Role of IncRNA and EZH2 Interaction/Regulatory Network in Lung Cancer

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Abstract

Lung cancer is the leading cause of cancer-related deaths worldwide. Long non-coding RNAs (lncRNAs) are non-protein-coding transcripts and longer than 200 nucleotides. LncRNAs have been demonstrated to modulate gene expression at transcriptional, post-transcriptional, as well as epigenetic levels in lung cancer. Interestingly, compelling studies have revealed that lncRNAs participated in the EZH2 oncogenic regulatory network. EZH2 plays an important role in the initiation, progression and metastasis of cancer. On one hand, lncRNAs can directly bind to EZH2, recruit EZH2 to the promoter region of genes and repress their expression. On the other hand, lncRNAs can also serve as EZH2 effectors or regulators. In this review, we summarized the types of lncRNA-EZH2 interaction and regulatory network identified till date and discussed their influence on lung cancer. Better understanding regarding the interaction and regulatory network will provide new insights on lncRNA- or EZH2-based therapeutic development in lung cancer.

Key words: lung cancer; lncRNA; EZH2; regulation; interaction

Introduction

Lung cancer is the most common cause of cancer death, with an estimated 1.6 million deaths in 2012 worldwide [1]. Approximately 85% lung cancers are classified as non–small cell lung cancer (NSCLC) which includes squamous cell carcinoma (SCC), lung adenocarcinoma (LAD), and large cell carcinoma (LCC) histologic subtypes, and the other 15% as small cell lung cancer (SCLC) [2, 3]. Although knowledge regarding lung cancer biology, advances in diagnostic techniques and therapeutic strategies have been improved, the prognosis remains poor with an overall 5-year survival of only 15% [4]. Therefore, there is a strong need to better understand the pathogenesis, early diagnostic biomarkers and therapeutic targets for lung cancer.

Accumulated evidences have demonstrated important roles of long non-coding RNAs (lncRNAs) in various diseases, particularly in cancer. LncRNAs refer to non-protein coding transcripts longer than 200 nucleotides [5, 6]. Although lncRNAs are not translated into proteins, they function to regulate gene transcription at transcriptional level, post-transcriptional level and epigenetic level [7]. The dysregulation of lncRNAs has been demonstrated in various human cancers, including lung cancer, and promoted tumor formation and progression [8, 9]. In this review, we
focused on lncRNAs and Enhancer of Zeste Homolog 2 (EZH2) interaction and regulatory network in lung cancer.

**Functions and mechanisms of lncRNAs in lung cancer**

lncRNAs has been emerged as novel master regulators, playing a major regulatory role in various biological processes, such as cell cycle regulation, proliferation, survival, apoptosis, migration, invasion and chemoresistance [10, 11]. To data, a large number of lncRNAs that play a key role in cell function regulation may be used as potential biomarkers for the diagnosis, treatment and prognosis of various cancers, including lung cancer [12, 13]. For instance, MALAT1 (Metastasis-associated lung adenocarcinoma transcript 1) is shown to be upregulated and linked to clinicopathological features in patients with lung cancer, which may serve as a potential prognostic marker to predict poorer prognosis in patients [14, 15]. HOTAIR (HOX transcript antisense-RNA) exhibited significantly higher expression in lung cancer and its elevated expression was correlated with lymph node metastasis and poor survival rate [16-18]. HOTAIR has been emerged as a key regulator of lung cancer and may be used as a diagnostic and therapeutic potential marker of lung cancer [19, 20].

As known, lncRNA is regulated by mechanisms similar to those of protein-coding genes, such as transcription factor binding, RNA splicing, DNA and histone modifications [21]. Numerous lncRNAs are demonstrated to be mediated by transcription factors, like p53, NF-κB, Oct4 and Sox2 [22, 23]. Jen et al. revealed that expression of NEAT1 and MALAT1 was transcriptionally regulated by Oct4 in lung cancer [24]. LncRNAs can also regulate various key cellular functions in lung cancer, such as gene expression regulation, genomic reprogramming, nuclear cytoplasmic trafficking, nuclear compartmentalization and RNA-splicing [25-27]. H19 promoted cell cycle progression by down-regulating miR-107 in NSCLC cells [28]. SBF2-AS1 could regulate cell cycle through epigenetic inhibition of P21 [29]. LncRNA-HIT (HOXA transcript induced by TGFβ) promoted migration and invasion of NSCLC cells by associating directly with ZEB1[30].

