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Revisiting Lung Cancer Metastasis: Insight From the Functions of Long Non-coding RNAs

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Abstract

Globally, lung cancer is the most common cause of cancer-related deaths. After diagnosis at all stages, <7% of patients survive for 10 years. Thus, diagnosis at later stages and the lack of effective and personalized drugs reflect a significant need to better understand the mechanisms underpinning lung cancer progression. Metastasis should be responsible for the high lethality and recurrence rates seen in lung cancer. Metastasis depends on multiple crucial steps, including epithelial–mesenchymal transition, vascular remodeling, and colonization. Therefore, in-depth investigations of metastatic molecular mechanisms can provide valuable insights for lung cancer treatment. Recently, long noncoding RNAs (lncRNAs) have attracted considerable attention owing to their complex roles in cancer progression. In lung cancer, multiple lncRNAs have been reported to regulate metastasis. In this review, we highlight the major molecular mechanisms underlying lncRNA-mediated regulation of lung cancer metastasis, including (1) lncRNAs acting as competing endogenous RNAs, (2) lncRNAs regulating the transduction of several signal pathways, and (3) lncRNA coordination with enhancer of zeste homolog 2. Thus, lncRNAs appear to execute their functions on lung cancer metastasis by regulating angiogenesis, autophagy, aerobic glycolysis, and immune escape. However, more comprehensive studies are required to characterize these lncRNA regulatory networks in lung cancer metastasis, which can provide promising and innovative novel therapeutic strategies to combat this disease.

Keywords

microRNA, long noncoding RNA, lung cancer, metastasis, invasion, migration, immune escape

Abbreviations

AICD, activation-induced cell death; AKT, protein kinase B; Ang, angiopoietin; ATP, adenosine triphosphate; BCYRN1, brain cytoplasmic RNA 1; CDH1, cadherin 1; ceRNA, competing endogenous RNA; cGAS, cyclic GMP-AMP synthase; CTL, cytotoxic T lymphocyte; DACH1, Dachshund homolog 1; DGCR5, DiGeorge syndrome critical region gene 5; DLX6-AS1, distal-less homeobox 6 antisense 1; EIF4A3, eukaryotic translation initiation factor 4A3; EMT, epithelial–mesenchymal transition; EPHB6, EPH receptor B6; ERK, extracellular signal-regulated kinase; EZH2, enhancer of zeste homolog 2; FER1L4, Fer-1-like protein 4; FLVCR1-AS1, feline leukemia virus subgroup C receptor 1 antisense RNA 1; FOXD3-AS1, forkhead box D3 antisense RNA 1; GATA6-AS1, GATA6 antisense RNA 1; GSPT1, G1–S phase transition 1; H3K27, histone H3 lysine 27; HCG11, HLA complex group 11; HIF-1α, hypoxia-inducible factor-1α; Hk, hexokinase; HMGB1, high-mobility group protein B1; HOTAIR, HOX transcript antisense intergenic RNA; HOTAIRM1, HOTAIR myeloid-specific 1; IFN-β, interferon-β; IGFBP4-1, insulin-like growth factor binding protein 4 to 1; LAD, lung adenocarcinoma; LCAT1, lung cancer-associated transcript 1; LCPAT1, lung cancer

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progression-associated transcript 1; LIFR-AS1, leukemia inhibitory factor receptor antisense RNA 1; LIMK, Lin11, Isl-1, and Mec-3 kinase; Lnc-EPIC1, long noncoding RNA EPIC1; lncRNAs, long noncoding RNA; LSCC, lung squamous cell carcinoma; MALAT1, metastasis-associated LAD transcript 1; MAPK, mitogen-activated protein kinase; MDM2, mouse double minute 2; MDSC, myeloid-derived suppressor cell; MEG3, maternally expressed gene 3; miRNA, microRNA; MMP9, matrix metalloproteinase 9; mRNA, messenger RNA; ncRNA, noncoding RNA; NEAT1, nuclear paraspeckle assembly transcript 1; NEDD9, neural precursor cell-expressed developmentally downregulated 9; NF-κB, nuclear factor kappa B; NKILA, NF-κB interacting lncRNA; Nrf2, nuclear factor erythroid 2 p45-related factor 2; NSCLC, nonsmall cell lung cancer; NSCLCAT1, nonsmall cell LCAT1; PCAT6, prostate cancer-associated transcript 6; PDE2A, phosphodiesterase 2A; PDIA3P, protein disulfide isomerase family A member 3 pseudogene 1; PD-L1, programmed death ligand 1; PGK1, phosphoglycerate kinase 1; PI3K, phosphoinositide 3-kinase; PKM2, M2 isoform of pyruvate kinase; PM-2.5, particulate matter-2.5; PRC2, polycomb repressive complex 2; PRR11, proline-rich 11; PVT1, plasmacytoma variant translocation 1; RAC1, Rac family small GTPase 1; RKIP, raf kinase inhibitor protein; ROS, reactive oxygen species; RSF1-IT2, remodeling and spacing factor 1-intronic transcript 2; SCLC, small cell lung cancer; SNHG20, small nucleolar RNA host gene 20; SOCS5, suppressor of cytokine signaling 5; Sox2ot, SOX2 overlapping transcript; SPRY4-IT1, SPRY4 intronic transcript 1; SRCIN1, SRC kinase signaling inhibitor 1; STAT3, signal transducer and activator of transcription 3; STING, stimulator of interferon gene; SUMO1P3, small ubiquitin-like modifier 1 pseudogene 3; TAZ, transcriptional coactivator with PDZ-binding motif; TGF-β, transforming growth factor β; TINCR, terminal differentiation-induced noncoding RNA; TNK2-AS1, tyrosine kinase nonreceptor 2 antisense RNA 1; TP73-AS1, tumor protein P73 antisense RNA 1; TSLNC8, tumor-suppressive role of lncRNA on chromosome 8p12; TUG1, taurine upregulated gene 1; TUSC3, tumor suppressor candidate 3 expression; UCA1, urogenital carcinoma antigen 1; VAL, vimentin-associated lncRNA; VEGFA, vascular endothelial growth factor A; VEGFR2, VEGF receptor 2; Wnt, wingless/integrated; YAP, Yes-associated protein; ZEB1, zinc-finger e-box binding homeobox 1; ZNF471, zinc-finger protein 471.

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Introduction

Lung cancer is the most lethal malignancy accounting for 18% of total cancer deaths.[1] Cancer statistics from 2021 indicated that the disease accounted for ∼22% of cancer-related deaths, with 235,760 new cases of bronchial and lung cancer diagnosed in the United States.[2] In China, the age-standardized mortality rate for lung cancer is 18.1%, which ranks first in the cancer spectrum.[3] After lung cancer diagnosis at all stages, <7% of patients survive for 10 years.[3] The disease typically incorporates two pathological subtypes: nonsmall cell lung cancer (NSCLC) and small cell lung cancer (SCLC). NSCLC is the main subtype and includes lung adenocarcinoma (LAD), lung squamous cell carcinoma (LSCC), and large-cell carcinoma. These cancers are induced by smoking, radon exposure, viral infection, and other harmful factors.[4–6]

Lung cancer metastasis is a key factor implicated in lung cancer recurrence and death.[7] Generally, the metastatic cascade contains several discrete stages: nascent tumor cells invade surrounding tissues and intravasate into the vascular system where they survive in the circulatory system. They then extravasate through dysfunctional vascular walls into target tissues or organ sites where they expand and grow.[8] During the local invasion, normal epithelial cells undergo depolarization, losing cell–cell interactions, transforming into mesenchymal cells, and acquiring a metastatic phenotype.[9] This complicated process is termed epithelial–mesenchymal transition (EMT) and is the driving force of tumor cell invasion.[10] Nascent tumor cells then break epithelial junctions by exploiting matrix-degrading enzymes induced by EMT to access the circulation via leaky and circuitous tumor vasculature induced by angiogenesis.[11] However, after detaching from primary sites, disseminated tumor cells must resist programmed apoptosis termed anoikis.[12] Finally, disseminated tumor cells colonize at distant sites.[13] Metastasis is a complex and intricate cancer behavior; therefore, a better understanding of metastatic processes will help us overcome the heavy burden of lung cancer.[13]

The Encyclopedia of DNA Elements project indicates that the human genome is generally transcribed into multiple nonprotein-coding RNA molecules, commonly referred to as noncoding RNAs (ncRNAs).[14] In general, based on molecular size, ncRNAs are categorized into two major types: short ncRNAs and long ncRNAs (lncRNAs).[15] Short ncRNAs are composed of <200 nucleotides and include microRNAs (miRNAs), small interfering RNAs, and small nuclear RNAs.[16] Conversely, lncRNAs are a novel group of RNA transcripts measuring >200 nucleotides, but they do not encode peptides.[17] Many studies have reported that lncRNAs participate in multiple physiological processes, including cell proliferation, regulation of apoptosis, invasion, and cellular energy metabolism.[18,19] Similarly, their aberrant expression is particularly related to several diseases, especially cancers.[20] Several studies have demonstrated that the abnormal expression of lncRNAs exerts key functions in lung cancer tumorigenesis and metastasis.[21–23] Emerging studies have also reported that lncRNAs are promising therapeutic targets for treating lung cancer metastasis.[21,22] Therefore, exploring the regulatory mechanisms underpinning lncRNA expression in lung cancer metastasis is warranted.

