capture and detection of tumor-specific exosomal lncRNAs, potentially leading to novel liquid biopsy platforms for early diagnosis and monitoring.

In conclusion, while lncRNAs face numerous challenges in clinical application, further research is essential to address these issues. Specifically, future efforts should prioritize bridging the translation gap for exosomal lncRNA biomarkers through standardization and improved detection methods and addressing drug-delivery challenges through innovative engineering approaches, ultimately unlocking their full potential in lung cancer management.

7. Conclusions

Lung cancer is the most common type of cancer in the respiratory system. The pathogenesis of lung cancer is highly complex and remains incompletely understood. Understanding the mechanisms underlying lung cancer is crucial for developing effective therapeutic strategies. Accumulating evidence indicates that numerous dysregulated lncRNAs contribute to lung cancer development and progression. These molecules are implicated in a range of biological processes, including proliferation, apoptosis, invasion, metastasis and angiogenesis. Moreover, aberrant lncRNA expression can be readily detected in the body fluids of patients and shows strong correlations with TNM stage, highlighting their potential as non-invasive biomarkers and therapeutic targets (Fig. 3).

Despite these promising findings, clinical application of lncRNAs faces several challenges, such as the lack of standardized detection methods, potential off-target effects and limited cohort validation. Addressing these limitations will be critical for their effective application in clinical practice. Future research should focus on translating these findings into clinical applications, such as integrating lncRNA signatures into AI-based diagnostic tools to improve early detection and personalized treatment strategies. Nevertheless, lncRNAs represent valuable diagnostic and prognostic markers and may serve as promising candidates for targeted therapies in lung cancer. Future studies should continue to identify aberrantly expressed lncRNAs and their precise functional roles in tumor biology and to explore innovative lncRNA-based therapeutic approaches.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

Not applicable.

Authors' contributions

RP prepared the original manuscript draft. CW and YT participated in conceptualization. FZ and YZ participated in guiding the preparation and design of this manuscript. QZ reviewed and edited the paper. Data authentication is not applicable. 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.

References

1. Nooreldeen R and Bach H: Current and future development in lung cancer diagnosis. Int J Mol Sci 22: 8661, 2021.
2. Hirsch FR, Scagliotti GV, Mulshine JL, Kwon R, Curran WJ Jr, Wu YL and Paz-Ares L: Lung cancer: Current therapies and new targeted treatments. Lancet 389: 299-311, 2017.
3. Bridges MC, Daulagala AC and Kourtidis A: LNCcation: lncRNA localization and function. J Cell Biol 220: e202009045, 2021.
4. Ponting CP, Oliver PL and Reik W: Evolution and functions of long noncoding RNAs. Cell 136: 629-641, 2009.
5. Zhang Y, Wang X, Hu C and Yi H: Shiny transcriptional junk: LncRNA-derived peptides in cancers and immune responses. Life Sci 316: 121434, 2023.
6. Entezari M, Ghanbarirad M, Taheriazam A, Sadrkhanloo M, Zabolian A, Goharrizi MASB, Hushmandi K, Aref AR, Ashrafizadeh M and Zarrabi A: Long non-coding RNAs and exosomal lncRNAs: Potential functions in lung cancer progression, drug resistance and tumor microenvironment remodeling. Biomed Pharmacother 150: 112963, 2022.
7. Borsani G, Tonlorenzi R, Simmler MC, Dandolo L, Arnaud D, Capra V, Grompe M, Pizzuti A, Muzny D, Lawrence C, *et al*: Characterization of a murine gene expressed from the inactive X chromosome. Nature 351: 325-329, 1991.
8. Tan YT, Lin JF, Li T, Li JJ, Xu RH and Ju HQ: LncRNA-mediated posttranslational modifications and reprogramming of energy metabolism in cancer. Cancer Commun (Lond) 41: 109-120, 2021.
9. Li B, Wang W, Miao S, Li G, Lv Y, Xiang C and Pei R: HOXA11-AS promotes the progression of oral squamous cell carcinoma by targeting the miR-518a-3p/PDK1 axis. Cancer Cell Int 19: 140, 2019.
10. Liu HC, Zhu WY and Ren LY: LncRNA H19 inhibits proliferation and enhances apoptosis of nephroblastoma cells by regulating the miR-675/TGFBI axis. Eur Rev Med Pharmacol Sci 26: 3800-3806, 2022.
11. Zhang C, Wang L, Jin C, Zhou J, Peng C, Wang Y, Xu Z, Zhang D, Huang Y, Zhang Y, *et al*: Long non-coding RNA Lnc-LALC facilitates colorectal cancer liver metastasis via epigenetically silencing LZTS1. Cell Death Dis 12: 224, 2021.
12. Fu J, Yu L, Yan H, Tang S, Wang Z, Dai T, Chen H, Zhang S, Hu H, Liu T, *et al*: LncRNAs in non-small cell lung cancer: Novel diagnostic and prognostic biomarkers. Front Mol Biosci 10: 1297198, 2023.
13. Esposito R, Bosch N, Lanzós A, Polidori T, Pulido-Quetglas C and Johnson R: Hacking the cancer genome: Profiling therapeutically actionable long Non-coding RNAs using CRISPR-Cas9 screening. Cancer Cell 35: 545-557, 2019.