**Functions and mechanisms of EZH2 in lung cancer**

EZH2 (Enhancer of zeste homolog 2), a 751-amino acid histone-lysine methyltransferase, is located on human chromosome 7q35 [31]. It is the enzymatic subunit of polycomb-repressive complex 2 (PRC2). PRC2 functions as a histone H3 lysine 27 (H3K27) methyltransferase and promotes transcriptional silencing via regulating chromatin structure through posttranslational modification of histones [32, 33]. The PRC2 complex is mainly composed of a trimeric core of SUZ12, EED and EZH1/2 [34]. Sequence analysis showed that EZH family is organized into four homologous domains, where the cysteine-rich region and the SET domain functions in maintaining histone methyl transferase (HMT) activity, and the N-terminal domains H1 and H2 are the protein interaction domains that are required for establishing and maintaining proper PRC2 functions [35, 36].

EZH2 is capable of mono-, di-, and tri-methylation of H3K27 and essential for epigenetic gene silencing [37]. It has been proved to regulate various biological functions and cellular signals in lung cancer. Liu and colleagues reported that knockdown of EZH2 exerted inhibitory effects on proliferation of NSCLC cells, which is achieved through direct binding of EZH2 to the PUMA promoter, thus epigenetically repressing the PUMA expression [38]. Murai et al. revealed that EZH2 promoted SCLC progression by suppressing the TGF-β-Smad-ASCL1 pathway [39]. Another study by Li and colleagues showed that EZH2 inhibited lung cancer cell proliferation through binding to the Nrf2 promoter, where the expression of H3K27me3 was increased and Nrf2 was repressed [40]. Moreover, the EZH2 interaction with lncRNAs could regulate numerous gene expressions at the epigenetic level.

On the other hand, EZH2 expression and activity in cancer cells can be altered at multiple levels. It can be transcriptionally induced by multiple factors, for example, p53 and C-MYC [41, 42], or can be post-transcriptionally regulated through the interaction of miRNAs or lncRNAs [43]. MiR-138 was downregulated in NSCLC tissues and cells, and it can bind to the 3’ UTR of EZH2 and suppress the expression levels of EZH2 mRNA and protein [44]. Zhang et al. reported that miR-101 inhibited cell proliferation and invasion in NSCLC cells by directly repressing EZH2 expression [45].

Compelling studies have revealed that lncRNA is a novel player in the EZH2-related cellular biological functions. To summarize and detail the previously findings, we are focusing in the following paragraphs on the up-to-date characterized lncRNAs and EZH2 interaction/regulatory network in lung cancer (Table 1 and Figure 1).

**LncRNAs and EZH2 interaction in lung cancer**

These lncRNAs are capable of directly binding to EZH2 and epigenetically silencing gene expression.
Table 1. LncRNAs bind with EZH2 in lung cancer.