In this review, we comprehensively explored lncRNAs in lung cancer metastasis and summarized key mechanisms

behind their regulation with a view to advance our knowledge of lung cancer metastasis.

Overview of lncRNAs: Biogenesis, Classification, and Function

LncRNAs are endogenous transcripts transcribed by RNA polymerase II, with many lncRNAs harboring a 7mC cap and poly-A tail similar to messenger RNA (mRNA).[17] lncRNAs are located in both coding and noncoding gene regions. Based on their relative proximity to neighboring genes and genomic origins, lncRNAs are broadly classified into six categories (Figure 1): (1) intergenic lncRNAs originating from intergenic regions of protein-coding genes; (2) intronic lncRNAs transcribed from intronic regions of protein-coding genes; (3) bidirectional lncRNAs produced from the promoter of a coding transcript, but in a divergent direction; (4) sense lncRNAs that cover exons of neighboring protein-coding genes in the same direction; (5) antisense lncRNAs transcribed in the opposite direction to a neighboring coding transcript; and (6) enhancer lncRNAs generated from enhancer regions.[17,24]

It was reported that lncRNA functions are strongly associated with their subcellular localization.[25] Evidence from human cells using single-molecule RNA fluorescence in situ-hybridization revealed diverse lncRNA subcellular localization patterns, including specific nuclear locations and nonspecific localization to both the nucleus and cytoplasm.[26] The wide-ranging subcellular localization of lncRNAs suggests diverse modes of action (Figure 2).

lncRNAs play important roles in nuclear architecture as they are involved in the creation and maintenance of nuclear paraspeckles.[27] Additionally, lncRNAs modify gene expression by guiding chromatin modifiers to genomic loci.[28] Other lncRNAs accumulate in the cytoplasm where they function as sponges for miRNAs to regulate gene expression.[29]

lncRNAs also play crucial roles in transcription as they interact with transcription factors to activate or interfere with these processes.[30] Moreover, lncRNAs posttranscriptionally regulate gene expression by interacting with RNA-binding proteins to influence splicing and translation.[31] Further, lncRNAs control protein stability by regulating proteasome-mediated degradation.[32]

Molecular Mechanisms of lncRNAs in Lung Cancer Metastasis

lncRNAs Regulate Lung Cancer Metastasis by Sponging miRNAs

miRNAs regulate gene expression by regulating mRNA at the posttranscriptional level.[33] A previous study has reported that lncRNAs sponge certain miRNAs to alter miRNA abundance and suppress downstream target gene expression.[34] This molecular model is termed competing endogenous RNA (ceRNA) that is essential for cancer progression.[35] Here, we describe several lncRNAs that serve as ceRNAs to regulate lung cancer metastasis (Table 1).

Oncogenic lncRNAs act as ceRNAs. lncRNA lung cancer-associated transcript 1 (LCAT1) is upregulated in LAD tissues and is closely correlated with poor prognosis. LCAT1 directly sponges miR-4715 to 5p to increase the expression of the Rac family small GTPase 1 (RAC1), thus promoting tumor metastasis in vivo.[36]

Elevated metastasis-associated LAD transcript 1 (MALAT1) expression is related to a high metastatic risk in patients with early stage LAD.[37] Gutschner et al[38] reported that MALAT1

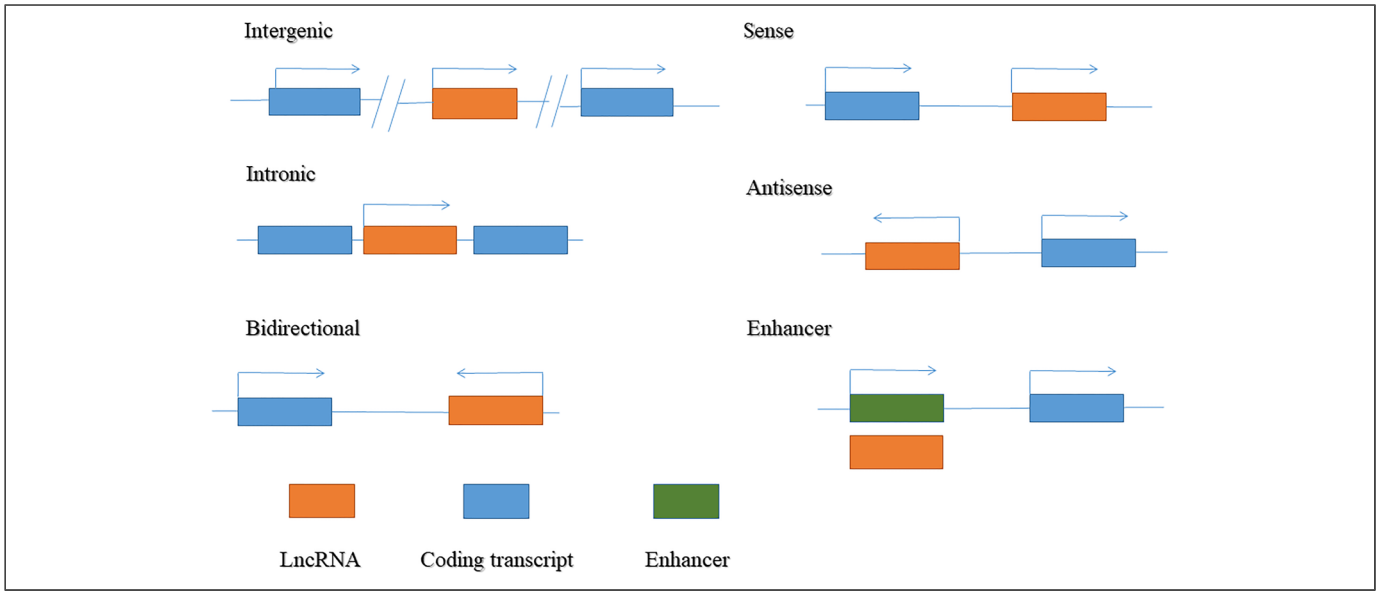

Figure 1. Classification of long non-coding RNA (lncRNA).

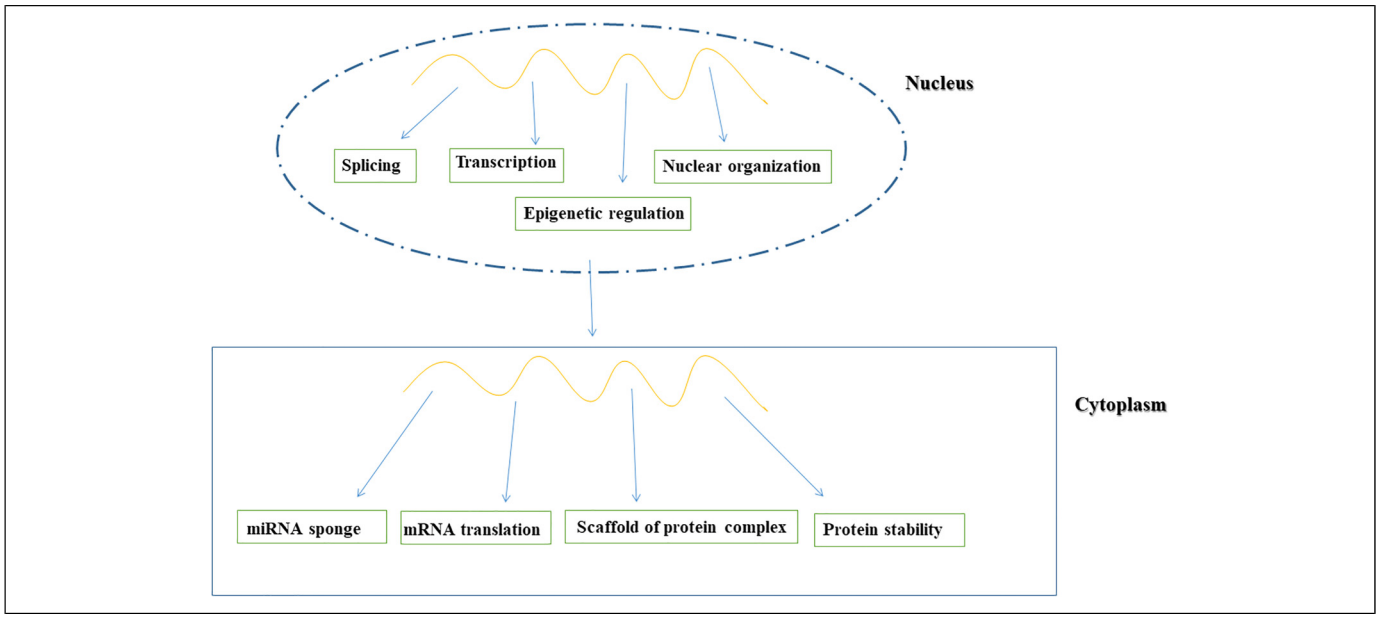

Figure 2. Function of long non-coding RNA (lncRNA).

