Long non-coding RNAs in small cell lung cancer: A potential opening to combat the disease (Review)

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Abstract. Lung cancer is the top cause of cancer-associated mortality in men and women worldwide. Small cell lung cancer (SCLC) is a subtype that constitutes ~15% of all lung cancer cases. Long non-coding RNAs (lncRNAs), possessing no or limited protein-coding ability, have gained extensive attention as a potentially promising avenue by which to investigate the biological regulation of human cancer. lncRNAs can modulate gene expression at the transcriptional, post-transcriptional and epigenetic levels. The current review highlights the developing clinical implications and functional roles of lncRNAs in SCLC, and provides directions for their future utilization in the diagnosis and treatment of SCLC.

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Abbreviations: SCLC, small cell lung cancer; NSCLC, non-SCLC; EGFR, epidermal growth factor receptor; lncRNAs, long non-coding RNAs; snoRNAs, small nucleolar RNAs; snRNAs, small nuclear RNAs; ncRNAs, non-coding RNAs; miRNAs, microRNAs; HOTAIR, HOX transcript antisense intergenic RNA; HOX, homeobox; PRC2, polycomb repressive complex 2; TERC, telomerase RNA; TERT, telomerase reverse transcriptase; TFs, transcription factors; ceRNAs, competitive endogenous RNAs; HOTTIP, HOXA transcript at the distal tip; WDR5, WD repeat domain 5; EZH1, enhancer of zeste homolog 1; BCL-2, B-cell leukemia/lymphoma-2; CELF1, CUGBP Elav-like family member 1; EZH2, enhancer of zeste homolog 2; EMT, epithelial-to-mesenchymal transition; HOXA1, homeobox A1; TUG1, taurine upregulated gene 1; CCAT2, colon cancer-associated transcript 2; PVT1, plasmacytoma variant translocation 1; CCAT1, colon cancer associated transcript 1

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1. Introduction

Lung cancer, recognized as the leading cause of cancer-associated mortality worldwide, is classified into small cell lung cancer (SCLC) and non-SCLC (NSCLC). SCLC constitutes ~15% of all confirmed cases of lung cancer worldwide (1-3). Distinct from NSCLC, SCLC is unique in its inclination for quick metastasis and sensitivity to initial systemic cytotoxic chemotherapy. Systemic chemotherapy is the solid foundation of treatment for the limited and extensive stages of this disease. Nevertheless, the commonly adopted management standard of platinum-oriented chemotherapy has reached an efficacy bottleneck, mainly due to chemoresistance and relapse in SCLC patients (4). Despite plentiful clinical trials in the past four decades, systematic treatment for SCLC patients has not changed markedly. As a result, the majority of patients live for only 1 year or less following diagnosis, with the overall 5-year survival rate staying low at <7% (5). The widely employed technique to diagnose SCLC from a tiny amount of malignant cells, in combination with a lack of proved predictive biomarkers that would require tissue biopsies and relatively rare surgical resection, has cut down the source of SCLC tissue for more profound studies (5). In NSCLC, a growing number of gene fusions or mutations instruct treatment selections for specific patient subgroups, particularly those with anaplastic lymphoma kinase or epidermal growth factor receptor (EGFR) (6) mutations. In marked contrast, numerous experimental and targeted agents regarding SCLC have failed to yield convincing clinical benefits (7). Novel and effective therapies for SCLC patients are urgently required. Regarding the molecular mechanisms of carcinogenesis, medical communities have mostly concentrated on genes with protein-coding capacity. Unexpectedly, the ENCODE project identified that up to three-quarters of the human genome could be transcribed, though <3% of it encodes protein. This unexpected fact indicated that non-coding RNAs (ncRNAs) make up the vast majority of the human transcriptome (8). Long ncRNAs (lncRNAs) are >200 nucleotides in size and possess no or a very low protein-coding ability. Bioinformatics platforms and high-throughput sequencing emerging in recent

years have facilitated uncovering the mystique of lncRNAs, which function as key molecules in wide-ranging cellular processes, including cell growth, adhesion, proliferation and apoptosis (9,10). lncRNA deregulation is involved in numerous human diseases, and there is also increasing evidence suggesting that lncRNAs are involved in SCLC pathogenesis and clinical outcomes (11-15). Digging deeper into the biological functions and molecular mechanisms of lncRNAs will enable researchers to further understand the biology of SCLC and develop lncRNA-oriented therapeutics.

2. Molecular mechanisms of lncRNAs

What is lncRNA? The manifestation of lncRNAs owes much to the studies on the size, function and evolution of the human genome. Along with the development of DNA-RNA hybridization techniques, scientists have gradually become aware that the majority of the genome, which was initially labeled as 'junk DNA', does not encode proteins (16). However, subsequent studies demonstrating that small nucleolar RNAs (snoRNAs) and small nuclear RNAs (snRNAs) have a certain impact on post-transcriptional RNA processing propelled further investigation into non-coding sequences (17,18). In the early 2000s, whole-transcriptome sequencing arose and carried forward the identification and annotation of numerous lncRNAs (19-21). ncRNAs can be large or small in size. Linearized ncRNAs with a length of >200 bp and with no or low protein-coding ability are known as lncRNAs. Small ncRNAs (<200 bp) are categorized into PIWI-interacting RNAs, small interfering RNAs, microRNAs (miRNAs) and classical housekeeping ncRNAs, including transfer RNAs, ribosomal RNAs, snRNAs and snoRNAs. The FANTOM5 project has identified 19,175 potential functional lncRNAs in the human genome (22), yet few of them have been thoroughly investigated (23). Accumulating studies have supported the theory that at different levels, aberrant expression of lncRNAs serves crucial roles in cancer development, affecting cell growth, proliferation, apoptosis and metastasis via diverse mechanisms (12,13,15,24).