| LncRNA | Cancer type | Expression | Bind to EZH2 | Function mechanism | Associated clinical features | Associated cell process | Ref |
|--------|-------------|------------|--------------|-------------------|-----------------------------|-------------------------|-----|
| TUG1   | SCLC        | up         | EZH2         | LIMK2b expression | correlates with clinical stage and shorter survival time | promotes cell growth migration and invasion, increases chemoresistance | [50] |
|        | LAD         | up         | EZH2         | BAX expression    | associates with enhanced tumor size, degree of differentiation, lymph node metastases, distant metastasis and TNM stage. | promotes cell viability and decreases cell apoptosis | [55] |
| TUG1   | NSCLC       | down       | EZH2         | CELF1 expression | -                           | inhibits cell proliferation | [56] |
| TUG1   | NSCLC       | down       | EZH2         | HOXB7 expression | associates with higher TNM stage and tumor size | inhibits cell proliferation | [57] |
| XIST   | NSCLC       | up         | EZH2         | KLF2 expression  | associates with shorter survival and poorer prognosis | promotes cell proliferation, migration and invasion | [61] |
| SNHG20 | NSCLC       | up         | EZH2         | P21 expression   | associates with advanced tumor, TNM stage and tumor size, poorer OS | promotes cell proliferation, migration and invasion | [73] |
| LINCO133 | NSCLC    | up         | EZH2, LSD1   | KLF2, P21 and E-cadherin expression | associates with poor prognosis and short survival time | increases cell proliferation, migration and invasion, decreases cell apoptosis | [80] |
| LINCO0673 | NSCLC   | up         | EZH2         |   |   |   | |
| LINCO0152 | LAD      | up         | EZH2         | IL24 expression  | associates with tumor size, lymph node metastasis, TNM-stage correlates with advanced TNM stage, larger tumor size, and lymph node metastasis, shorter survival time | increases cell proliferation | [87] |
| LINCO0511 | NSCLC    | up         | EZH2         | P57 expression   | associates with oncogenesis, tumor size, metastasis, and poor prognosis | affected cell proliferation, invasiveness, metastasis, and apoptosis | [102] |
| LINCO1207 | LAD      | up         | EZH2         | BAD expression   | associates with TNM stage, advanced TNM stage and shorter survival | increases cell proliferation, decreases cell apoptosis | [105] |
| AGAP2-AS1 | NSCLC  | up         | EZH2, LSD1   | KLF2 and LAT52 expression | correlates with poor prognostic outcomes | increases cell proliferation, migration and invasion, and inhibits cell apoptosis. | [108] |
| HOXAI1-AS5 | NSCLC   | up         | EZH2, DNMT1  | miR-200b expression | indicates poor prognosis | promotes cell invasive abilities | [121] |
| FEZF1-AS1 | NSCLC   | up         | EZH2, LSD1   | Wnt/β-catenin signaling | correlates with FOXF1 expression | promotes cell proliferation, invasion and EMT | [129] |
| FOXF1-AS1 | NSCLC   | down       | EZH2         | FOXF1 expression  | associates with tumor migration, invasion and metastasis | inhibits cell migration and invasion by regulating EMT | [136] |

TUG1

TUG1 (Taurine-upregulated gene 1) is mapped on chromosome 22q12.2, and has a length of 7100 nt [46]. It was initially detected in a genomic screen for genes upregulated following taurine treatment in developing mouse retinal cells. Later studies demonstrated that TUG1 played an important role in the initiation and progression of malignancies [46]. The expression of TUG1 in human cancer has been shown to overexpress in a variety of cancers, for example, bladder cancer, gastric cancer, osteosarcoma, hepatocellular carcinoma, and colorectal cancer [47]. Recent investigations have indicated that TUG1 could regulate gene expression by binding with EZH2, affecting cell proliferation in human gastric cancer and hepatocellular carcinoma [48, 49].

TUG1 is upregulated in SCLC tissues and cell lines and promoted cell proliferation, migration and invasion, as well as chemoresistance [50]. It affected cell functions through regulation of LIMK2b expression by binding to EZH2. LIMK2b is located at 300bp of TUG1 and is a member of LIMK2, belonging to the LIM kinase family [51]. LIMK2 encodes a kinase that phosphorylates cofilin and then regulates actin dynamics, and is involved in tumor growth, migration and invasion [52-54]. Another study revealed that TUG1 was overexpressed in LAD cells and serum samples and inhibited cell apoptosis through suppressing expression of the pro-apoptotic protein BAX via physically binding with EZH2 [55].

However, TUG1 was significantly decreased in NSCLC tissues compared to surrounding non-tumor lung tissues [56, 57]. The different TUG1 expression on SCLC and NSCLC might be due to its tissue-specific expression patterns of lncRNAs. Knockdown of TUG1 significantly promoted the proliferation of NSCLC cells. TUG1 is induced by p53 and negatively regulates HOXB7 (homeobox B7) by binding to PRC2, and participates in the AKT and MAPK pathway. Lin

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et al. revealed that TUG1, which is involved in pre-mRNA alternative splicing, RNA editing, RNA decay, and translation was bound to EZH2/EED in NSCLC cells by RIP assay and negatively regulated CELF1 (Elav-like family member 1) [58].

Studies have shown either upregulation or downregulation of TUG1 in lung cancer, suggesting its complex role in cancer biology. More studies are needed to better understand the role of TUG1 in lung cancer.

XIST

XIST (X inactivate-specific transcript) is derived from XIST gene and is essential for transcriptional silencing of one X-chromosome during mammalian female development [59, 60]. It is overexpressed in numerous human cancers, including lung cancer, and serves as an oncogene [61-64].