promotes lung tumor nodule formation in vivo; however, detailed mechanisms remain unclear. Recently, several studies indicated that MALAT1 acted as a ceRNA to increase the expression of metastasis-related genes, including zinc-finger transcription repressor SNAI2 (SLUG), neural precursor cell-expressed developmentally downregulated 9 (NEDD9), and programmed death ligand 1 (PD-L1), by competitively sponging miR-204, miR-145 to 5p, and miR-200a-3p.[39–41]

Wang et al[42] revealed that urogenital carcinoma antigen 1 (UCA1) is upregulated during NSCLC progression. Using receiver operating characteristic curve analysis, these authors showed that plasma UCA1 demonstrates a considerable diagnostic value for detecting NSCLC. Moreover, UCA1 promoted NSCLC metastasis by sponging miRNA-193a to increase high-mobility group protein B1 (HMGB1) expression.[43] HMGB1 is a highly conserved nuclear DNA-binding protein with an essential role in gene transcription,[60] eg, remodeling and spacing factor 1-intronic transcript 2 (RSF1-IT2) is transcriptionally activated by HMGB1.[44] Highly expressed RSF1-IT2 promoted NSCLC metastasis by sponging miR-129 to 5p and upregulating the expression of snail family transcriptional repressor 1. Importantly, upregulated RSF1-IT2 induced by HMGB1 was strongly associated with tumor metastasis in xenograft nude mice.[44] These findings suggest that HMGB1 and its related lncRNAs may be potential therapeutic targets for NSCLC.

The miR-200 family suppresses EMT by directly targeting EMT markers, such as E-cadherin, zinc-finger e-box binding homeobox 1 (ZEB1), and ZEB2.[61] Imprinted maternally expressed transcript (H19) is one such oncogenic lncRNA reported to promote NSCLC metastasis by acting as a ceRNA of miR-200a.[45] Intriguingly, lncRNA plasmacytoma variant translocation 1 (PVT1), which is upregulated in NSCLC and related to positive lymph node metastasis, was shown to sponge miR-200a and miR-200b to increase matrix metalloproteinase 9 (MMP9) expression, thereby promoting NSCLC metastasis.[46,47] These studies identified a novel mechanism whereby the miR-200 family serves as an upstream regulator of MMP9.

Similarly, HOX transcript antisense intergenic RNA (HOTAIR) was shown to facilitate NSCLC migration and metastasis by modulating miR-203 and miR-613 expression.[48,49] Using bioinformatics, Chen et al[50] revealed that HOTAIR shares conserved binding sites for miR-217 with Dachshund homolog 1 (DACH1). Moreover, silencing HOTAIR suppressed NSCLC cell migration and invasion by enhancing miR-217 expression, which was reversed by DACH1.[50] Therefore, HOTAIR can function as a potential marker for NSCLC diagnosis and treatment.

Small ubiquitin-like modifier 1 pseudogene 3 (SUMO1P3) is upregulated in NSCLC and promotes cell invasion and migration by sponging miR-136.[51] Intriguingly, SUMO1P3 expression was not associated with clinical prognosis in patients with NSCLC, suggesting that SUMO1P3 may be regulated by other oncogenes or tumor suppressor genes during NSCLC development.[51] This association warrants further investigation.

Distal-less homeobox 6 antisense 1 (DLX6-AS1) is an oncogenic lncRNA known to facilitate NSCLC cell invasion and migration by regulating the miR-27b-3p/G1–S phase transition 1 (GSPT1) and miR-144/proline-rich 11 (PRR11) axis. These interactions may contribute to a comprehensive understanding of tumorigenesis in lung cancer.[52,53]

Tumor-Suppressive lncRNAs act as ceRNAs. DiGeorge syndrome critical region gene 5 (DGCR5) plays a crucial role in cell

Table 1. LncRNAs Regulate Lung Cancer Metastasis Through Sponging miRNAs.

LncRNA	Expression	Cancer type	Molecular mechanism	Function	Reference
LCAT1	Up	LAD	Sponges miR-4715 to 5p to upregulate RAC1	Promotes tumor metastasis in vivo.	Yang et al[36]
MALAT1	Up	LAD	Regulates miR-204/SLUG; miR-145 to 5p/NEDD9; and miR-200a-3p/PD-L1	Promotes cell EMT and metastasis; promotes lung tumor nodules formation Correlates with high metastatic risk in patients with early stage lung cancer	Ji et al,[37] Gutschner et al,[38] Li et al,[39] Yu et al,[40] and Wei et al[41]
UCA1	Up	NSCLC	Regulates miR-193a/HMGB1	Promotes cell invasion and migration Plasma UCA1 severs as a valuable biomarker for the diagnosis of NSCLC	Wang et al[42] and Wu and Zhou[43]
RSF1-IT2	Up	NSCLC	HMGB1 activates its transcription; regulates miR-129 to 5p/SNAIL1	Promotes cell invasion, migration in vitro and lung metastasis in vivo	Wu et al[44]
H19	Up	NSCLC	Regulates miR-200a/ZEB1 and miR-200a/ZEB2	Promotes cell EMT, invasion, and migration	Zhao et al[45]
PVT1	Up	NSCLC	Regulates miR-200a/MMP9 and miR-200b/MMP9	Facilitates cell invasion and migration Correlates with lymph node metastasis	Yang et al[46] and Chen et al[47]
HOTAIR	Up	NSCLC	Sponges miR-203 and miR-613; regulates miR-217/DACH1	Facilitates cell migration and invasion	Zhang et al,[48] Jiang et al,[49] and Chen et al[50]
SUMO1P3	Up	NSCLC	Sponges miR-136	Promotes cell invasion and migration	Zhang et al[51]
DLX6-AS1	Up	NSCLC	Regulates miR-27b-3p/GSPT1 and miR-144/ PRR11	Promotes cell invasion and migration	Sun et al[52] and Huang et al[53]
DGCR5	Down	NSCLC	Regulates miR-211 to 5p/EPHB6 and miR-873 to 5p/TUSC3	Inhibits cell migration and invasion Relates with lymph node metastasis	Kang et al[54] and Luo et al[55]
FOXD3-AS1	Down	NSCLC	Regulates miR-150/ SRCIN1	Inhibits cell invasion and associates with lymph node metastasis	Ji et al[56]
LIFR-AS1	Down	NSCLC	Regulates miR-942 to 5p/ZNF471	Inhibits metastasis both in vitro and in vivo	Wang et al[57]
GATA6-AS1	Down	NSCLC	Regulates miR-543/RKIP axis	Inhibits cell invasion and migration	Gong et al[58]
HCG11	Down	NSCLC	Sponges miR-522 to 3p to upregulate SOCS5	Inhibits tumor metastasis and growth both in vivo and in vitro	Fan et al[59]

Abbreviations: DACH1, Dachshund homolog 1; DGCR5, DiGeorge syndrome critical region gene 5; DLX6-AS1, distal-less homeobox 6 antisense 1; EMT, epithelial–mesenchymal transition; EPHB6, EPH receptor B6; FOXD3-AS1, Forkhead box D3 antisense RNA 1; GATA6-AS1, GATA6 antisense RNA 1; GSPT1, G1–S phase transition 1; HCG11, HLA complex group 11; HMGB1, high-mobility group protein B1; HOTAIR, HOX transcript antisense intergenic RNA; LAD, lung adenocarcinoma; LCAT1, lung cancer-associated transcript 1; LIFR-AS1, leukemia inhibitory factor receptor antisense RNA 1; MALAT1; metastasis-associated LAD transcript 1; miRNA, microRNA; lncRNA, long noncoding RNA; MMP9, matrix metalloproteinase 9; NEDD9, neural precursor cell-expressed developmentally downregulated 9; NSCLC, nonsmall cell lung cancer; PD-L1, programmed death ligand 1; PRR11, proline-rich 11; PVT1, plasmacytoma variant translocation 1; RAC1, Rac family small GTPase 1; RKIP, raf kinase inhibitor protein; RSF1-IT2, remodeling and spacing factor 1-intronic transcript 2; SLUG, zinc-finger transcription repressor SNAI2; SOCS5, suppressor of cytokine signaling 5; SRCIN1, SRC kinase signaling inhibitor 1; SUMO1P3, small ubiquitin-like modifier 1 pseudogene 3; TUSC3, tumor suppressor candidate 3 expression; UCA1, urogenital carcinoma antigen 1; ZEB1, zinc-finger e-box binding homeobox 1; ZEB2, zinc-finger e-box binding homeobox 2; ZNF471, zinc-finger protein 471.

proliferation, invasion, and metastasis in different cancers.[62] In NSCLC, DGCR5 inhibits tumor cell migration and metastasis by regulating miR-211 to 5p and EPH receptor B6 (EPHB6) expression.[54] Luo et al[55] reported that increased DGCR5 expression is related to a low incidence of lymph node metastasis in patients with LSCC. Their study also revealed that DGCR5 interacts with miR-873 to 5p and upregulates tumor suppressor candidate 3 expression (TUSC3), thereby suppressing A549 cell (human adenocarcinoma alveolar basal epithelial cells) migration and invasion.[55] Collectively, these findings suggested that DGCR5 may function as a potential therapeutic target for lung cancer.