Four archetypes of lncRNAs. lncRNAs are a set of ubiquitous genes participating in various biological mechanisms. There are four archetypes in which lncRNAs execute their molecular functions, namely as signals, decoys, guides and scaffolds (25). The signal archetype of lncRNAs may serve as markers of functionally significant biological events, as their expression exhibits cell type, time and space specificity. For example, lncRNA homeobox (HOX) transcript antisense intergenic RNA (HOTAIR) located in the HOXC locus exists in posterior and distal cells, whereas another HOXC lncRNA, Frigidair, is expressed in an anterior pattern. Conversely, lncRNA HOXA transcript at the distal tip (HOTTIP), located in the far end of the human HOXA cluster, is expressed in distal cells (26,27). The decoys archetype is a type of lncRNA that regulates transcription through binding to and then carrying away protein targets, yet it does not exert extra functions. Decoys display as 'molecular sinks' for chromatin modifiers, transcription factors or other regulatory factors, all of which are RNA-binding proteins (25). For instance, by directly binding to and sequestering nuclear transcription factor Y subunit that

drives a DNA damage-induced apoptotic program, lncRNA p21-associated ncRNA DNA damage-activated suppresses apoptotic gene expression to facilitate cell cycle arrest, leading to the promotion of cell survival (28). Knockdown of lncRNAs of this archetype may imitate the gain-of-function of the target proteins, while a rescue phenotype could be induced by loss-of-function of the lncRNA and its effector (25). The guides archetype of lncRNA can bind chromatin modifying proteins and direct the localization of ribonucleoprotein complexes to specific targets in a *cis* or *trans* manner. The well-known *cis* mechanism, mammalian X inactivation center, specifies a set of ncRNAs, X-inactive specific transcript (Xist) included (29,30). A 1.6-kb lncRNA, RepA RNA, stemming from the 5' end of Xist, produces polycomb repressive complex 2 (PRC2) in *cis*. PRC2 is involved in extra X-chromosome inactivation (31). In contrast to *cis*-regulatory lncRNAs, certain lncRNAs serve their chromosome-wide transcriptional roles in *trans*, such as lncRNA HOTAIR, which is capable of directing PRC2 to target genes in *trans* (32-34). The scaffolds archetype of lncRNA can act a platform where components are assembled, precisely regulating the sophisticated molecular interactions and signaling transductions involved in diverse biological signaling processes (35). For example, telomerase catalytic activity necessitates the combination of two common telomerase units, the telomerase RNA (TERC) and the telomerase reverse transcriptase (TERT). TERC is an essential lncRNA unit that offers the template for repeat synthesis, and it also possesses domains that promote TERT binding, catalytic activity and stability of the complex (36). Certain morbid states, including dyskeratosis congenital, presumably result from mutations altering the equilibrium between different conformations of TERC, more specifically, through destruction of the RNA scaffold structure where modular biding sites for telomeric regulatory proteins are located (37).

lncRNAs modulate gene expression at distinct levels. lncRNAs exert functions in an enormous range of biological processes by promoting or inhibiting the transcription and translation of protein-coding genes. Unlike highly conserved small ncRNAs that participate in gene silencing transcriptionally and post-transcriptionally (38-40), lncRNAs are poorly conserved and can modulate target gene expression via various mechanisms at different levels.

Transcriptional level. At the transcriptional level, lncRNAs have the following roles: i) Functioning as decoys for RNA polymerase II or transcription factors (TFs) to inhibit their binding to enhancers or promoters of target genes, therefore specifically promoting or repressing target gene expression (26); ii) alteration of TF localization or modification to promote or inhibit gene transcription (40); iii) interaction with DNA to form a triple helix structure, thereby affecting target gene transcription (41); and iv) presenting as competitive endogenous RNAs (ceRNAs) to inhibit the transcription of target genes (42).

Post-transcriptional level. At the post-transcriptional level, lncRNAs have the following roles: i) Providing different transcripts by regulating pre-mRNA alternative splicing (43); ii) combining with mRNAs to synthesize

Table I. Information of five lncRNAs involved In SCLC.

lncRNA	Genomic location	Dysregulation	Functions	Mechanism	Publication year	(Refs.)
HOTTIP	7p15.2	Upregulation	Chemoresistance, shorter survival, clinical stage	HOTTIP/miR-574-5p/EZH1 axis, HOTTIP/miR-216a/ BCL-2 axis	2017, 2018	(57,58)
HOTAIR	12q13.13	Upregulation	Lymphatic invasion, chemoresistance	Regulation of HOXA1 methylation and target genes	2013, 2016	(66,67)
TUG1	22q12.2	Upregulation	Chemoresistance, clinical stage and shorter survival	Regulation of LIMK2b via binding with EZH2	2017	(76)
CCAT2	8q24.21	Upregulation	Malignant status, poor prognosis	Unknown	2016	(85)
PVT1	8q24.21	Upregulation	Lymph node metastasis, distal metastasis, and clinical stage	Unknown	2016	(95)

SCLC, small cell lung cancer; HOTTIP, HOXA transcript at the distal tip; EZH1, enhancer of zeste homolog 1; BCL-2, B-cell leukemia/lymphoma-2; HOTAIR, HOX transcript antisense intergenic RNA; TUG1, taurine upregulated gene 1; CCAT2, colon cancer-associated transcript 2; PVT1, plasmacytoma variant translocation 1; HOXA1, homeobox A1; LIMK2b, LIM domain kinase 2; EZH2, enhancer of zeste homolog 2; miR, microRNA; lncRNA, long non-coding RNA.

double-stranded RNA complexes, thereby effectively enhancing the stability of mRNAs (44); and iii) interaction with miRNAs to regulate signaling events (45).