14. Palanca-Ballester C, Rodriguez-Casanova A, Torres S, Calabuig-Fariñas S, Exposito F, Serrano D, Redin E, Valencia K, Jantus-Lewintre E, Diaz-Lagares A, *et al*: Cancer epigenetic biomarkers in liquid biopsy for high incidence malignancies. Cancers (Basel) 13: 3016, 2021.
15. Ge L, Zhao S, Sun J, Cheng J and Wang S: Role of long noncoding RNAs in Smoking-induced lung cancer: An in silico study. Comput Math Methods Med 2022: 7169353, 2022.
16. Cruz CRV, Ferrer JLM and Garcia RL: Concomitant and decoupled effects of cigarette smoke and SCAL1 upregulation on oncogenic phenotypes and ROS detoxification in lung adenocarcinoma cells. Sci Rep 11: 18345, 2021.
17. Chen J, Wang R, Zhang K and Chen LB: Long non-coding RNAs in non-small cell lung cancer as biomarkers and therapeutic targets. J Cell Mol Med 18: 2425-2436, 2014.

18. Yu P, He X, Lu F, Li L, Song H and Bian X: Research progress regarding long-chain non-coding RNA in lung cancer: A narrative review. J Thorac Dis 14: 3016-3029, 2022.
19. Hu Q, Ma H, Chen H, Zhang Z and Xue Q: LncRNA in tumorigenesis of non-small-cell lung cancer: From bench to bedside. Cell Death Discov 8: 359, 2022.
20. Lv X, Yang L, Xie Y and Momeni MR: Non-coding RNAs and exosomal non-coding RNAs in lung cancer: Insights into their functions. Front Cell Dev Biol 12: 1397788, 2024.
21. Ao YQ, Gao J, Jiang JH, Wang HK, Wang S and Ding JY: Comprehensive landscape and future perspective of long noncoding RNAs in non-small cell lung cancer: It takes a village. Mol Ther 31: 3389-3413, 2023.
22. Jiang L, Li Z and Wang R: Long non-coding RNAs in lung cancer: Regulation patterns, biologic function and diagnosis implications (Review). Int J Oncol 55: 585-596, 2019.
23. Eidem TM, Kugel JF and Goodrich JA: Noncoding RNAs: Regulators of the mammalian transcription machinery. J Mol Biol 428: 2652-2659, 2016.
24. Kopp F and Mendell JT: Functional classification and experimental dissection of long noncoding RNAs. Cell 172: 393-407, 2018.
25. Huang Y, Ling A, Pareek S and Huang RS: Oncogene or tumor suppressor? Long noncoding RNAs role in patient's prognosis varies depending on disease type. Transl Res 230: 98-110, 2021.
26. Lee JT: Epigenetic regulation by long noncoding RNAs. Science 338: 1435-1439, 2012.
27. Sun Q, Hao Q and Prasanth KV: Nuclear long noncoding RNAs: Key regulators of gene expression. Trends Genet 34: 142-157, 2018.
28. Herrera-Solorio AM, Armas-López L, Arrieta O, Zúñiga J, Piña-Sánchez P and Ávila-Moreno F: Histone code and long non-coding RNAs (lncRNAs) aberrations in lung cancer: Implications in the therapy response. Clin Epigenetics 9: 98, 2017.
29. Hakami MA, Hazazi A, Abdulaziz O, Almasoudi HH, Alhazmi AYM, Alkhalil SS, Alharthi NS, Alhuthali HM, Almalki WH, Gupta G and Khan FR: HOTAIR: A key regulator of the Wnt/β-catenin signaling cascade in cancer progression and treatment. Pathol Res Pract 253: 154957, 2024.
30. Tsai MC, Manor O, Wan Y, Mosammaparast N, Wang JK, Lan F, Shi Y, Segal E and Chang HY: Long noncoding RNA as modular scaffold of histone modification complexes. Science 329: 689-693, 2010.
31. Tripathi V, Ellis JD, Shen Z, Song DY, Pan Q, Watt AT, Freier SM, Bennett CF, Sharma A, Bubulya PA, *et al*: The nuclear-retained noncoding RNA MALAT1 regulates alternative splicing by modulating SR splicing factor phosphorylation. Mol Cell 39: 925-938, 2010.
32. Nojima T and Proudfoot NJ: Author Correction: Mechanisms of lncRNA biogenesis as revealed by nascent transcriptomics. Nat Rev Mol Cell Biol 23: 853, 2022.
33. Alinejad T, Hao Z, Zhou W, Zareh D, Farajtabrizi E, Mossahebi-Mohammadi M and Chen CS: Knockdown of long noncoding RNA MALAT1 enhances the anti-cancer effects of polysaccharides *Glehnia littoralis* in lung cancer cells possibly via the regulation of miR-145/SOX9 axis. Int Immunopharmacol 164: 115323, 2025.
34. Zhou Y and Chen B: GAS5-mediated regulation of cell signaling (Review). Mol Med Rep 22: 3049-3056, 2020.
35. Ghafouri-Fard S and Taheri M: Maternally expressed gene 3 (MEG3): A tumor suppressor long non coding RNA. Biomed Pharmacother 118: 109129, 2019.