Forkhead box D3 antisense RNA 1 (FOXD3-AS1) is downregulated in NSCLC and associated with lymph node metastasis.[56] Overexpressed FOXD3-AS1 restrains H1299 cell (human nonsmall cell lung carcinoma cell line) invasion by indirectly upregulating SRC kinase signaling inhibitor 1 (SRCIN1) expression by targeting miR-150.[56] Therefore, FOXD3-AS1 is a potential target for improved NSCLC treatment.

lncRNA leukemia inhibitory factor receptor antisense RNA 1 (LIFR-AS1) displayed significantly lower expression in NSCLC tissues than in normal tissues. In vivo and in vitro studies by Wang et al[57] demonstrated that LIFR-AS1 sponges miR-942 to 5p to increase zinc-finger protein 471 (ZNF471) expression. Notably, ZNF471 served as a tumor suppressor by inhibiting tumor growth and metastasis.[57] Therefore, LIFR-AS1 inhibited NSCLC metastasis via the miR-942 to 5p/ZNF471 axis.

Gong et al[58] determined a hitherto unknown role for the lncRNA GATA6 antisense RNA 1 (GATA6-AS1)/miR-543/raf kinase inhibitor protein (RKIP) regulatory axis. These authors discovered that the axis inhibits NSCLC metastasis and proposed it as a valuable therapeutic approach for patients with late-stage metastatic NSCLC.[58] Moreover, in vivo and in vitro studies showed that the novel lncRNA, HLA complex group 11 (HCG11), which is downregulated in NSCLC, upregulated the expression and activity of suppressor of cytokine signaling 5 (SOCS5) by sponging miR-522 to 3p and suppressing tumor metastasis and growth.[59]

LncRNAs Regulate Lung Cancer Metastasis by Regulating Signaling Pathways

In recent years, cancer-related classical signaling pathways have been recognized as crucial factors in the complicated regulatory network of cancer progression and have provided key clues for overcoming cancer.[63–65] Studies have revealed that lncRNAs regulate lung cancer metastasis via several diverse signaling pathways, such as phosphoinositide 3-kinase (PI3K),[66] mitogen-activated protein kinase (MAPK),[67] wingless/integrated (Wnt)/β-catenin,[68] Hippo,[69] and p53[70] (Figure 3).

PI3K Signaling Pathway. PI3K/protein kinase B (AKT) is one of the most important intercellular signaling pathways contributing to cancer progression, metastasis, and metabolism.[71,72] For example, the knockdown of long intergenic noncoding RNA 00152 repressed NSCLC cell migration and invasion by reducing PI3K/AKT pathway activity.[73] Liu et al[74] reported that lncRNA tumor protein P73 antisense RNA 1 (TP73-AS1) expression is significantly increased in LAD tissues and is associated with poor prognosis. Moreover, TP73-AS1 contributed to cell migration and invasion by activating the PI3K/AKT signaling pathway.[74] The novel lncRNA, Fer-1-like protein 4 (FER1L4) was downregulated in both in vivo and in vitro NSCLC models. Overexpressed FER1L4 suppressed cell metastasis by reducing PI3K and AKT expression.[75] Additionally, lncRNA HOXB cluster antisense RNA 3 significantly increased PI3Kp85a protein expression and activating the PI3K/AKT pathway to exacerbate NSCLC invasion and migration both in vitro and in vivo.[76]

Vimentin-associated lncRNA (VAL) is a potent oncogenic molecule upregulated during AKT overexpression in LAD cells.[77] Mechanistically, AKT overactivation induced VAL by enhancing the transcriptional activity of signal transducer and activator of transcription 3 (STAT3). This process promoted tumor invasion, anoikis resistance, and metastasis[77] and indicated that VAL was an essential lncRNA in overactivated AKT-mediated LAD metastasis.

MAPK Signaling Pathway. MAPKs are classical serine/tyrosine-activated kinases that regulate cell proliferation, apoptosis, and differentiation.[78] The MAPK signal transduction pathway is divided into four branches: (1) extracellular signal-regulated kinase (ERK), (2) c-Jun NH2-terminal kinase, (3) p38/MAPK, and (4) ERK5.[78]

lncRNAs are essential MAPK pathway regulators, eg, transcribed ultraconserved element 338 was reported to facilitate NSCLC cell invasion and migration by directly activating MAPK signaling.[67] LINC00852 is another oncogenic lncRNA that targeted the S100 calcium-binding protein A9 to promote LAD spinal metastasis by activating the MAPK pathway.[79] Therefore, LINC00852 is a promising target for early intervention against LAD spinal metastasis.

Additionally, Zhu and He[80] reported that terminal differentiation-induced noncoding RNA (TINCR) is significantly elevated in NSCLC cell lines and tissues. Upregulated TINCR expression was related to enhanced NSCLC cell migration and viability by increasing the kinase activity of v-raf murine sarcoma viral oncogene homolog B (BRAF) to activate the MAPK signaling pathway. Furthermore, TINCR promoted xenograft tumor growth in mouse models.[80] Therefore, the BRAF/MAPK pathway is essential for the oncogenic role of TINCR.

Wnt/β-Catenin Signaling Pathway. The Wnt/β-catenin signaling pathway is a major regulatory factor in cancer metastasis.[81] Protein disulfide isomerase family A member 3 pseudogene 1 (PDIA3P) is a novel lncRNA that activates tumorigenesis in NSCLC cells.[82] Enhanced PDIA3P expression significantly promoted cell metastasis and tumor growth in vivo. In addition, PDIA3P activated the Wnt/β-catenin signaling pathway during NSCLC development,[82] suggesting that PDIA3P is an essential regulator of the Wnt/β-catenin pathway. Moreover, lncRNA feline leukemia virus subgroup C receptor 1 antisense RNA 1 (FLVCR1-AS1) was upregulated in NSCLC, with high FLVCR1-AS1 levels related to lymph node metastasis and advanced tumor histological grades. FLVCR1-AS1 silencing directly inhibited β-catenin and c-Myc expression, thereby inhibiting NSCLC cell invasion and migration.[83]

Brain cytoplasmic RNA 1 (BCYRN1) is another oncogenic lncRNA upregulated in several malignant tumors, including