Tantai et al. revealed that XIST was up-regulated in NSCLC tissues and serum, and might serve as a potential diagnostic marker [65, 66]. High expression of XIST might be linked to poorer prognosis and shorter survival in NSCLC patients [61]. XIST silencing inhibited NSCLC cell proliferation, migration and invasion. Mechanistically, RIP and RNA pull-down assays showed that XIST could directly bind to EZH2, and then suppress the transcription of KLF2. KLF2 belongs to the Kruppel-like factor family, which contain Cys2/His2 zinc-finger domains [67]. KLF2 is down-regulated in various cancers, where it inhibits cell proliferation and acts as a tumor suppressor [67]. Thus, XIST might be a potential candidate biomarker and target for treatment of NSCLC, but more studies are needed to better understand the importance of XIST.

SNHG20

SNHG20 (Small nucleolar RNA host gene 20) is mapped on chromosome 17q25.2, and is 2183 nt lncRNA in length [68]. SNHG20 is overexpressed in ovarian cancer, colon cancer and hepatocellular carcinoma, and predicts poor prognosis [69-71]. It promotes cell proliferation, and cell invasion by EMT. Knockdown of SNHG20 suppresses β-catenin expression and inhibits the activity of Wnt/β-catenin signaling [69, 72].

SNHG20 is upregulated in NSCLC tissues and is associated with bigger tumor size, advanced TNM stage, as well as poorer survival rate [73]. SNHG20 functions as an oncogene by promoting NSCLC cell proliferation, migration, and repressing cell apoptosis. Further mechanistic analyses revealed that SNHG20 could interact with EZH2. Moreover, SNHG20 silencing decreases EZH2 by binding to the promoter region of P21 and represses its expression. P21 is a cyclin-dependent kinase (CDK) inhibitor, and functions in multiple cellular processes during cell growth by directly binding to kinases related to G1/S transition [74]. Therefore, SNHG20 plays an important role in NSCLC progression by epigenetically silencing of P21 transcription via binding with EZH2.

LINC01133

LINC01133 is encoded by chromosome 1q23.2 and is a 1154 nt lncRNA long [75]. LINC01133 expression is downregulated in colorectal cancer tissues and inhibits the EMT in colorectal cancer cells by directly interacting with SRSF6, a splicing factor that regulates the proliferation as an oncoprotein [76-78]. However, LINC01133 was found to be statistically overexpressed in osteosarcoma tumor tissues and cell lines and promotes the proliferation, migration and invasion of osteosarcoma cells [79]. It specifically targeted miR-422a, and played a tumor suppressive role in osteosarcoma progression. The differences might be due to the tissue-specific expression patterns of lncRNAs.

Interestingly, LINC01133 is overexpressed in LSCC tissues and predicted poor survival rates, but not in the LAD samples [75]. However, another study revealed that LINC01133 was up-regulated...
in both NSCLC types and indicated poor prognosis [80]. By performing RNA pulldown assay, the authors found that LINC01133 could directly bind to EZH2, which in turn directly binds to the promoter regions of KLF2, P21 and E-cadherin and represses their transcription. LINC01133 promotes cell proliferation via inhibiting KLF2 and P21, while reduced cell migration and invasion through repressing E-cadherin expression in NSCLC cells.

**LINC00673**

LINC00673 is located on chromosome 17q25.1, and has a transcript length of 2275 nt [81]. LINC00673 upregulation has been reported in various kinds of cancers, such as pancreatic cancer, gastric cancer and tongue squamous cell carcinoma [82-84]. It is identified as a potential onco gene that promotes cell proliferation and invasion and inhibits cell apoptosis. Furthermore, LINC00673 functions through different mechanisms, including regulation of epigenetic signatures and gene expression. It can directly interact with EZH2 and LSD1 in gastric cancer cells, thereby suppressing KLF2, KLF4 and LATS2 expression levels [82, 83]. It has been reported to negatively regulate miR-205 in hepatocellular carcinoma, and suppress PI3K/AKT signaling in glioma [85].