36. Lu KH, Li W, Liu XH, Sun M, Zhang ML, Wu WQ, Xie WP and Hou YY: Long non-coding RNA MEG3 inhibits NSCLC cells proliferation and induces apoptosis by affecting p53 expression. BMC Cancer 13: 461, 2013.
37. Bergmann JH and Spector DL: Long non-coding RNAs: Modulators of nuclear structure and function. Curr Opin Cell Biol 26: 10-18, 2014.
38. Huang Y, Qiao Y, Zhao Y, Li Y, Yuan J, Zhou J, Sun H and Wang H: Large scale RNA-binding proteins/LncRNAs interaction analysis to uncover lncRNA nuclear localization mechanisms. Brief Bioinform 22: bbab195, 2021.
39. Wang N, Zhao Q, Huang Y, Wen C, Li Y, Bao M and Wu L: Lnc-TMEM132D-AS1 as a potential therapeutic target for acquired resistance to osimertinib in non-small-cell lung cancer. Mol Omics 19: 238-251, 2023.
40. Wang W, Lu Y, Qin GM, Ni LF, Xu BX, Liu CF, Yu BF, Wang HL and Pang M: LncRNA RP11-297P16.4 promotes the invasion and metastasis of non-small-cell lung carcinoma by targeting the miR-145-5p/MMP-2/9 axis. Biomedicines 13: 617, 2025.
41. de Visser KE and Joyce JA: The evolving tumor microenvironment: From cancer initiation to metastatic outgrowth. Cancer Cell 41: 374-403, 2023.
42. Li Z, Zhu T, Yao F, Shen X, Xu M, Fu L, Wu Y, Ding J, Zhang J and Zhao J: LINC00665 promotes glycolysis in lung adenocarcinoma cells via the let-7c-5p/HMMR axis. J Bioenerg Biomembr 56: 181-191, 2024.
43. Hua Q, Jin M, Mi B, Xu F, Li T, Zhao L, Liu J and Huang G: LINC01123, a c-Myc-activated long non-coding RNA, promotes proliferation and aerobic glycolysis of non-small cell lung cancer through miR-199a-5p/c-Myc axis. J Hematol Oncol 12: 91, 2019.
44. Tang L, Wang S, Wang Y, Li K and Li Q: LncRNA-UCA1 regulates lung adenocarcinoma progression through competitive binding to miR-383. Cell Cycle 22: 213-228, 2023.
45. Liu Y, Liang L, Ji L, Zhang F, Chen D, Duan S, Shen H, Liang Y and Chen Y: Potentiated lung adenocarcinoma (LUAD) cell growth, migration and invasion by lncRNA DARS-AS1 via miR-188-5p/KLF12 axis. Aging (Albany NY) 13: 23376-23392, 2021.
46. Chen W, Li X, Du B, Cui Y, Ma Y and Li Y: The long noncoding RNA HOXA11-AS promotes lung adenocarcinoma proliferation and glycolysis via the microRNA-148b-3p/PKM2 axis. Cancer Med 12: 4421-4433, 2023.
47. Wang Q, Zhang W, Yin D, Tang Z, Zhang E and Wu W: Gene amplification-driven lncRNA SNHG6 promotes tumorigenesis via epigenetically suppressing p27 expression and regulating cell cycle in non-small cell lung cancer. Cell Death Discov 8: 485, 2022.
48. Zheng X, Zhang J, Fang T, Wang X, Wang S, Ma Z, Xu Y, Han C, Sun M, Xu L, *et al*: The long non-coding RNA PIK3CD-AS2 promotes lung adenocarcinoma progression via YBX1-mediated suppression of p53 pathway. Oncogenesis 9: 34, 2020.
49. Li M, Shi M, Hu C, Chen B and Li S: MALAT1 modulated FOXP3 ubiquitination then affected GINS1 transcription and drived NSCLC proliferation. Oncogene 40: 3870-3884, 2021.
50. Han X, Jiang H, Qi J, Li J, Yang J, Tian Y, Li W, Jing Q and Wang C: Novel lncRNA UPLA1 mediates tumorigenesis and prognosis in lung adenocarcinoma. Cell Death Dis 11: 999, 2020.
51. Jin S, He J, Zhou Y, Wu D, Li J and Gao W: LncRNA FTX activates FOXA2 expression to inhibit non-small-cell lung cancer proliferation and metastasis. J Cell Mol Med 24: 4839-4849, 2020.
52. Cao G, Tan B, Wei S, Shen W, Wang X, Chu Y, Rong T and Gao C: Down-regulation of MBNL1-AS1 contributes to tumorigenesis of NSCLC via sponging miR-135a-5p. Biomed Pharmacother 125: 109856, 2020.
53. Yang Q, Wang M, Xu J, Yu D, Li Y, Chen Y, Zhang X, Zhang J, Gu J and Zhang X: LINC02159 promotes non-small cell lung cancer progression via ALYREF/YAP1 signaling. Mol Cancer 22: 122, 2023.