Epigenetic level. At the epigenetic level, lncRNAs have the following roles: i) The regulation of histone modifications, including acetylation, methylation and ubiquitination, among others (46); ii) participating in chromatin remodeling and conformational alterations by combining with chromatin modification complexes that are crucial for gene transcription (47); and iii) participating in gene silencing via modulating DNA methylation in the promoter region of target genes (48).

To summarize, lncRNAs participate in diverse transcriptional, post-transcriptional and epigenetic molecular mechanisms, covering regulation of chromatin structure or modification, transcription, splicing and translation, therefore regulating a multitude of physiological and pathological courses, including cell proliferation, differentiation, apoptosis, the heat shock response, cancer development and chemoresistance (49-51). Amongst these functions, the regulation of gene expression is of paramount significance in elucidating how lncRNAs promote or suppress tumorigenesis. Genome-wide studies of tumor samples have verified plentiful lncRNAs that are linked to distinct types of cancer. Dysregulated expression of lncRNAs can stimulate carcinogenesis and metastasis. However, from an overall perspective, the function of lncRNAs may not be one-sided, and could be tumor-promoting or tumor-suppressing.

3. Expression of lncRNAs in SCLC

Representing one of the largest classes of transcripts, lncRNAs possess highly diverse characteristics and functions. Progress in high-throughput sequencing technology has accelerated the identification of lncRNAs as key regulatory molecules

participating in various cellular processes and their dysregulation in human diseases. Although only a few lncRNAs have been well described thus far, accumulating evidence suggests that lncRNAs contribute to tumor biology. Given the aforementioned difficulties, breakthroughs in SCLC research remain stagnant compared with those in other types of cancer. However, it remains worthwhile to investigate the research status of SCLC from an lncRNA point of view, as this field may open novel and optimistic windows to elucidate SCLC molecular mechanisms. In the following text, previous findings in the expression of lncRNAs in SCLC are reviewed. The roles that HOTTIP, HOTAIR, taurine upregulated gene 1 (TUG1), colon cancer-associated transcript 2 (CCAT2) and plasmacytoma variant translocation 1 (PVT1) serve in SCLC are discussed and also briefly presented in Table I. A schematic diagram of these genes in SCLC and their mechanisms is shown in Fig. 1. The dysregulations and functions of these five lncRNAs in other malignancies are also summarized, as a contrast and enlightenment to their roles in SCLC (Table II).