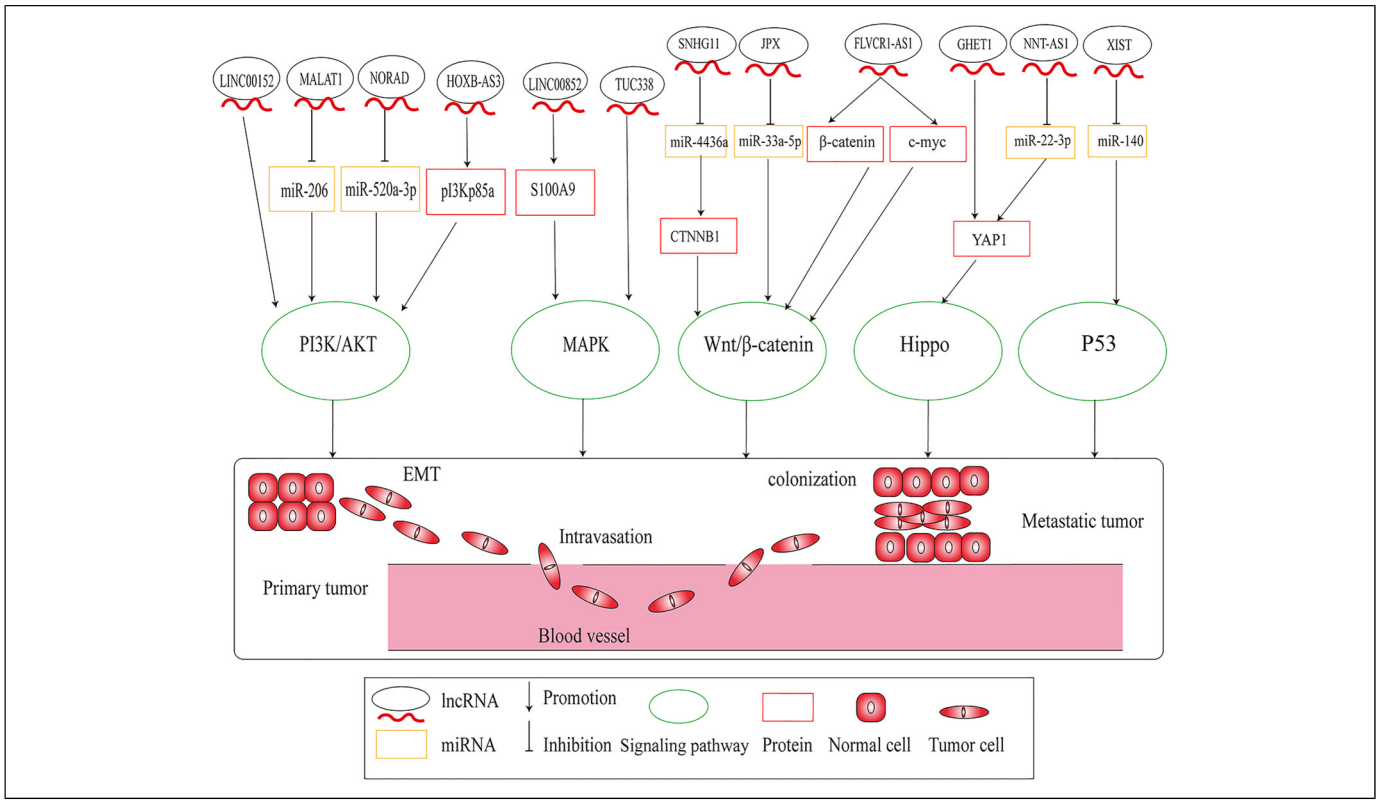

Figure 3. Long noncoding RNAs (lncRNAs) regulate lung cancer metastasis through regulating signaling pathways.

lung cancer, gastric cancer, and glioma.[84] Wang et al[85] demonstrated that BCYRN1 is upregulated in NSCLC and promotes cell proliferation and metastasis by increasing the expression of cell cycle regulatory proteins, such as cyclin D1, and stimulating the Wnt/β-catenin signaling pathway. This study showed that BCYRN1 facilitated NSCLC progression via the Wnt/β-catenin pathway, thus highlighting a promising therapeutic target for NSCLC treatment.

Hippo Signaling Pathway. The Hippo signaling pathway influences tissue growth and regeneration by inhibiting Yes-associated protein (YAP) and the transcriptional coactivator with PDZ-binding motif (TAZ). Dysregulated Hippo signaling facilitates uncontrolled cell proliferation and is associated with tumorigenesis.[86,87] Gastric carcinoma highly expressed transcript 1 knockdown inhibited NSCLC cell EMT and invasion by decreasing YAP1 expression.[88] Cadherin 1 (CDH1) is a cell–cell adhesion molecule that establishes cell polarity and regulates epithelial differentiation and proliferation.[89] Evidence indicated that CDH1 downregulation promoted tumor metastasis.[90] The oncogenic lncRNA nonsmall cell LCAT1 (NSCLCAT1) reportedly promoted NSCLC cell metastasis by regulating the Hippo signaling pathway by transcriptionally inhibiting CDH1.[91] Therefore, the functional inhibition of NSCLCAT1 may prove to be a novel therapeutic strategy to control metastatic NSCLC.

P53 Signaling Pathway. As the guardian of the genome, p53 plays a central role in regulating genomic stability, DNA damage repair, cell proliferation, and apoptosis.[92] p53 is deregulated in many cancers and regulates the expression of multiple target genes resulting in tumor growth inhibition.[93] Generally, p53 levels are controlled by the ubiquitin–proteasome pathway.[94] The E3 ubiquitin ligase, mouse double minute 2 (MDM2), acts as a p53 suppressor by promoting its ubiquitination.[94] Notably, lncRNA maternally expressed gene 3 (MEG3) was reported to activate p53 by inhibiting MDM2, leading to suppressed cell invasion in NSCLC.[70]

Additionally, lncRNAs may function as downstream targets of p53, eg, NONMMUT015812 was remarkably increased in mice with LAD and promoted cell invasion and migration. Intriguingly, p53 negatively regulated NONMMUT015812 expression.[95] PVT1b is a stress-specific PVT1 isoform activated by p53; activated PVT1b promoted transcriptional inhibition of Myc and inhibited cellular proliferation in LAD cell lines.[96] Furthermore, PVT1b loss enhanced tumor growth that indicated a potential to control lung cancer development by regulating PVT1b activity.[96]

Overall, p53 signaling pathway functions in lung cancer are partially manifested by inhibiting tumor growth and metastasis, and as such, lncRNAs may play crucial roles in these processes.

Although lncRNAs regulate cancer-related signaling pathways, the current literature is not comprehensive. Notably,

several pathways have not yet been characterized with respect to lung cancer metastasis, eg, Ras and mesenchymal–epithelial transition factor signaling pathways. Therefore, more research is required to explore downstream genes associated with these pathways during lung cancer metastasis.

LncRNAs Regulate Lung Cancer Metastasis by Coordinating With Enhancer of Zeste Homolog 2 (EZH2)

LncRNAs Bind to EZH2. EZH2 maps to chromosome 7q35 and is a histone–lysine methyltransferase subunit of polycomb repressive complex 2 (PRC2).[97] PRC2 serves as a methyltransferase of histone H3 lysine 27 (H3K27) and facilitates transcriptional inhibition by modulating chromatin structures via posttranslational histone modification.[98]

EZH2 catalyzes the mono-, di-, and trimethylation of H3K27 and plays a crucial role in epigenetic gene silencing.[99] Compelling evidence has suggested that EZH2 modulates many biological functions in lung cancer.[100] Li et al[101] showed that EZH2 functions as an anticancer molecule by directly binding to the nuclear factor erythroid 2 p45-related factor 2 (Nrf2) promoter, thus reducing Nrf2 expression and upregulating H3K27me3, leading to tumor growth reduction. Another study by Xia et al[102] reported that EZH2 exerts positive effects on lung cancer cell migration and invasion by upregulating chemokine ligand 5 expression. However, detailed mechanisms remain unclear.

LncRNAs can interact with EZH2 to affect lung cancer metastasis,[100] eg, lncRNA taurine upregulated gene 1 (TUG1) was overexpressed in SCLC and facilitated cell migration, invasion, and proliferation.[103] The lncRNA affected cell metastasis by modulating Lin11, Isl-1, and Mec-3 kinase 2b (LIMK2b) expression via EZH2 binding.[103] As a member of LIMK2, LIMK2b is mapped on 300 kp of TUG1 and participated in tumor growth and metastasis by encoding a kinase that regulated cofilin phosphorylation and promoted actin dynamics.[104,105] Therefore, TUG1 promoted SCLC metastasis by inhibiting LIMK2b expression via EZH2 binding.

Small nucleolar RNA host gene 20 (SNHG20) served as an oncogenic molecule by enhancing NSCLC proliferation and migration.[106] Notably, SNHG20 inhibited p21 transcription by recruiting EZH2 to its promoter.[106] p21 belongs to the cyclin-dependent kinase inhibitor family, mediates the growth inhibitory effects of transforming growth factor β (TGF-β), and inhibits tumorigenesis.[107] Therefore, EZH2-mediated p21 repression is essential for the oncogenic role of SNHG20. However, other mechanisms whereby SNHG20 functions in NSCLC development require more exploration.

Moreover, prostate cancer-associated transcript 6 (PCAT6) and UFC1 are other lncRNAs that promote NSCLC metastasis by interacting with EZH2.[108,109]

LncRNAs Serve as EZH2 Regulators or Effectors. In addition to repressing gene expression by binding to EZH2, lncRNAs also serve as EZH2 regulators or effectors,[100] eg, lncRNA SOX2 overlapping transcript (Sox2ot) facilitated tumor metastasis and indicated poor prognosis in esophageal cancer, pancreatic ductal adenocarcinoma, osteosarcoma, and ovarian cancer.[110] Sox2ot was also upregulated in NSCLC and predicted shorter patient survival.[111,112] Upregulated Sox2ot also promoted NSCLC cell migration and invasion.[113] Depleted Sox2ot downregulated EZH2 expression and precluded cell growth, and similarly, increased EZH2 expression reversed the effects induced by Sox2ot knockdown.[111] These data suggested that Sox2ot mediated NSCLC progression partially by modulating EZH2 expression.