54. Zhu Q, Zhang C, Qu T, Lu X, He X, Li W, Yin D, Han L, Guo R and Zhang E: MNX1-AS1 promotes phase separation of IGF2BP1 to Drive c-Myc-mediated Cell-cycle progression and proliferation in lung cancer. Cancer Res 82: 4340-4358, 2022.
55. Min S, Zhang L, Zhang L, Liu F and Liu M: LncRNA MIR100HG affects the proliferation and metastasis of lung cancer cells through mediating the microRNA-5590-3p/DCBLD2 axis. Immun Inflamm Dis 12: e1223, 2024.
56. Hong J, Gu R, Cheng W, Lu C and Wang X: LncRNA MACC1-AS1 facilitates the cell growth of small cell lung cancer by sequestering miR-579-3p and mediating NOTCH1-pathway. Int J Biol Macromol 281: 136579, 2024.
57. Ma J, Zhang P, Wang Y, Lu M, Cao K, Wei S, Qi C, Ling X and Zhu J: LncRNA HAR1A inhibits non-small cell lung cancer growth by downregulating c-MYC transcripts and facilitating its proteasomal degradation. Int Immunopharmacol 142: 113264, 2024.
58. Zhai H, Xiang X, Pu J, Niu X, Gao J, Mu D, Du J, Li Y, Qu L, Liu B, *et al*: LncRNA SLC7A11AR promotes lung adenocarcinoma progression by inhibiting ferroptosis via promoting SLC7A11 expression. Int J Biol Sci 21: 4549-4566, 2025.
59. Ke B, Zhong H, Gong Y, Chen X, Yan C and Shi L: LINC00323 knockdown suppresses the proliferation, migration, and vascular mimicry of non-small cell lung cancer cells by promoting ubiquitinated degradation of AKAP1. Noncoding RNA Res 11: 131-140, 2025.
60. Wang RQ, Long XR, Zhou NN, Chen DN, Zhang MY, Wen ZS, Zhang LJ, He FZ, Zhou ZL, Mai SJ, *et al*: Lnc-GAN1 expression is associated with good survival and suppresses tumor progression by sponging mir-26a-5p to activate PTEN signaling in non-small cell lung cancer. J Exp Clin Cancer Res 40: 9, 2021.

61. Gerstberger S, Jiang Q and Ganesh K: Metastasis. Cell 186: 1564-1579, 2023.
62. Li R, Lin Y, Hu F, Liao Y, Tang J, Shen Y, Li H, Guo J and Xie L: LncRNA TEX41 regulates autophagy by increasing Runx2 expression in lung adenocarcinoma bone metastasis. Am J Transl Res 15: 949-966, 2023.
63. Yang L, Liu Q, Zhang X, Liu X, Zhou B, Chen J, Huang D, Li J, Li H, Chen F, *et al*: DNA of neutrophil extracellular traps promotes cancer metastasis via CCDC25. Nature 583: 133-138, 2020.
64. Wang Y, Liu F, Chen L, Fang C, Li S, Yuan S, Qian X, Yin Y, Yu B, Fu B, *et al*: Neutrophil Extracellular Traps (NETs) promote non-small cell lung cancer metastasis by suppressing lncRNA MIR503HG to activate the NF-κB/NLRP3 inflammasome pathway. Front Immunol 13: 867516, 2022.
65. Huang Y, Hong W and Wei X: The molecular mechanisms and therapeutic strategies of EMT in tumor progression and metastasis. J Hematol Oncol 15: 129, 2022.
66. Pan J, Fang S, Tian H, Zhou C, Zhao X, Tian H, He J, Shen W, Meng X, Jin X, *et al*: lncRNA JPX/miR-33a-5p/Twist1 axis regulates tumorigenesis and metastasis of lung cancer by activating Wnt/β-catenin signaling. Mol Cancer 19: 9, 2020.
67. Zhong Y, Yang L, Xiong F, He Y, Tang Y, Shi L, Fan S, Li Z, Zhang S, Gong Z, *et al*: Long non-coding RNA AFAP1-AS1 accelerates lung cancer cells migration and invasion by interacting with SNIP1 to upregulate c-Myc. Signal Transduct Target Ther 6: 240, 2021.
68. Nie W, Hu MJ, Zhang Q, Lu J, Qian FF, Zhang LL, Hu F, Li CH, Cao SH, Li JW, *et al*: DUBR suppresses migration and invasion of human lung adenocarcinoma cells via ZBTB11-mediated inhibition of oxidative phosphorylation. Acta Pharmacol Sin 43: 157-166, 2022.
69. Chen Y, Shi H, Dong Y and Cui W: LncRNA MSTO2P affects the proliferation, invasion and migration of non-small cell lung cancer by regulating the Wnt/β-catenin pathway. Discov Oncol 16: 150, 2025.
70. Ma Y, Zhou X, Yu M, Cheng X, Yang J, Ren J, Zheng C, Li J, Qian X, Yi J, *et al*: SPAT inhibits LUAD metastasis by targeting SF1-mediated splicing. Cell Death Dis 16: 598, 2025.
71. Chen J, Fan C, Song S and Zhang D: LncRNA EP300-AS1 interacts with PTBP1 to destabilize PRMT5 mRNA and suppresses NSCLC growth and metastasis. Cell Death Dis 16: 607, 2025.