HOTTIP. HOTTIP, as the lncRNA encoded by the HOTTIP gene that is located at the HOXA locus, was initially identified in human fibroblasts distributed in anatomically distal regions of the body (52). Wang *et al* (53) verified the direct coupling of HOTTIP and the adaptor protein, WD repeat domain 5 (WDR5) to target WDR5/lysine methyltransferase 2A complexes across HOXA, thereby impelling histone lysine 4 trimethylation and the transcription of various 5' HOXA genes. Multiple studies confirmed the positive correlation between the expression level of HOTTIP and HOXA genes in a variety of malignancies (52,54-56). In brief, HOTTIP could activate HOX genes by recruiting histone-modifying enzymes to suppress tumor-suppressor genes. Sun *et al* (57,58) completed pioneering studies unveiling the underlying molecular mechanism of HOTTIP
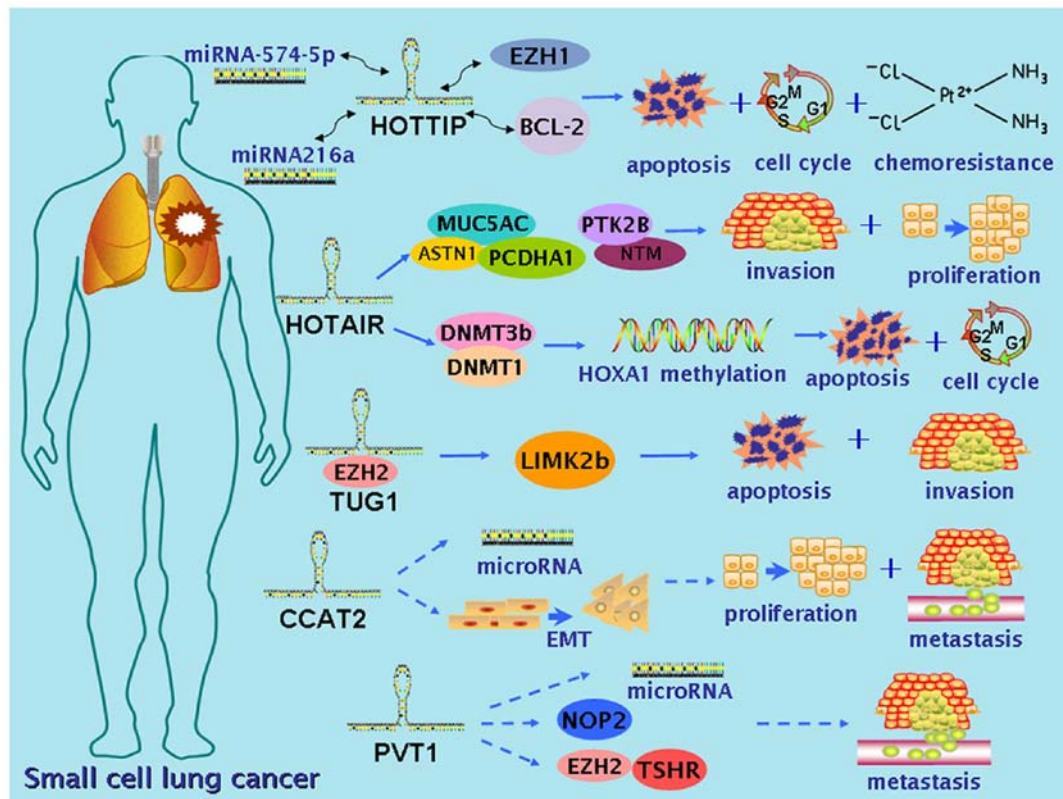
Figure 1. Schematic diagram of five lncRNAs expressed in SCLC and their mechanisms. lncRNAs exert their oncogenic effect on SCLC through interactions with various molecules involved in multiple pathways. Blue lines represent mechanisms that have been investigated in SCLC, while blue dotted lines represent mechanisms that have been investigated in other malignancies, but not yet in SCLC. Black curves with arrows at both ends represent targeting associations. Detailed information can be found in the main text. SCLC, small cell lung cancer; HOTTIP, HOXA transcript at the distal tip; EZH1, enhancer of zeste homolog 1, BCL-2, B-cell leukemia/lymphoma-2; HOTAIR, HOX transcript antisense intergenic RNA; TUG1, taurine upregulated gene 1; CCAT2, colon cancer-associated transcript 2; PVT1, plasmacytoma variant translocation 1; MUC5AC, mucin 5AC; ASTN1, astrotactin 1; PCDHA1, protocadherin α 1; PTK2B, protein tyrosine kinase 2 β; NTM neurotrimin; DNMT3b, DNA methyltransferase 3 β; DNMT1, DNA methyltransferase 1; HOXA1, homeobox A1; EZH2, enhancer of zeste homolog 2; LIMK2b, LIM domain kinase 2; EMT, epithelial-to-mesenchymal transition; NOP2, NOP2 nucleolar protein; TSHR, thyroid stimulating hormone receptor; AMPKβ2, AMP-activated protein kinase β-2; miRNA, microRNA; lncRNA, long non-coding RNA.

in SCLC utilizing a series of experiments conducted *in vitro* and *in vivo*. At first, gene expression array analysis revealed the overexpression of HOTTIP in H69 and H69R cell lines, and the result was further supported by the significant overexpression of HOTTIP, as detected by reverse transcription-quantitative polymerase chain reaction (RT-qPCR) in 50 clinical SCLC tissues prior to chemotherapy, compared with their non-cancerous counterparts. In addition, higher HOTTIP expression was significantly associated with a poorer prognosis. Manipulation of HOTTIP loss- and gain- of function experiments in SCLC cell lines also demonstrated that HOTTIP overexpression contributed to cell proliferation, as it led to a decreased number of G2-phase cells and an increased number of S-phase cells. *In vivo*, HOTTIP loss and gain of function experiments conducted in xenograft nude mice showed that mice with knockdown of HOTTIP had a smaller mean tumor volume in comparison to those in the negative control group. Afterwards, by employing web-based bioinformatics platform RNA22-seq (https://cm.jefferson.edu/), miR-574-5p and enhancer of zeste homolog 1 (EZH1) were predicted to possess targeted binding sites for HOTTIP, and this association was later verified by RT-qPCR. Therefore, it was assumed that HOTTIP may exert its effect on SCLC through a regulatory network of miRNA-574-5p-HOTTIP-EZH1 (57).

Notably, the hypothesis was verified by a subsequent co-transfection dual luciferase reporter assay, indicating that HOTTIP acts as an oncogene by sponging miR-574-5p to abrogate the expression of polycomb group protein EZH1 induced by miR-574-5p, thereby promoting the progression of SCLC (57). In another study by Sun *et al* (58), a similar experimental design was applied to investigate the role of HOTTIP in SCLC, and the association of HOTTIP with SCLC chemoresistance was also investigated, which enriched the clinical value of the study. The expression of HOTTIP and HOXA13 was markedly upregulated in SCLC cell lines and biopsy samples. Overexpression of HOTTIP impaired the anti-chemoresistance effects of etoposide, irinotecan and cisplatin toward SCLC cells *in vitro* and *in vivo*, whereas knockdown of HOTTIP exhibited a reversed effect. In addition, the finding that knockdown of HOTTIP suppressed HOXA13 expression, combined with the result of a rescue experiment by HOXA13 overexpression implied that HOTTIP exerts its function in SCLC chemoresistance and progression partly via manipulating HOXA13. Likewise, the online bioinformatics tool RNA22-seq excavated miR-216a as possessing targeted binding sites with HOTTIP, and unexpectedly, an atoptosis-related gene, B-cell leukemia/lymphoma-2 (BCL-2). Subsequent experiments confirmed that HOTTIP could