The SPRY4 intronic transcript 1 (SPRY4-IT1) was downregulated in NSCLC and related to poor prognosis.[114] Overexpressed SPRY4-IT1 suppressed EMT and increased apoptosis in NSCLC cells.[114] Furthermore, EZH2 inhibited SPRY4-IT1 expression by binding to its promoter region.[114] In EZH2-depleted cells, which showed impaired metastasis, SPRY4-IT1 silencing rescued oncogenic phenotypes, suggesting that SPRY4-IT1 suppression played a key role in EZH2-mediated oncogenesis.[114] Similarly, Wei et al[115] reported that EZH2 induces the suppression of lncRNA SVUGP2, leading to enhanced NSCLC migration and invasion. Overall, these studies suggest that downregulated SPRY4-IT1 or SVUGP2 may predict a higher metastatic risk for patients with NSCLC.

Many lncRNAs regulate lung cancer metastasis by interacting with EZH2 (Table 2). Moreover, lncRNAs can be regulated by EZH2. Thus far, lncRNA–EZH2 regulatory network data implicated in epigenetic regulation are preliminary; however, the comprehensive investigation of these processes will undoubtedly identify a mass of as-yet untapped therapeutic targets for lung cancer.

Regulatory Patterns of lncRNAs in Lung Cancer Metastasis

Metastasis is a characteristic cancer behavior[116] and is reflected not only by tumor invasion and dissemination but also by a series of changes in physiological activities. While these changes are conducive to tumor metastasis, lncRNAs are now recognized as essential regulatory molecules implicated in these processes (Figure 4 and Table 3).

LncRNAs Involved in Angiogenesis

Angiogenesis is the generation of new vasculature from preexisting blood capillaries or postcapillary venules and is a key process supplying nutrients and removing metabolites to promote tumor growth.[132] Tumor-induced neovascularization frequently exhibits morphological alterations characterized by premature and circuitous vascular structures.[116] High permeability in new vasculature structures promotes the direct entry of tumor cells into the circulation.[133] Moreover, the irregular and unstable structure of these neovascular systems lead to a

Table 2. LncRNAs Regulate Lung Cancer Metastasis Through Interacting with EZH2.

LncRNA	Cancer type	Expression	Molecular mechanism	Function	Reference
TUG1	SCLC	Up	Represses LIMK2b expression via binding to EZH2	Promotes metastasis	Niu et al[103]
SNHG20	NSCLC	Up	Represses p21 expression via binding to EZH2	Promotes metastasis	Chen et al[106]
PCAT6	NSCLC	Up	Represses LATS2 expression via binding to EZH2	Promotes metastasis	Shi et al[108]
UFC1	NSCLC	Up	Represses PTEN expression via binding to EZH2	Promotes metastasis	Zang et al[109]
Sox2ot	NSCLC	Up	Promotes EZH2 expression	Promotes metastasis	Hou et al,[111] Kamel et al,[112] and Zhang et al[113]
SPRY4-IT1	NSCLC	Down	EZH2 reduces its expression	Inhibits metastasis	Sun et al[114]
SVUGP2	NSCLC	Down	EZH2 reduces its expression	Inhibits metastasis	Wei et al[115]

Abbreviations: EZH2, enhancer of zeste homolog 2; LATS2, large tumor suppressor kinase 2; LIMK2b, Lin11, Isl-1, and Mec-3 kinase 2b; lncRNA, long noncoding RNA; NSCLC, nonsmall cell lung cancer; PCAT6, prostate cancer-associated transcript 6; SCLC, small cell lung cancer; SNHG20, small nucleolar RNA host gene 20; Sox2ot, SOX2 overlapping transcript; SPRY4-IT1, SPRY4 intronic transcript 1; TUG1, taurine upregulated gene 1.

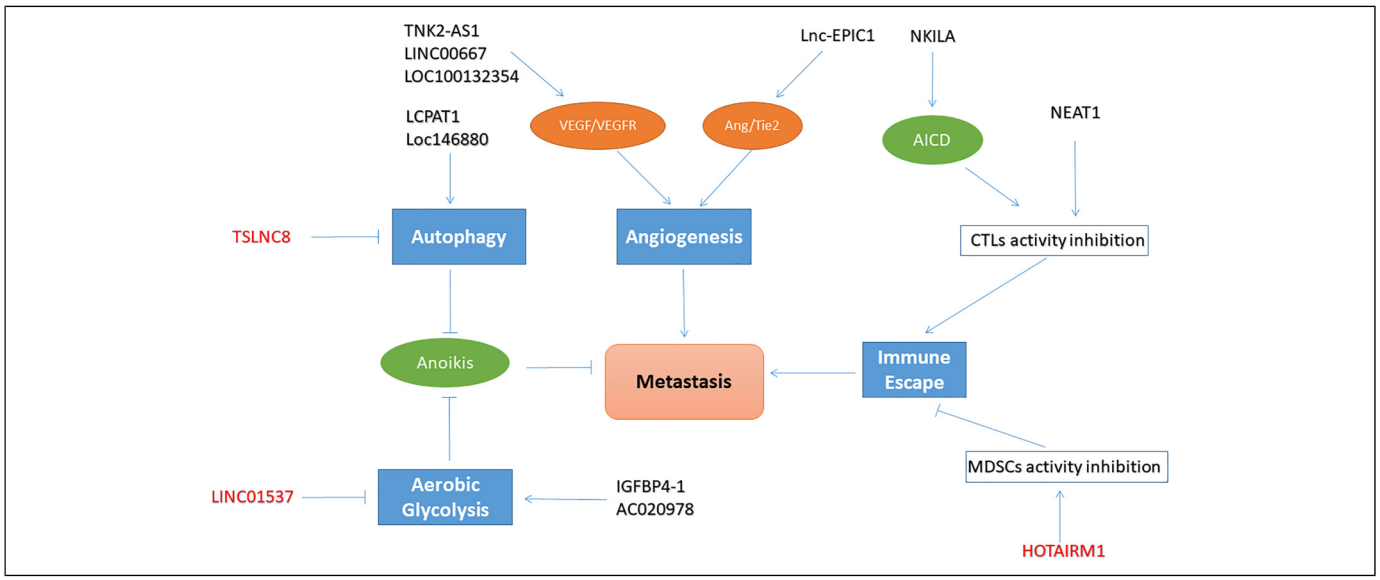

Figure 4. The regulatory patterns of long noncoding RNAs (lncRNAs) in lung cancer metastasis.

dense vascular bed that increases contact surfaces between tumors and the bloodstream, promoting tumor access to the circulation and facilitating distant metastasis.[133] Therefore, angiogenesis is instrumental in primary tumor metastasis and growth.

Generally, angiogenesis is regulated by proangiogenic signaling pathways, including the vascular endothelial growth factor/vascular endothelial growth factor receptor and angiopoietin (Ang)/Tie2 pathways.[134] LncRNA tyrosine kinase nonreceptor 2 antisense RNA 1 (TNK2-AS1) is upregulated in NSCLC tissues.[117] TNK2-AS1 enhances NSCLC metastasis and interacts with STAT3 to elevate its stability by inhibiting proteasome-mediated degradation. STAT3 also binds to the TNK2-AS1 promoter to activate its transcription. Moreover, this positive feedback mechanism elevates vascular endothelial growth factor A (VEGFA) expression to promote angiogenesis.[117] Similarly, Wang et al[118] reported that LOC100132354 promotes metastasis and induces angiogenesis in LAD by activating the VEGFA/VEGF receptor 2 (VEGFR2) pathway. Another study demonstrated that LINC00667 promoted cell migration and pathological angiogenesis in NSCLC by increasing VEGFA mRNA stability by recruiting eukaryotic translation initiation factor 4A3 (EIF4A3).[119]

Moreover, lncRNA EPIC1 (Lnc-EPIC1) reportedly facilitated cell viability and invasion in NSCLC.[120] Elevated Lnc-EPIC1 expression stimulated angiogenesis by activating the Ang2/Tie2 pathway, and furthermore, Lnc-EPIC1 overexpression simultaneously enhanced new blood vessel formation in vivo.[120]

Unequivocally, metastasis and angiogenesis are central topics in cancer, with lncRNAs participating in lung cancer metastasis by regulating angiogenesis. Nevertheless, the precise molecular processes underpinning lncRNA-regulated angiogenesis in lung cancer metastasis are poorly characterized. Further research is warranted to uncover the clinical significance of lncRNAs in lung cancer angiogenesis.

LncRNAs Involved in Autophagy

Autophagy is an intricate biological process that maintains cellular homeostasis via lysosome-dependent degradation.[135] The process is activated under specific conditions, such as cellular stress, nutrient deficiency, and hypoxia.[136] As a highly conserved process, autophagy plays vital roles in cellular energy

Table 3. The Regulatory Patterns of LncRNAs in Lung Cancer Metastasis.