72. Xu L, Kuang H, Peng H, Wu S, Bai Y, Jia X and Yao W: A LINC00472-encoded polypeptide impedes migration and proliferation through modulation of the HDAC2/SP1 axis in non-small cell lung cancer cells. Cancer Cell Int 25: 263, 2025.
73. Wu Z, Zhao Y, Peng Y, Liu P, Huang Q, Wo Y, Pan Y, Zheng D, Yuan C, Shang Y, *et al*: LncRNA TMEM99 Complexes with IGF2BP2 to inhibit autophagy in lung adenocarcinoma. Adv Sci (Weinh) 12: e07871, 2025.
74. Fang F, Zhao M, Meng J, He J, Yang C, Wang C, Wang J, Xie S, Jin X and Shi W: Upregulation of TTYH3 by lncRNA LUCAT1 through interacting with ALYREF facilitates the metastasis in non-small cell lung cancer. Cancer Biol Ther 26: 2464966, 2025.
75. Liao Y, Wu X, Wu M, Fang Y, Li J and Tang W: Non-coding RNAs in lung cancer: Emerging regulators of angiogenesis. J Transl Med 20: 349, 2022.
76. Zhang Y, Liu J, Zou T, Qi Y, Yi B, Dissanayaka WL and Zhang C: DPSCs treated by TGF-β1 regulate angiogenic sprouting of three-dimensionally co-cultured HUVECs and DPSCs through VEGF-Ang-Tie2 signaling. Stem Cell Res Ther 12: 281, 2021.
77. Cui Y, Liu H, Wang Z, Zhang H, Tian J, Wang Z, Song W, Guo H, Liu L, Tian R, *et al*: Fructose promotes angiogenesis by improving vascular endothelial cell function and upregulating VEGF expression in cancer cells. J Exp Clin Cancer Res 42: 184, 2023.
78. Chen J, Liu A, Wang Z, Wang B, Chai X, Lu W, Cao T, Li R, Wu M, Lu Z, *et al*: LINC00173.v1 promotes angiogenesis and progression of lung squamous cell carcinoma by sponging miR-511-5p to regulate VEGFA expression. Mol Cancer 19: 98, 2020.
79. Hou Y, Jia H, Cao Y, Zhang S, Zhang X, Wei P, Xie J, Dong W and Wang B: LncRNA EPIC1 promotes tumor angiogenesis via activating the Ang2/Tie2 axis in non-small cell lung cancer. Life Sci 267: 118933, 2021.
80. Badowski C, He B and Garmire LX: Blood-derived lncRNAs as biomarkers for cancer diagnosis: The good, the bad and the beauty. NPJ Precis Oncol 6: 40, 2022.
81. Yao X, Wang T, Sun MY, Yuming Y, Guixin D and Liu J: Diagnostic value of lncRNA HOTAIR as a biomarker for detecting and staging of non-small cell lung cancer. Biomarkers 27: 526-533, 2022.
82. Li C, Lv Y, Shao C, Chen C, Zhang T, Wei Y, Fan H, Lv T, Liu H and Song Y: Tumor-derived exosomal lncRNA GAS5 as a biomarker for early-stage non-small-cell lung cancer diagnosis. J Cell Physiol 234: 20721-20727, 2019.
83. Tantai J, Hu D, Yang Y and Geng J: Combined identification of long non-coding RNA XIST and HIF1A-AS1 in serum as an effective screening for non-small cell lung cancer. Int J Clin Exp Pathol 8: 7887-7895, 2015.
84. Min L, Zhu T, Lv B, An T, Zhang Q, Shang Y, Yu Z, Zheng L and Wang Q: Exosomal LncRNA RP5-977B1 as a novel minimally invasive biomarker for diagnosis and prognosis in non-small cell lung cancer. Int J Clin Oncol 27: 1013-1024, 2022.
85. He C, Huang D, Yang F, Huang D, Cao Y, Peng J and Luo X: High expression of lncRNA HEIH is helpful in the diagnosis of non-small cell lung cancer and predicts poor prognosis. Cancer Manag Res 14: 503-514, 2022.
86. Wang J, Zhang L, Wang C, Chen Y and Sui X: LINC00313/miR-4429 axis provides novel biomarkers for the diagnosis and prognosis of non-small cell lung cancer. Acta Biochim Pol 69: 343-348, 2022.
87. Yang Q, Kong S, Zheng M, Hong Y, Sun J, Ming X, Gu Y, Shen X and Ju S: Long intergenic noncoding RNA LINC00173 as a potential serum biomarker for diagnosis of non-small-cell lung cancer. Cancer Biomark 29: 441-451, 2020.
88. Zhang X, Guo H, Bao Y, Yu H, Xie D and Wang X: Exosomal long non-coding RNA DLX6-AS1 as a potential diagnostic biomarker for non-small cell lung cancer. Oncol Lett 18: 5197-5204, 2019.
89. Li W, Li W and Xu Z: LncRNA MIR99AHG serves as a diagnostic marker for early lung cancer and regulates cancer cell growth and metastasis via miR-194-5p. Discov Oncol 16: 1050, 2025.