Table II. Differential expression and mechanisms of five lncRNAs in SCLC and other malignancies.

lncRNA	Malignancy	Dysregulation	Functions/mechanisms	(Refs.)
HOTTIP	SCLC	Upregulation	Chemoresistance, tumor progression. HOTTIP/miR-574-5p/EZH1 network, HOTTIP/miR-216a/BCL-2 network	(57,58)
	Liver cancer	Upregulation	Metastasis and tumor progression. Regulation of HOXA13	(55)
	Gastric cancer	Upregulation	Cell proliferation, migration and invasion. Regulation of HOXA13 and HOTTIP/miR-331-3p/HER2 network	(54,117)
	Pancreatic cancer	Upregulation	Cell cycle, proliferation and invasion. Regulation of HOXA13	(56)
	Prostate cancer	Upregulation	Cell proliferation and apoptosis. Regulation of HOXA13, BAX and BCL-2	(118)
HOTAIR	SCLC	Upregulation	Cell proliferation, lymphatic invasion, and chemoresistance. Regulation of HOXA1 methylation and target genes	(66,67)
	Breast cancer	Upregulation	Metastasis, invasion, poor prognosis, and shorter survival. Regulation of Wnt signaling pathway	(80,119)
	Colorectal cancer	Upregulation	Metastasis, poor prognosis, and low survival. Chromatin modification and EMT	(120-122)
	Cervical cancer	Upregulation	FIGO stage, aggression and lymph node metastasis. Regulation of microRNA	(123-125)
	Gastric cancer	Upregulation	Venous infiltration, lymph node metastasis, chemoresistance and tumor staging. Regulation of E-cadherin, regulation of PI3K/AKT/MRP1 genes	(126-129)
TUG1	SCLC	Upregulation	Clinical stage, chemoresistance, and shorter survival. Regulation of LIMK2b	(76)
	Liver cancer	Upregulation	Cell proliferation, apoptosis, metastasis and glycolysis. Regulation of KLF2 transcription. Regulation of AMPKβ2 and HK2	(69,130)
	Gastric cancer	Upregulation	Cell proliferation and cell cycle arrest. Regulation of cyclin-dependent protein kinase inhibitors	(74)
	Pancreatic cancer	Upregulation	Cell proliferation and cell migration. Regulation of EZH2 and EMT	(131)
	Bladder cancer	Upregulation	Cell proliferation and apoptosis. Regulation of Wnt/β-catenin pathway	(72,132)
CCAT2	SCLC	Upregulation	Malignant status and poor prognosis	(85)
	Colorectal cancer	Upregulation	Lymph node metastasis, cell proliferation and differentiation. Regulation of microRNA	(77,133)
	Ovarian cancer	Upregulation	FIGO stage, cell proliferation, migration, and invasion. Regulation of microRNA	(82,134)
	Prostate cancer	Upregulation	EMT, cell proliferation, invasion, and migration. Regulation of EMT	(83)
	Breast cancer	Upregulation	Cell proliferation, invasion, chemoresistance, and poor prognosis. Regulation of Wnt signaling pathway	(80,81)
PVT1	SCLC	Upregulation	Lymph node metastasis, distal metastasis, and clinical stage	(95)
	Gastric cancer	Upregulation	Lymph node invasion, cell proliferation and invasion. Regulation of microRNA	(89,135,136)
	Livercancer	Upregulation	Cell proliferation and cell cycling. Regulation of NOP2	(90)
	Pancreatic cancer	Upregulation	Cell proliferation, migration, shorter survival and poor prognosis. Regulation of microRNA	(92,137)
	Thyroid cancer	Upregulation	Cell proliferation and cell cycle arrest. Regulation of EZH2 and TSHR	(91)

SCLC, small cell lung cancer; HOTTIP, HOXA transcript at the distal tip; EZH1, enhancer of zeste homolog 1, BCL-2, B-cell leukemia/lymphoma-2; HOXA13, homeobox A13; HER2, erb-b2 receptor tyrosine kinase 2; BAX, BCL-2 associated X; HOTAIR, HOX transcript antisense intergenic RNA; TUG1, taurine upregulated gene 1; CCAT2, colon cancer-associated transcript 2; PVT1, plasmacytoma variant translocation 1; HOXA1, homeobox A1; EMT, epithelial-to-mesenchymal transition; FIGO, International Federation of Gynecology and Obstetrics; PI3K, phosphatidylinositol 3-kinase; AKT, protein kinase B; MRP1, multidrug resistance-associated protein 1; LIMK2b, LIM domain kinase 2; KLF2, Kruppel like factor 2; MPKβ2, AMP-activated protein kinase subunit β2; HK2, hexokinase 2; NOP2, NOP2 nucleolar protein; EZH2, enhancer of zeste homolog 2; TSHR, thyroid stimulating hormone receptor; miR, microRNA; lncRNA, long non-coding RNA.

function as a competing 'sponge' through binding miR-216a, thereby diminishing its silencing effect toward BCL-2, contributing to the chemoresistance and progression of SCLC (58). Although the aforementioned findings may only be the tip of the iceberg, they widen the landscape of research into the molecular mechanism of SCLC, as a novel network composed of lncRNA, miRNA and specific cancer-related genes is put forward, providing inspiration for developing prognostic and therapeutic agents.