LncRNA	Cancer type	Expression	Model	Hallmark	Molecular mechanism	Function	Reference
TNK2-AS1	NSCLC	Up	Vitro	Angiogenesis	Interacts with STAT3 to upregulate VEGFA expression	Promotes angiogenesis and metastasis	Wang et al[117]
LOC100132354	LAD	Up	Vitro	Angiogenesis	Activates VEGFA/VEGFR2 pathway	Promotes angiogenesis and metastasis	Wang et al[118]
LINC00667	NSCLC	Up	Vitro and vivo	Angiogenesis	Stabilizes VEGFA mRNA by EIF4A3	Promotes angiogenesis and metastasis	Yang et al[119]
Lnc-EPIC1	NSCLC	Up	Vitro and vivo	Angiogenesis	Activates Ang2/Tie2 pathway	Promotes angiogenesis and metastasis	Hou et al[120]
LCPAT1	NSCLC	Up	Vitro	Autophagy	Promotes smoking and PM-2.5-joint induced autophagy	Promotes autophagy and metastasis	Lin et al[121]
Loc146880	LAD	Up	Vitro	Autophagy	PM-2.5 induce ROS production to elevate its expression Promotes PM-2.5-induced autophagy	Promotes autophagy and metastasis	Deng et al[122]
TSLNC8	NSCLC	Down	Vitro	Autophagy	Inhibits STAT3/HIF-1α pathway	Inhibits autophagy and metastasis	Fan et al[123]
IGFBP4-1	NSCLC	Up	Vitro	Aerobic glycolysis	Increasing the expression of HK2	Promotes glycolysis and metastasis	Yang et al[124]
AC020978	NSCLC	Up	Vitro	Aerobic glycolysis	Prevents PKM2 from ubiquitin-mediated degradation and increases PKM2-enhanced HIF-1α transcription activity	Promotes glycolysis and metastasis	Hua et al[125]
LINC01537	NSCLC	Down	Vitro	Aerobic glycolysis	Inhibits PGK1 expression by targeting PDE2A	Inhibits glycolysis and metastasis	Gong et al[126]
NEAT1	NSCLC	Up	Vitro and vivo	Immune escape	Downregulates tumor-infiltration cytotoxic T cells through cGAS/STING/IFN pathway	Promotes immune escape and metastasis	Ma et al[127] and Chen et al[128]
NKILA	NSCLC	Up	Vitro and vivo	Immune escape	Promotes AICD of CTLs via NF-κB pathway	Promotes immune escape and metastasis	Huang et al[129]
HOTAIRM1	LAD	Down	Vitro and vivo	Immune escape	Inhibits immunosuppressive activity of MDSCs	Inhibits immune escape and metastasis	Tian et al[130] and Chen et al[131]

Abbreviations: AICD, activation-induced cell death; Ang2, angiopoietin 2; cGAS, cyclic GMP-AMP synthase; CTL, cytotoxic T lymphocyte; EIF4A3, eukaryotic translation initiation factor 4A3; HIF-1α, hypoxia-inducible factor-1α; HK2, hexokinase 2; HOTAIR, HOX transcript antisense intergenic RNA; HOTAIRM1, HOTAIR myeloid-specific 1; IFN, interferon; IGFBP4-1, insulin-like growth factor binding protein 4 to 1; LAD, lung adenocarcinoma; LCPAT1, lung cancer progression-associated transcript 1; Lnc-EPIC1, long noncoding RNA EPIC1; MDSC, myeloid-derived suppressor cell; lncRNA, long noncoding RNA; mRNA, messenger RNA; NEAT1, nuclear paraspeckle assembly transcript 1; NF-κB, nuclear factor kappa B; NKILA, NF-κB interacting lncRNA; NSCLC, nonsmall cell lung cancer; PDE2A; phosphodiesterase 2A; PGK1, phosphoglycerate kinase 1; PKM2, M2 isoform of pyruvate kinase; PM-2.5, particulate matter-2.5; ROS, reactive oxygen species; STAT3, signal transducer and activator of transcription 3; STING, stimulator of interferon gene; TNK2-AS1, tyrosine kinase nonreceptor 2 antisense RNA 1; TSLNC8, tumor-suppressive role of lncRNA on chromosome 8p12; VEGFA, vascular endothelial growth factor A; VEGFR2, vascular endothelial growth factor receptor 2.

metabolism[135,136] and is classified into three forms: microautophagy, macroautophagy, and chaperone-mediated autophagy.[136] Macroautophagy, which is characterized by autophagosome engulfment of corrupted cytoplasmic elements and fusion with lysosomes to promote material degradation, is the most common autophagy type and displays contradictory effects during metastasis.[135,137–139] During primary metastatic stages, autophagy inhibits metastasis by precluding tumor necrosis and reducing subsequent inflammatory cell infiltration.[140] However, as metastasis invariably proceeds, autophagy promotes the process by protecting disseminating tumor cells from anoikis.[140,141] Therefore, autophagy is essential for metastasis.

In lung cancer, smoking and particulate matter-2.5 (PM-2.5) are critical environmental carcinogens that impair pulmonary function and facilitate tumorigenesis by inducing cell autophagy.[142,143] Recent studies have reported that lncRNAs play essential roles in autophagy induced by environmental carcinogens.[121,122] For example, lung cancer progression-associated transcript 1 (LCPAT1) knockdown suppressed smoking and PM-2.5-induced autophagy, thereby inhibiting EMT in NSCLC.[121]

Interestingly, in PM-2.5-exposed LAD cells, lncRNA loc146880 expression was upregulated due to excessive reactive oxygen species (ROS) production.[122] Elevated loc146880 enhanced autophagy, leading to increased cell invasion and EMT. However, loc146880 knockdown reversed these positive effects induced by PM-2.5.[122] Therefore, these data suggested that loc146880 enhanced autophagy to promote lung cancer metastasis in cancer cells exposed to PM-2.5.

Hypoxia also induces autophagy and promotes tumorigenesis.[144] Under hypoxia, the tumor-suppressive role of lncRNA on chromosome 8p12 (TSLNC8) reportedly suppressed the expression of autophagy-related proteins, including ATG14 and Beclin-1, leading to enhanced cell apoptosis and impaired NSCLC metastasis.[123] Furthermore, overexpressed TSLNC8 decreased hypoxia-inducible factor-1α (HIF-1α) levels and inhibited STAT3 phosphorylation, suggesting that TSLNC8 regulated hypoxia-induced autophagy and NSCLC progression in a STAT3-dependent manner.[123]

Thus, autophagy induced by smoking, PM-2.5, or hypoxia is a crucial mechanism during lung cancer metastasis, with lncRNAs increasingly recognized as essential molecules regulating this process. Therefore, more research is required to explore the complex relationship between autophagy and metastasis with the hope of identifying new lncRNA therapies for lung cancer treatment.

LncRNAs Involved in Aerobic Glycolysis

Reprogrammed energy metabolism, which enhances glycolysis and glucose uptake to accelerate cell proliferation, survival, and migration, has been identified as a malignancy hallmark.[116] Under normal physiological conditions, mitochondrial oxidative phosphorylation is the major energy source of the body that generates 30 or 32 adenosine triphosphate (ATP) molecules.[145] However, cancer cells are inclined to obtain energy by enhancing glycolysis, which only generates two ATP molecules.[146] To compensate for insufficient ATP production, cancer cells reprogram metabolism to enhance the rate of glucose uptake.[147] This specific phenomenon was first observed by Warburg in the 1920s and termed the Warburg effect or aerobic glycolysis; thus, increased glucose uptake permits the synthesis of more metabolites, such as lactic acids, lipids, and nucleic acids, which favor tumor growth.[146,148]

Elevated glycolysis enhances glucose utilization, decreases ROS production, and elevates the antioxidant ability of cancer cells to resist anoikis and promote metastasis.[149,150] Similarly, tumor cells were shown to alter metabolism in remote organs to accelerate implantation and metastasis.[151]

Emerging evidence has suggested that lncRNAs are key players in cancer metabolic remodeling processes by targeting metabolic enzymes, eg, UCA1 is upregulated in glioma cells and upregulates 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 2 expression, a critical glycolytic enzyme, to induce cell migration and invasion.[152] In lung cancer, lncRNAs are also shown to participate in metastasis partially by regulating glycolytic enzymes.[124]

The first step of glycolysis involves glucose phosphorylation to glucose 6-phosphate by hexokinases (HKs) that are crucial glycolytic enzymes regulating glucose metabolic rates; thus, elevated HK expression maintains a rapid glycolytic rate in cancer tissues, facilitating cell metastasis.[153] Geng et al[154] reported that hexokinase 2 (HK2) modulates the expression of zonula occludens-1, E-cadherin, vimentin, and N-cadherin and accelerates metastasis in hepatocellular carcinoma cells. A high expression of the lncRNA insulin-like growth factor binding protein 4 to 1 (IGFBP4-1) was associated with greater lymph node metastasis and facilitated lung cancer cell migration and invasion via metabolic reprogramming mechanism by increasing HK2 expression.[124]