90. Zang X, Gu J, Zhang J, Shi H, Hou S, Xu X, Chen Y, Zhang Y, Mao F, Qian H, *et al*: Exosome-transmitted lncRNA UFC1 promotes non-small-cell lung cancer progression by EZH2-mediated epigenetic silencing of PTEN expression. Cell Death Dis 11: 215, 2020.
91. Mohamed Gamal El-Din G, Ibrahim FK, Shehata HH, Osman NM, Abdel-Rahman OM and Ali M: Exosomal expression of RAB27A and its related lncRNA Lnc-RNA-RP11-510M2 in lung cancer. Arch Physiol Biochem 128: 1479-1485, 2022.
92. Wang L, Xie Y, Wang J, Zhang Y, Liu S, Zhan Y, Zhao Y, Li J, Li P and Wang C: Characterization of a novel LUCAT1/miR-4316/VEGF-A axis in metastasis and glycolysis of lung adenocarcinoma. Front Cell Dev Biol 10: 833579, 2022.
93. Teng Y, Kang H and Chu Y: Identification of an exosomal long noncoding RNA SOX2-OT in plasma as a promising biomarker for lung squamous cell carcinoma. Genet Test Mol Biomarkers 23: 235-240, 2019.
94. Li X, Wu Y and Jin Y: Exosomal LncRNAs and CircRNAs in lung cancer: Emerging regulators and potential therapeutic targets. Noncoding RNA Res 9: 1069-1079, 2024.
95. Cao Y, Liu X, Liu J, Su Z, Liu W, Yang L and Zhang L: Diagnostic value of exosomal noncoding RNA in lung cancer: A meta-analysis. Front Oncol 14: 1357248, 2024.
96. Lin S, He C, Song L, Sun L, Zhao R, Min W and Zhao Y: Exosomal lncCRLA is predictive for the evolvement and development of lung adenocarcinoma. Cancer Lett 582: 216588, 2024.
97. Shi L, Li B, Zhang Y, Chen Y, Tan J, Chen Y, Li J, Xiang M, Xing HR and Wang J: Exosomal lncRNA Mir100hg derived from cancer stem cells enhance glycolysis and promote metastasis of lung adenocarcinoma through mircroRNA-15a-5p/31-5p. Cell Commun Signal 21: 248, 2023.
98. Mao G, Mu Z and Wu DA: Exosomal lncRNA FOXD3-AS1 upregulates ELAVL1 expression and activates PI3K/Akt pathway to enhance lung cancer cell proliferation, invasion, and 5-luorouracil resistance. Acta Biochim Biophys Sin (Shanghai) 53: 1484-1494, 2021.
99. Saadh MJ, Abdulsahib WK, Daminov B, Sanghvi G, Ballal S, Sharma RSK, Pathak PK, Shankhyan A, Kumar A and Sead FF, Chaitanya MVNL: Unveiling the power of exosomal non-coding RNAs: Key drivers of lung cancer progression in the tumor microenvironment. Med Oncol 42: 308, 2025.
100. Albain KS, Swann RS, Rusch VW, Turrisi AT III, Shepherd FA, Smith C, Chen Y, Livingston RB, Feins RH, Gandara DR, *et al*: Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: A phase III randomised controlled trial. Lancet 374: 379-386, 2009.

101. Ju ZS, Sun B, Bao D and Zhang XF: Effect of lncRNA-BLACAT1 on drug resistance of non-small cell lung cancer cells in DDP chemotherapy by regulating cyclin D1 expression. Eur Rev Med Pharmacol Sci 24: 9465-9472, 2020.
102. Huang N, Guo W, Ren K, Li W, Jiang Y, Sun J, Dai W and Zhao W: LncRNA AFAP1-AS1 Supresses miR-139-5p and promotes cell proliferation and chemotherapy resistance of Non-small cell lung cancer by competitively upregulating RRM2. Front Oncol 9: 1103, 2019.
103. Lu G, Zhong H, Gao J and Zhang Y: Alginate microspheres encapsulating hox transcript antisense RNA siRNA regulate the Hedgehog-Gli1 pathway to alleviate epidermal growth factor receptor tyrosine kinase inhibitors resistance. J Biomater Appl 38: 877-889, 2024.
104. Gong N, Teng X, Li J and Liang XJ: Antisense Oligonucleotide-conjugated nanostructure-targeting lncRNA MALAT1 inhibits cancer metastasis. ACS Appl Mater Interfaces 11: 37-42, 2019.
105. Gutschner T, Hämmerle M, Eissmann M, Hsu J, Kim Y, Hung G, Revenko A, Arun G, Stentrup M, Gross M, *et al*: The noncoding RNA MALAT1 is a critical regulator of the metastasis phenotype of lung cancer cells. Cancer Res 73: 1180-1189, 2013.
106. Guo F, Cao Z, Guo H and Li S: The action mechanism of lncRNA-HOTAIR on the drug resistance of non-small cell lung cancer by regulating Wnt signaling pathway. Exp Ther Med 15: 4885-4889, 2018.