LINC00673 is found to be overexpressed in NSCLC tissues and correlated with tumor size, lymph node metastasis and TNM stage [86, 87]. LINC00673 increases proliferation, migration and invasion of NSCLC cells. It was found that the oncogenic activity of LINC00673 is partially attributable to its epigenetically inhibition of NCA LD (Neurocalcin delta) through binding to LSD1, which could directly bind to the NCA LD promoter region [86]. NCA LD belongs to the EF-hand calcium-binding protein superfamily, and functions in the regulation of neuronal signal transduction process. It is involved in the pathogenesis of human cancer [88, 89]. In another study, using RIP and RNA-pulldown assays, Ma and colleagues revealed that LINC00673 was directly associated with EZH2 in NSCLC cells, and represesed the expression of HOXA5 [87]. HOXA5 is identified as a tumor suppressor, which functions as a transcription factor and inhibits cancer cell metastasis through cytoskeletal remodeling regulation [90, 91]. Taken together, LINC00673 might be a new diagnostic marker and targeting it might be meaningful for treating patients with NSCLC.

**LINC00152**

LINC00152, which is 828 nt in length, is located on chromosome 2p11.2 [92]. It was first reported to be overexpressed in gastric tissues and cells and subsequently reported to be involved in cell proliferation, apoptosis, migration, and invasion of cancer cells [93, 94]. Mechanistic investigations revealed that LINC00152 promoted tumor growth through EGFR-mediated PI3/AKT pathway, and it also promoted cell cycle progression by binding to EZH2, thus suppressing p15 and p21 expression in gastric cancer cells [95]. Another study revealed that linc00152 bound to EZH2 and LSD1 epigenetically silenced P16 expression in renal cell carcinoma [96].

The role of LINC00152 in lung cancer has been recently highlighted. Feng et al. reported that LINC00152 was upregulated in lung cancer, and correlated with poor survival [97]. Silencing of LINC00152 inhibited cell proliferation in lung cancer cells through EGFR signaling independent pathway. In consistent with these results, Chen et al. also reported that LINC00152 expression was highly expressed in human LAD tissues and related to tumor progression [98]. Moreover, RIP assays revealed that LINC00152 directly bound to EZH2 and LSD1 in lung cancer cells, and RNA pulldown assays also confirmed the interaction between LINC00152 and EZH2 or LSD1. ChIP assays also showed that LINC00152 could recruit EZH2 to the IL24 promoter region and repressed its transcription by mediating H3K27me3.

**LINC00511**

LINC00511 (also known as onco-LncRNA-12) was originally found to be elevated and functioned as an oncogene in breast cancer [99, 100]. LINC00511 knockdown showed tumor-suppressive activities via cell proliferation inhibition in breast cancer cells. LINC00511 was also overexpressed in pancreatic ductal adenocarcinoma and exerted oncogene functions through up-regulating VEGFA via acting as a competing endogenous RNA on hsa-miR-29b-3p [101].

A recent study found that LINC00511 was upregulated in NSCLC tumor tissues and correlated with tumor size, TNM stage, and lymph node metastasis [102]. Knockdown of LINC00511 inhibited cell proliferation and metastasis in NSCLC cell lines. Interestingly, further mechanistical study revealed that LINC00511 could directly bind to EZH2 by means of RIP assay, and recruit EZH2 to the promoter region p57, which is an inhibitor of cyclin-dependent kinase, and is deemed to be a tumor-suppressor in numerous types of cancers [103, 104]. Thus, these results showed that LINC00511 is an oncogene in NSCLC.

**LINC01207**

LINC01207 is an intergenic IncRNA with 3212 nt
in length, locates in chromosome 4q32.3, and consists of 3 exons and 2 introns [105]. LINC01207 is found to be significantly up-regualted in LAD but not in LSCC tissues [106]. The higher expression of LINC01207 was associated with advanced TNM stage and poor survival of LAD patients. LINC01207 promotes cell proliferation and inhibits cell apoptosis, while dose not affect cell migration and invasion. Using RIP and ChIP assay, LINC01207 was found to directly bind with EZH2 and mediated H3K27-me3 at the promoter region of Bad, which is an important pro-apoptotic protein of the Bcl-2 family [107]. Furthermore, LINC01207 silencing up-regulates the expression of Bad. However, with only two manuscripts published regarding LINC01207, very little is known about this lncRNA. Further investigation is necessary before its role in cancer can be drawn.