The M2 isoform of pyruvate kinase (PKM2) is preferentially expressed during developmental embryo stages and in various tumor cells.[155] PKM2 transforms the final rate-limiting step of glycolysis and leads to cancer-specific glycolysis, thus promoting glucose uptake and lactic acid production.[155] In the nucleus, the direct reciprocity of PKM2 with TGF-β-induced factor homeobox 2 resulted in the recruitment of histone deacetylase 3 to the E-cadherin promoter.[156] This was followed by histone H3 deacetylation and the inhibition of E-cadherin transcription, thereby facilitating EMT in colon cancer cells.[156] LncRNA-AC020978 was upregulated and promoted cell metastasis in NSCLC cells[125]; it stabilized PKM2 by inhibiting ubiquitin-mediated degradation, increasing PKM2-enhanced HIF-1α transcription activity, and facilitating glycolytic metabolism and lung cancer metastasis.[125]

Phosphoglycerate kinase 1 (PGK1) is an essential metabolic enzyme in glycolysis; it catalyzes 1,3-bisphosphate glycerate to 3-phosphoglycerate and generates the first ATP in the glycolysis.[157] Several studies reported that PGK1 played an important role in cancer metastasis.[158,159] Xie et al[160] showed that PGK1 is upregulated in hepatocellular carcinoma tissues, and

overexpressed PGK1 is correlated with poor prognosis. Moreover, PGK1 knockdown dramatically decreased cell proliferation, migration, and invasion of hepatocellular carcinoma cells, suggesting a positive role of PGK1 in hepatocellular carcinoma metastasis.[160] Lowered expression of LINC01537 was associated with poor prognosis of lung cancer, whereas overexpressed LINC01537 limited aerobic glycolysis and inhibited metastasis in NSCLC cells.[126] Further investigations showed that LINC01537 regulated PGK1 expression by directly targeting phosphodiesterase 2A (PDE2A), a critical member of the PDE family that modulates mitochondrial cyclic adenosine monophosphate expression and is highly associated with energy metabolism processes.[126] Therefore, the LINC01537/PDE2A/PGK1 axis may be a potential target for inhibiting cellular energy metabolism and metastasis during NSCLC.

Since Weinberg identified metabolic reprogramming as an emerging cancer hallmark, several studies have validated the involvement of cancer metabolism during malignant processes.[116,150] LncRNAs regulate cancer glycolysis by modulating the expression of several metabolic enzymes, resulting in lung cancer metastasis. Importantly, several reports have suggested that lncRNAs may alter the distribution of glycolytic enzymes in human cancer cells, thus participating in cancer progression.[161,162] However, in lung cancer, these things are missing. Therefore, further research is required to comprehensively understand the complex interaction networks that lncRNAs operate in cancer metabolic and metastatic processes.

LncRNAs Involved in Immune escape

Tumorigenesis and metastatic cascades rely on the evolving molecular functions of cancer cells and interactions with the immune system.[163] During each stage of the metastatic process, the immune system strives to block cancer cell dissemination.[164] For instance, CD8+ T cells recognize tumor-related antigens and differentiate into cytotoxic T lymphocytes (CTLs), leading to the specific destructions of tumor cells.[163,165] Accordingly, nascent tumor cells evolve evasive mechanisms to evade the immune system, including increasing the expression of immunosuppressive factors, enlisting immunosuppressive cells, and inhibiting the antitumor functions of CTLs.[163,164] These processes decrease cancer cell immunogenicity, thereby establishing an immunosuppressive tumor microenvironment contributing to tumor metastasis.

Evidence has suggested that lncRNAs help lung tumor cells evade antitumor immune responses, thus facilitating tumor growth and metastasis. Notably, lncRNA regulation during lung cancer immune escape broadly covers two areas: (1) the influence of lncRNAs on T cell activity and function and (2) lncRNA regulation of myeloid-derived suppressor cell (MDSC) activity and function.[127,129,130]

Nuclear paraspeckle assembly transcript 1 (NEAT1) is an oncogenic lncRNA facilitating lung cancer progression[128]; however, its molecular mechanism is unclear. Ma et al[127] reported that NEAT1 knockdown represses NSCLC cell viability and invasion and upregulates tumor-infiltration CTLs. Further investigations revealed that NEAT1 silencing upregulated cyclic GMP-AMP synthase (cGAS), a stimulator of interferon gene (STING) levels, and increased interferon-β (IFN-β) expression.[127] cGAS is a sensitive DNA sensor that responds to cytosolic DNA and mediates immune responses.[166] Moreover, activated cGAS promotes activation of the STING pathway to produce downstream factors, such as IFN-β.[167] IFN-β belongs to the type 1 IFN family that exerts significant stimulatory effects toward T cell activation, thereby improving T cell immune responses and inhibiting cancer progression.[168] Taken together, NEAT1 putatively promotes NSCLC metastasis by inhibiting cGAS-STING- IFN-β signaling to repress T cell activation and help tumor cells evade immunosurveillance.

Activation-induced cell death (AICD) is a specific mechanism regulating T cell activity and function.[169] It is a vital immune protection process that activates Fas (cluster of diffraction 95)-Fas ligand signaling to restrict excessive T cell activation.[169] However, AICD may be used to evade immunological assault to exert significant effects on cancer development.[169] Evidence has revealed that nuclear factor kappa B (NF-κB) interacting lncRNA (NKILA) participates in cancer metastasis by regulating the NF-κB pathway.[170,171] Huang et al[129] suggested that NKILA knockdown suppresses the AICD sensitivity of lung cancer cells lysates-activated CTLs, which was abrogated by NF-κB downregulation, suggesting that NKILA regulated AICD via the NF-κB pathway. More importantly, in NKILA-deletion mice, tumor apoptosis was elevated, and tumor growth was inhibited.[129] Collectively, NKILA silencing in tumor-specific CTLs may combat tumor immune escape by restricting AICD via NF-κB signaling, thereby inhibiting tumor development and probably metastasis. These findings underscore the importance of lncRNAs in tumor immune escape and suggest that engineered lncRNAs in adoptively transferred T cells may be a novel cancer immunotherapy.

MDSCs are immature immunosuppressive cells that differentiate into macrophages and monocytes.[172] However, under pathological circumstances, particularly cancer, MDSCs differentiation is impeded; thus, they accumulate.[173–175] MDSCs also facilitate cancer metastasis by suppressing CTL responses and inducing regulatory T cells by generating inhibitory molecules, such as arginase 1, myeloperoxidase, and ROS.[176] Previous studies showed that lncRNAs played critical roles in regulating MDSCs suppressive activities.[177,178] Notably, lncRNA HOTAIR myeloid-specific 1 (HOTAIRM1) was downregulated in LAD and associated with advanced lymph node metastasis.[131] Elevated HOTAIRM1 inhibited MDSCs immunosuppressive activities that improved antitumor responses, retarded tumor growth, and delayed tumor metastasis.[130] These findings indicated that HOTAIRM1 could be an immunotherapeutic target for lung cancer treatment.

These findings provide invaluable molecular clues on how lncRNAs influence immune responses in tumor cells by regulating T cell and MDSC activity, thus promoting metastasis. However, how lncRNAs modulate the immune microenvironment of lung cancer remains uncharacterized. More comprehensive research is required to explore these linkages.

Conclusion and Perspectives

Metastasis causes high lethality and recurrence rates in lung cancer. Emerging studies have increasingly identified lncRNAs as promising therapeutic targets for treating this disease. This review provided a comprehensive understanding of the main molecular mechanisms and regulatory roles of several lncRNAs and their impact on lung cancer metastasis. LncRNAs are an essential type of ncRNAs that regulate lung cancer metastasis via three main molecular mechanisms: (1) lncRNAs act as ceRNAs; (2) lncRNAs regulate the transduction of several signal pathways; and (3) lncRNAs coordinate with EZH2. Thus, lncRNAs exert multiple functions toward lung cancer metastasis by regulating angiogenesis, autophagy, aerobic glycolysis, and immune escape. Interestingly, the molecular mechanism of one particular lncRNA involves several aspects, eg, SNHG3 not only sponges miR-340 to 5p[179] and miR-515 to 5p[180] but also activates the TGF-β pathway to promote lung cancer metastasis.[181] However, lncRNA research is still in its infancy; therefore, future investigations should explore the regulatory mechanisms of lncRNAs and their impact on lung cancer metastasis.

Moreover, dysregulated lncRNAs stably exist in internal environments, exhibit specific expression profiles in different lung cancer subtypes, and provide potential options for lung cancer treatment. Current research on lncRNAs as diagnostic and therapeutic biomarkers should focus on their application to clinical settings; however, this requires comprehensive verification and authentication in large-scale studies. Going forward, this research strategy will significantly improve lncRNA therapeutic outcomes in treating metastatic lung cancer.

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