HOTAIR. HOTAIR is one of the most well-characterized lncRNAs and is overexpressed in certain malignancies, including breast, colorectal, hepatocellular, gastrointestinal and non-small cell lung cancer (59). First identified in 2007, HOTAIR resides in the HOXC locus. Previous reports revealed that the molecular mechanism of HOTAIR is its transcription from the HOXC gene as an antisense transcript and then binding to PRC2 (composed of EZH2, polycomb protein SUZ12 and polycomb protein EED) and lysine-specific demethylase/CoREST/REST complex as a scaffold, leading to catalyzation of trimethylation of histone H3 on lysine 27 (H3K27) and spontaneous demethylation of H3K4, and repression of the transcription of HOXD genes (27,60). With regard to DNA methylation, EZH2, a compartment of PRC2, directly interacts with DNA methyltransferases. This interaction assists in maintaining DNA methylation and stabilizing the repression of certain genes, including various tumor suppressors (61). As targets of HOTAIR, the homeobox-containing genes are a set of regulators that transcriptionally encode DNA-binding homeodomains that participate in controlling normal development (51,62). In addition, abnormal expression of HOX genes is associated with oncogenesis and paramorphia (61,63). Additionally, by inducing epithelial-to-mesenchymal transition (EMT), HOTAIR associates with tumorigenesis (64). HOTAIR also triggers ubiquitin-mediated proteolysis via interaction with RNA-binding protein MEX3B and E3 ubiquitin-protein ligase DZIP3 (65). Ono *et al* (66) studied the association of HOTAIR with SCLC cellular processes and clinical characteristics. The study assessed HOTAIR expression in 35 surgically resected SCLC tissues and 10 SCLC cell lines, and observed that expression of HOTAIR in pure SCLC was markedly overexpressed compared with that in those combined with lung adenocarcinoma (LUAD), large cell carcinoma or large cell neuroendocrine carcinoma, and that HOTAIR overexpression was clearly associated with relapse and lymphatic invasion. *In vitro* experiments indicated that the expression of HOTAIR in half of the SCLC cell lines was elevated compared with that in normal cells. Knockdown of HOTAIR reduced cellular invasiveness and proliferative activity of SBC-3 cells. Gene expression analysis revealed that a reduction in HOTAIR led to upregulated expression of mucin production-related genes, including mucin 5AC, and cell adhesion-related genes, including astrotactin 1 and proto-cadherin α1, and downregulated expression of genes such as neurotrimin and protein tyrosine kinase 2β, participating in neuronal growth and signal transduction, respectively (66). Recently, Fang *et al* (67) investigated the role of HOTAIR expression in the chemoresistance of SCLC and its underlying mechanism. The study assessed the impact of HOTAIR on SCLC chemoresistance *in vitro* and observed that HOTAIR expression was also markedly upregulated in drug-resistant cell lines compared with that in the parental cell lines. The study showed that downregulated expression of HOTAIR promoted cell cycle arrest and apoptosis to increase sensitivity to antitumor drugs, while repressing tumor growth *in vivo*. In addition, increased HOXA1 methylation was observed in the drug-resistant cells. An enzyme-linked immunosorbent assay revealed that a reduction of HOTAIR lessened HOXA1 methylation via reducing the expression of DNA (cytosine-5)-methyltransferase (DNMT)3b and DNMT1. RNA immunoprecipitation validated the interaction between HOXA1 and HOTAIR. Together, these findings indicated that HOTAIR mediates chemoresistance by increasing HOXA1 methylation. Hence, HOTAIR could serve as a possible target for novel therapeutics to combat chemoresistance. Based on these previous findings, lncRNA HOTAIR is involved in the relapse and lymphatic invasion in SCLC patients, and it could also act as a biomarker for prognosis and chemotherapy response, and as a therapeutic target to overcome the chemoresistance of SCLC.

TUG1. TUG1 was initially described as a spliced and poly-adenylated lncRNA necessary for the development of photoreceptors in mice retina (68). Increasing evidence has demonstrated that TUG1 serves a crucial role in a number of human tumors, including hepatocellular carcinoma, osteosarcoma, glioma, esophageal, gastric and bladder cancer (69-74). Aberrant expression of PRC2-related lncRNAs is involved in tumorigenesis and progression. In a previous study, TUG1 was found to be induced by p53, prior to binding to PCR2 and influencing certain genes involved in the modulation of mitosis, spindle construction and cell-cycle phasing (34). Yang *et al* (75) revealed that a combination of methylated PRC2 and TUG1 manipulates the relocation of growth-control genes between interchromatin granules and polycomb bodies in response to growth signals, therefore portraying a role that TUG1 serves in the relocation of transcription units to coordinate gene expression (75). Niu *et al* (76) investigated the functions of TUG1 in the cell proliferation and chemoresistance of SCLC, and its underlying molecular mechanism (76). The study analyzed TUG1 expression in tissue samples from SCLC patients (n=33) who had undergone biopsy or bronchofiberscopy, and elevated TUG1 expression was found in cancerous tissues compared with that in adjacent non-cancerous tissues. Statistical analysis showed that higher expression of TUG1 was associated with shorter survival time, advanced clinical stage and cigarette smoking. *In vitro* Cell Counting Kit-8 and colony formation assays indicated that silencing TUG1 markedly reduced cell growth. The results from flow cytometry analysis conducted to assess the effect of TUG1 on cell apoptosis suggested that knockdown of TUG1 promoted apoptosis and led to a significant accumulation of G1-phase cells, and that downregulated TUG1 expression increased apoptosis in H44DDP and H69AR cell lines exposed to anticancer drugs. The chemoresistance-inducing ability of TUG1 *in vivo* was further investigated using a mouse xenograft model, and the result was consistent with that of the *in vitro* experiment. Moreover, TUG1 could modulate LIM domain kinase 2 expression through binding with EZH2, and

subsequently led to increased cell growth and chemoresistance in SCLC. Outcomes of this study could be guidance to the development of innovative TUG1-directed prognostic and therapeutic strategies.