AGAP2-AS1

AGAP2-AS1 (AGAP2 antisense RNA 1) is an antisense lncRNA with 1567 nt in length, and is transcribed from a gene mapped on chromosome 12q14.1[108]. AGAP2-AS1 was found to be upregulated in gastric cancer tissues and cell lines, and its upregulation may be activated partly by SP1, which is a transcription factor [109]. Knockdown of AGAP2-AS1 significantly inhibited gastric cell proliferation, migration and invasion. In addition, AGAP2-AS1 binds with EZH2 and LSD1, and epigenetically suppresses the expression of P21 and E-cadherin in gastric cancer cells [109].

The expression of AGAP2-AS1 was up-regulated in NSCLC tissues, and correlated with tumor stage, lymph nodes metastasis and survival time [108, 110]. AGAP2-AS1 exerts oncogene functions by inducing cell proliferation, migration and inhibiting apoptosis in NSCLC cells. Further RNA IP assays indicated that AGAP2-AS1 could directly bind to EZH2 and LSD1, and then recruited them to LATS2 promoter regions and repressed the transcription of LATS2. LATS2 is a regulator of cellular homeostasis and tumor-suppressor and downregulated in multiple human cancers [111]. Due to its significant correlation with clinical NSCLC progression, AGAP2-AS1 might be a potential biomarker or therapeutic target.

HOXA11-AS

HOXA11-AS is an lncRNA transcribed from the opposite strand of the HOXA11 gene [112]. It is 5100 nt in length, and is mapped on chromosome 7p15.2. HOXA11-AS is initially discovered in mouse embryonic cDNA library. It is reported that HOXA11-AS takes part in cancer development including glioma, epithelial ovarian cancer, gastric cancer, cervical cancer, colorectal cancer [113-117]. HOXA11-AS can promote cell proliferation and invasion by sponging miR-124, and mediating the expression of Sp1 as a ceRNA of miR-124 [118, 119]. It can also promote cell proliferation through LATS1 expression inhibition via bridging to EZH2 [120].

LncRNA HOXA11-AS was significantly higher in NSCLC tissues compared with adjacent normal tissues, and demonstrated a poor prognosis in NSCLC patients [118, 121]. It is also markedly expressed in NSCLC cells. Knockdown of HOXA11-AS inhibited the proliferation, migration, invasion, as well as the EMT process [121]. Mechanically, RIP assays revealed that HOXA11-AS directly interacts with EZH2 and DNMT1. Subsequently, EZH2 and DNMT1 are recruited to the promoter regions of miR-200b and repressed its expression. miR-200b is well known to function as a tumor suppressor, for example, miR-200b suppresses migration and invasion in NSCLC cells via targeting FSCN1 [122, 123]. Thus, HOXA11-AS may be a promising candidate for further investigation as therapeutic target for NSCLC therapy.

FEZF1-AS1

LncRNA FEZF1-AS1 (FEZ family zinc finger 1 antisense RNA 1) is located on the opposite strand of gene FEZF1 in chromosome 7, and is 2564 nt long [124]. It is up-regulated in various cancers, including colorectal carcinoma, gastric cancer, stomach adenocarcinoma, pancreatic ductal adenocarcinoma and osteosarcoma [124-128]. Generally, higher expression of FEZF1-AS1 was correlated with larger tumor size, higher clinical stage and poorer survival. Moreover, knockdown of FEZF1-AS1 significantly inhibited cancer cell proliferation, migration and invasiveness.

In accordance with other cancer types, FEZF1-AS1 was overexpressed in NSCLC tissues and correlated with poor differentiation grade, lymph node metastasis, advanced TNM stage and poor prognosis [129, 130]. It exerts oncogenic activity by promoting cell proliferation, migration and invasion, as well as EMT process of NSCLC cells. Using RIP assays, He and colleagues revealed that FEZF1-AS1 could bind to EZH2 and LSD1, which then reduced their binding to the E-cadherin promoter regions. Furthermore, downregulation of FEZF1-AS1 suppressed Wnt/β-catenin signaling in NSCLC, which was significantly associated with tumor metastasis [131].