107. Chery J: RNA therapeutics: RNAi and antisense mechanisms and clinical applications. Postdoc J 4: 35-50, 2016.
108. Pedram Fatemi R, Salah-Uddin S, Modarresi F, Khoury N, Wahlestedt C and Faghihi MA: Screening for small-molecule modulators of long noncoding RNA-protein interactions using AlphaScreen. J Biomol Screen 20: 1132-1141, 2015.
109. Tu H, Zhang Z, Li J, Shi S and Costa M: Loss of MEG3 contributes to the enhanced migration and invasion in arsenic-induced carcinogenesis through NQO1/FSCN1 pathway. Am J Cancer Res 13: 2307-2322, 2023.
110. You H, Fan M, Yin L, Na F and You L: Enhanced multi-omics analysis reveals a lncRNA signature with 12 RNA modifications to predict tumor heterogeneity and potential therapy in non-small cell lung cancer. Discov Oncol 16: 1873, 2025.
111. Chen C, Liu WR, Zhang B, Zhang LM, Li CG, Liu C, Zhang H, Huo YS, Ma YC, Tian PF, *et al*: LncRNA H19 downregulation confers erlotinib resistance through upregulation of PKM2 and phosphorylation of AKT in EGFR-mutant lung cancers. Cancer Lett 486: 58-70, 2020.
112. Liu X, Huang Z, Qian W, Zhang Q and Sun J: Silence of lncRNA UCA1 rescues drug resistance of cisplatin to non-small-cell lung cancer cells. J Cell Biochem 120: 9243-9249, 2019.
113. Li C, Fan K, Qu Y, Zhai W, Huang A, Sun X and Xing S: 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 235: 3721-3730, 2020.
114. Hua G, Zeng ZL, Shi YT, Chen W, He LF and Zhao GF: LncRNA XIST contributes to cisplatin resistance of lung cancer cells by promoting cellular glycolysis through Sponging miR-101-3p. Pharmacology 106: 498-508, 2021.
115. Xu X, Zhou X, Chen Z, Gao C, Zhao L and Cui Y: Silencing of lncRNA XIST inhibits non-small cell lung cancer growth and promotes chemosensitivity to cisplatin. Aging (Albany NY) 12: 4711-4726, 2020.
116. Xu Y, Tan X, Yang Q, Fang Z and 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 24: 81-93, 2024.
117. Sun Z, Mai H, Xue C, Fan Z, Li J, Chen H, Huo N, Kang X, Tang C, Fang L, *et al*: Hsa-LINC02418/mmu-4930573I07Rik regulated by METTL3 dictates anti-PD-L1 immunotherapeutic efficacy via enhancement of Trim21-mediated PD-L1 ubiquitination. J Immunother Cancer 11: e007415, 2023.
118. Kathuria H, Millien G, McNally L, Gower AC, Tagne JB, Cao Y and Ramirez MI: NKX2-1-AS1 negatively regulates CD274/PD-L1, cell-cell interaction genes, and limits human lung carcinoma cell migration. Sci Rep 8: 14418, 2018.
119. Wu J, Li L, Zhang H, Zhao Y, Zhang H, Wu S and Xu B: A risk model developed based on tumor microenvironment predicts overall survival and associates with tumor immunity of patients with lung adenocarcinoma. Oncogene 40: 4413-4424, 2021.
120. Wang LF, Wu LP and Wen JD: LncRNA AC079630.4 expression associated with the progression and prognosis in lung cancer. Aging (Albany NY) 13: 18658-18668, 2021.
121. Chen X, Guo J, Zhou F, Ren W, Pu J, Mutti L, Niu X and Jiang X: Over-Expression of Long Non-Coding RNA-AC099850.3 correlates with tumor progression and poor prognosis in lung adenocarcinoma. Front Oncol 12: 895708, 2022.
122. Liu C, Li X, Hao Y, Wang F, Cheng Z, Geng H and Geng D: STAT1-induced upregulation of lncRNA KTN1-AS1 predicts poor prognosis and facilitates non-small cell lung cancer progression via miR-23b/DEPDC1 axis. Aging (Albany NY) 12: 8680-8701, 2020.
123. Song J, Sun Y, Cao H, Liu Z, Xi L, Dong C, Yang R and Shi Y: A novel pyroptosis-related lncRNA signature for prognostic prediction in patients with lung adenocarcinoma. Bioengineered 12: 5932-5949, 2021.
124. Kumar KR, Cowley MJ and Davis RL: Next-Generation sequencing and emerging technologies. Semin Thromb Hemost 50: 1026-1038, 2024.
125. Qi JZ, Zhao TT and Qi SS: Functions of long non-coding RNA LNC11649 in non-small cell lung cancer cells as a reprocessed form of MALAT1. Neoplasma 69: 1322-1337, 2022.
126. Chen L, Wang L, Xiong Z, Zhu X and Chen L: Exploring the prognostic significance and immunotherapeutic potential of Single-Cell Sequencing-Identified long noncoding RNA (LncRNA) in patients With Non-small cell lung cancer. Cureus 15: e48436, 2023.
127. Chen X and Zhang L: Integrative analysis revealed LINC00847 as a potential target of tumor immunotherapy. Appl Biochem Biotechnol 195: 6345-6358, 2023.