CCAT2. CCAT2 was first introduced in 2013 as an lncRNA located in the 8q24 gene desert region, and it possesses a tumor-related single nucleotide polymorphism rs6983276. Additionally, overexpression of CCAT2 in colon cancer was observed, and it was considered to serve an oncogenic role, promoting colorectal cancer cell proliferation and motility, metastasis and chromosomal instability by regulating myc and Wnt pathways (77). A CCAT2 genetic polymorphism, rs6983267, is associated with platinum-based chemotherapy sensitivity in lung cancer patients (78). Since its discovery, the oncogenic role of CCAT 2 has been increasingly demonstrated in different tumors, including gastric, breast, lung, liver, colon, cervical, ovarian, bladder, prostate and esophageal cancer (79-84). The stimulatory effects on the Wnt/β-catenin signaling pathway, cancer metabolism and EMT may underlie its oncogenic action (79). CCAT2 is upregulated in an estimated two-thirds of breast cancer patients (80). High CCAT2 expression was associated with a poor curative effect from cyclophosphamide/methotrexate/fluorouracil-containing adjuvant chemotherapy in breast cancer patients with lymph node metastasis (80). Chen *et al* (85) detected CCAT2 expression in 102 human SCLC tissues, 15 paired non-tumor tissues, SCLC cell lines (DMS-53 and H446) and a normal bronchial epithelial cell line (16HBE). The association between clinicopathological factors and CCAT2 expression was subsequently analyzed. The study reported that CCAT2 level was significantly overexpressed in SCLC tissue and cell lines compared with that in normal lung tissues. Subgroup analyses also indicated that higher expression of CCAT2 was correlated with malignant status and poor prognosis in SCLC patients. Moreover, knockdown of CCAT2 to inhibit SCLC cell growth and metastasis *in vitro* was observed. To conclude, CCAT2 may serve as an oncogene and a negative prognostic indicator in SCLC.

PVT1. PVT1 is an lncRNA homologous to the mouse plasmacytoma variant translocation gene (Pvt1), which was first identified as being frequently involved in a variant translocation in plasmacytoma in the mid-80s in mice (86,87). Soon after, the PVT1 locus emerged as a site of variant translocations in Burkitt lymphoma. Subsequent studies support the role of PVT1 as a cancer risk locus in relation to the well-known myc oncogene (88). PVT1 presents the capacity to facilitate cell growth and suppress cell apoptosis in the tumorigenesis of various types of cancer, including gastric (89), liver (90), thyroid (91) and pancreatic (92) cancer, and non-small cell lung cancer (93). The expression of PVT1 in tumor samples of these types of cancer is elevated. *In vitro* and *in vivo* experiments conducted by Wang *et al* (90) demonstrated that PVT1 promotes cell proliferation, cell cycling and the acquisition of stem cell-like properties in hepatocellular carcinoma cell by stabilizing NOP2 nucleolar protein (90). However, the underlying mechanisms of the functional exertion of PVT1 and its interaction with downstream targets remain largely unknown. Partially known molecular functions of PVT1 can

be categorized into three key pathways: Partaking in DNA rearrangement, encoding microRNAs and intercommunicating with myc (94). Recently, Huang *et al* (95) first identified the role of PVT1 in SCLC. In the study, PVT1 expression was detected in SCLC tissues, paired normal gastric tissues and two SCLC cell lines. Meanwhile, the association of PVT1 expression levels with clinical features of 120 enrolled SCLC patients was analyzed. RT-PCR analysis showed that PVT1 expression was significantly higher in SCLC tissues and cell lines than in their normal counterparts, and positive correlations between PVT1 overexpression and the status of clinical stage, lymph node metastasis and distal metastasis in SCLC were noted. Furthermore, multivariate analysis revealed that PVT overexpression could be an independent prognostic biomarker for the survival of SCLC patients. Cell migration and invasion were significantly suppressed *in vitro* by silencing of PVT1 in SCLC. To conclude, PVT1 possesses the potency to be a novel marker and a prospect to develop targeted therapy for SCLC. However, further investigations are required for thorough elucidation of the molecular mechanism of PVT1 in SCLC.