FOXF1-AS1

FOXF1-AS1 (also referred as FENDRR) is located in chromosome 16q24.1, with 3099 nt in length [132]. FOXF1-AS1 is transcribed from the negative strand of
FOXF1 (Forkhead box protein F1), originally identified to be coimmunoprecipitated with SUZ12 in human fetal lung and foot fibroblasts [133]. It was overexpressed with FOXF1 in osteosarcoma tissues and correlated with lung metastasis[134]. However, Xu et al. found that FOXF1-AS1 expression was down-regulated in gastric cancer tissues and correlated with poor prognosis [135].

FOXF1-AS1 was found to be significantly down-regulated in lung cancer tissues and cells, and associated with tumor migration, invasion and metastasis [136]. Moreover, loss of FOXF1-AS1 was also correlated with stem-like properties require EZH2. FOXF1-AS1 could demonstrated to bind with EZH2 by means of RIPSeq and RIP assay. It was also found that FOXF1-AS1 functions through targeting FOXF1, in consistence with that FOXF1 expression was lower in LAD and LSCC. FOXF1 belongs to the forkhead box family of transcription factors and regulates cell proliferation and function in tumorigenesis by a large number of studies [137]. As the expression of FOXF1-AS1 is not consistent in cancers, it is not easy to accurately define its role in lung cancer with only one signal manuscript published.

LncRNAs as EZH2 effectors/regulators in lung cancer

Similar to protein-coding genes, the transcription of IncRNA was shown to be regulated by some key transcription factors. For example, IncRNA-p21 transcription is promoted by p53 [138], while E2F1 regulated IncRNA ERIC expression[139], and also serve as EZH2 effectors. On the other hand, IncRNAs can also be regulated by EZH2.

Sox2ot (SOX2 overlapping transcript) is located on human chromosome 3q26.3 [140]. Sox2ot is transcribed in the same orientation as Sox2 (sex determining region Y-box 2), and indicated to regulate SOX2 transcription as an important enhancer [141, 142]. SOX2 is a transcription factor of the SRY-related HMG-box family that has been shown to play key roles in many stages of mammalian development. Sox2ot is upregulated and linked with cancer metastasis and poor prognosis in several types of carcinomas, such as gastric cancer, breast cancer, ovarian cancer and esophageal cancer [143-145]. Sox2ot is also overexpressed in lung cancer, especially in LSCCs, indicating poor survival of lung cancer patients [146]. It promoted cancer cell proliferation by inducing G2/M cell cycle arrest. Knockdown of Sox2ot decreased the expression levels of EZH2 mRNA and protein. Meanwhile, enhanced expression of EZH2 reversed the G2/M arrest induced by Sox2ot depletion. This indicated that Sox2ot-mediated lung cancer cell proliferation through regulating EZH2.

SPRY4-IT1 (SPRY4 intronic transcript 1) is mapped on human chromosome 5q31.3, transcribed from the second intron within the SPRY4 gene [147]. It is an inhibitor of the MAPK signaling pathway [148]. SPRY4-IT1 is upregulated in various kinds of tumor tissues and cell lines and identified as an oncogene via promoting tumor progression and metastasis [149]. The expression of SPRY4-IT1 is also upregulated in LAD tissues and cell lines [150]. However, Sun et al. reported that SPRY4-IT1 was down-regulated and correlated with advanced pathological stage, lymph node metastasis and poor survival of NSCLC [151]. Overexpression of SPRY4-IT1 is found to inhibit the migration and invasion through its regulation of EMT, while promote apoptosis of NSCLC cells. By performing Chip assays, the authors revealed that EZH2 could directly bind to the promoter region of SPRY4-IT1 and suppress its expression. Moreover, in EZH2-knockdown cells, depletion of SPRY4-IT1 partially reversed the oncogenic phenotype, suggesting that SPRY4-IT1 is involved in the EZH2 oncogenesis.

Conclusion

Numerous IncRNAs have been demonstrated to contribute to cancer cell functions through silencing of tumor suppressors via interaction with EZH2. EZH2 plays an important role in maintaining the integrity of cellular epigenetics, and is highly relevant to human cancer. Moreover, EZH2 expression and activity in cancer cells can be altered at multiple levels, and regulated by IncRNAs. Improving our understanding regarding the role of IncRNA-EZH2 regulatory and interaction network in tumorigenesis helps to diagnose and develop varied therapeutic strategies for lung cancer.

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Competing Interests

The authors have declared that no competing interest exists.

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