128. Li Z, Pan C, Wang Z, Deng X, Zhu Q, Wu W and Chen L: LncRNA PCBP1-AS1 correlated with the functional states of cancer cells and inhibited lung adenocarcinoma metastasis by suppressing the EMT progression. Carcinogenesis 42: 931-939, 2021.
129. Zhao Y, Zhou C, Zuo L, Yan H, Gu Y, Liu H, Yu G and Zhou X: Identification of cancer cell-intrinsic biomarkers associated with tumor progression and characterization of SFTA3 as a tumor suppressor in lung adenocarcinomas. BMC Cancer 25: 36, 2025.
130. Gautier-Isola M, Lopes Goncalves R, Truchi M, Lacoux C, Scribe C, Cadis H, Guardini L, Bekisz S, Ilié M, Hofman P, *et al*: LINC01116, a hypoxia-lncRNA marker of pathological lymphangiogenesis and poor prognosis in lung adenocarcinoma. Mol Oncol: Dec 9, 2025 doi: 10.1002/1878-0261.70175 (Epub ahead of print).
131. Huang Y, Zhu S, Yao S, Zhai H, Liu C and Han JJ: Unraveling aging from transcriptomics. Trends Genet 41: 218-235, 2025.
132. Zhu J, Fan Y, Xiong Y, Wang W, Chen J, Xia Y, Lei J, Gong L, Sun S and Jiang T: Delineating the dynamic evolution from preneoplasia to invasive lung adenocarcinoma by integrating single-cell RNA sequencing and spatial transcriptomics. Exp Mol Med 54: 2060-2076, 2022.
133. Guo Q, Liu Q, He D, Xin M, Dai Y, Sun R, Li H, Zhang Y, Li J, Kong C, *et al*: LnCeCell 2.0: An updated resource for lncRNA-associated ceRNA networks and web tools based on single-cell and spatial transcriptomics sequencing data. Nucleic Acids Res 53: D107-D115, 2025.
134. Wu Y, Wang Y, Wei M, Han X, Xu T and Cui M: Advances in the study of exosomal lncRNAs in tumors and the selection of research methods. Biomed Pharmacother 123: 109716, 2020.
135. Tang P, Sun D, Xu W, Li H and Chen L: Long non-coding RNAs as potential therapeutic targets in non-small cell lung cancer (Review). Int J Mol Med 52: 68, 2023.
136. Mishra A and Mishra S: Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) lncRNA conformational dynamics in complex with RNA-Binding Protein with Serine-Rich domain 1 (RNPS1) in the Pan-cancer splicing and gene expression. ACS Omega 9: 42212-42226, 2024.
137. Monroy-Eklund A, Taylor C, Weidmann CA, Burch C and Laederach A: Structural analysis of MALAT1 long noncoding RNA in cells and in evolution. Rna 29: 691-704, 2023.
138. Vannini I, Ferracin M, Fabbri F and Fabbri M: Overexpression of ultraconserved region 83-induces lung cancer tumorigenesis. PLoS One 17: e0261464, 2022.
139. Statello L, Ali MM and Kanduri C: In vivo administration of therapeutic antisense oligonucleotides. Methods Mol Biol 2254: 273-282, 2021.
140. Chen Y, Li Z, Chen X and Zhang S: Long non-coding RNAs: From disease code to drug role. Acta Pharm Sin B 11: 340-354, 2021.
141. Li Y, Lin M, Wang S, Cao B, Li C and Li G: Novel angiogenic regulators and Anti-Angiogenesis drugs targeting angiogenesis signaling pathways: Perspectives for targeting angiogenesis in lung cancer. Front Oncol 12: 842960, 2022.

142. Zeng L, Wen H, Jiao T, Zhang Q, Zhao X, Zhang L and Yang S: LINC02178 drives lung adenocarcinoma progression and serves as a therapeutic target for nanodelivery-based intervention. Sci Rep 15: 39344, 2025.
143. Wang S, Han C, Liu T, Ma Z, Qiu M, Wang J, You Q, Zheng X, Xu W, Xia W, *et al*: FAM83H-AS1 is a noncoding oncogenic driver and therapeutic target of lung adenocarcinoma. Clin Transl Med 11: e316, 2021.
144. Alhajlah S: The molecular mechanisms of various long non-coding RNA (lncRNA) in human lung tumors: Shedding light on the molecular mechanisms. Pathol Res Pract 256: 155253, 2024.
145. Liu Z, Jiang H, Zhao R, Quan Q and Huang X: Long Noncoding RNA IPW is a novel diagnostic and predictive biomarker in lung adenocarcinoma. Genet Test Mol Biomarkers 27: 18-26, 2023.
146. Zhang X, Ma L and Wang J: Cross-regulation between redox and epigenetic systems in tumorigenesis: Molecular mechanisms and clinical applications. Antioxid Redox Signal 39: 445-471, 2023.
147. Tian Y, Li S, Song J, Ji T, Zhu M, Anderson GJ, Wei J and Nie G: A doxorubicin delivery platform using engineered natural membrane vesicle exosomes for targeted tumor therapy. Biomaterials 35: 2383-2390, 2014.