Thus far, the present review has summarized and discussed five lncRNAs (HOTTIP, HOTAIR, TUG1, CCAT2 and PVT1) involved in SCLC. However, these lncRNAs are also involved in NSCLC, which accounts for ~85% of all lung cancer cases. It is of merit to include information on the roles that these lncRNAs serve in NSCLC, as a contrast and possibly, enlightenment. HOTTIP was reported to be significantly upregulated in NSCLC and to function as an oncogene by regulating HOXA13, which coincides with the findings observed in other malignancies, implying that HOXA13 is a key element through which HOTTIP promotes carcinogenesis (96). Moreover, overexpression of HOTTIP was found to motivate LUAD cell proliferation and chemoresistance via regulating the protein kinase B (AKT) signaling pathway (97). As for HOTAIR, multiple studies also demonstrated its overexpression in NSCLC, and it is involved in the initiation and development of NSCLC through interacting with unc-51-like autophagy-activating kinase 1 to suppress autophagy (98), targeting caveolin 1 (99) and miR-613 (100). Based on the available literature, there is controversy with regard to the expression of TUG1 in NSCLC. Studies by Lin *et al* (101) and Zhang *et al* (102) revealed that TUG1 was downregulated in NSCLC, while a study by Liu *et al* (103) showed that it was upregulated. According to the study by Liu *et al*, TUG1 could inhibit apoptosis by silencing BCL-2 associated X via interacting with EZH2 (103). TUG1 RNA could target PRC2 in the promotor region of CUGBP Elav-like family member 1 (CELF1) and CELF1 expression was therefore negatively regulated (101). Zhang *et al* (102) suggested that TUG1 acted as a growth regulator in NSCLC partly through controlling HOXB7. CCAT2 exerted overexpression in NSCLC (104,105), and could promote oncogenesis via overexpression of zinc finger and BTB domain containing 7A (104). With regard to PVT1, it is of note that accumulating recent studies (106-109) investigated the roles of upregulated PVT1 in NSCLC via the ceRNA-regulated network, which is a trending hotspot in the research field. PVT1 was demonstrated to exert its oncogenic functions by sponging miR199a5p (106), miR-126 (107), miR-497 (108) and miR-195 (109).

4. Conclusions and future directions

SCLC is a fatal disease with an aggressive and brutal nature; it comprises ~15% of all lung cancer cases. The management of SCLC remains challenging, while disease outcome has remained poor, mainly due to limited options for effective treatment. The majority of the cases are at an irreversible advanced stage when diagnosed and rapidly develop treatment resistance despite a high success rate of initial chemotherapy and radiation. The pathogenesis of SCLC has been investigated by researchers across the world; nevertheless, the implicit molecular mechanism remains mostly unidentified. In light of next-generation sequencing techniques and bioinformatics tools, lncRNAs have been shown to exert distinguishable functions in a broad range of human diseases, including the most concerning types of cancer. Although great discoveries and advances in cancer pathogenesis and therapeutics have been made over the decade, the elucidation of the SCLC molecular mechanism and its frontline treatment have developed slowly due to obstacles from various aspects, including difficulty in sample collection, research funding, late diagnosis, rapid progression and chemoresistance. Investigation into the role of lncRNAs in SCLC is underway, yet no lncRNAs have been extensively investigated, let alone clinically utilized for prognosis, diagnosis or therapeutic design. According to the available published literature, the current research state of SCLC is relatively superficial compared with that of NSCLC. Thus, more research is urgently required.

Despite the aforementioned challenges, there have been certain notable novel findings that have the potential to advance the field. Given the scarcity of SCLC tissues, a multidisciplinary, interoperable, cross-institutional approach is required to collect adequate SCLC tissues for more trans-lational research projects. Emerging techniques, including next-generation sequencing and bioinformatics, have created opportunities to conduct larger scale and deeper studies on SCLC. The past decade has witnessed the emergence of lncRNAs involved in various types of cancer. For example, lncRNA prostate cancer antigen 3 and lncRNA highly upregulated in liver cancer can be detected in prostate and liver cancer, respectively, and serve as sensitive diagnostic markers (110,111). As an intensively studied lncRNA, lncRNA metastasis-associated lung adenocarcinoma transcript 1 is found to be involved in multiple malignancies, including lung, colon, breast and liver cancer, indicating its general participation in cancer cell proliferation (112). Overexpression of lncRNA antisense noncoding RNA in the INK4 locus is observed in a number of types of cancer and is associated with a poor prognosis in gastric and prostate cancer (113). lncRNA CCAT1 could be used as a clinically detectable marker to predict the therapeutic responsiveness of bromodo-main and extraterminal inhibitors in patients with colorectal cancer (114). lncRNA maternally expressed gene 3, which acts as a tumor-suppressor via promoting p53 accumulation and recruiting PRC2, is downregulated in multiple primary human tumors (115). As these lncRNAs have been verified as promising predictive markers for diagnosis, prognosis and chemotherapy sensitivity in cancer patients, they also have the potential to lead to a greater understanding of SCLC tumorigenesis and chemoresistance, and could serve as efficient therapeutic targets. The diagnostic sensitivity and specificity may be enhanced by joint detection of dispa-rate lncRNAs, and this may become particularly useful in non-invasive screening for early-stage SCLC patients. The functional roles of lncRNAs involve diverse signaling pathways and investigation into these pathways may yield crucial signaling targets that could be blocked to impede tumor progression. Signaling pathways frequently altered in cancer include phosphoinositide 3-kinase/AKT, Kirsten rat sarcoma viral oncogene homolog/V-raf murine sarcoma b-viral oncogene homolog B1, retrovirus-associated DNA sequences/mitogen-activated protein kinase, EGFR, fibroblast growth factor receptor, Wnt and myc, among others (116). Currently, among nearly 20,000 identified lncRNAs, only five have been investigated in SCLC. Therefore, more efforts should be put into this field of great potential. As a large genetic information treasury and a potential opening to combat diseases, lncRNAs will play no small part in identi-fying SCLC mechanisms.

Availability of data and materials

Not applicable.

Authors' contributions

TTL contributed to the literature retrieval and manuscript preparation. RQH and JM contributed to the manuscript modification and commented on multiple aspects of the manuscript. ZYL, XHH and GC jointly supervised the construction of the study, and contributed to the design and approval of the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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