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Mini-review

HOX cluster-embedded antisense long non-coding RNAs in lung cancer

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ABSTRACT

Homeobox (HOX) genes play vital roles in embryonic development and oncogenesis. In humans, there are 39 *HOX* genes found in four clusters that are located on different chromosomes. The *HOX* clusters also contain numerous non-protein-coding RNAs, including some lncRNAs. The *HOX* cluster-embedded lncRNAs (*HOX*-lncRNAs), most notably, HOTTIP and HOTAIR play a major role in the regulation of their adjacent coding genes. Recently, most *HOX*-lncRNAs have been shown to impact tumorigenesis and cancer progression. Several *HOX*-lncRNAs, including HOTTIP, HOXA11-AS, HOTAIRM1, HOXA-AS3, HOXA10-AS, HOTAIR, and HAGLR, are dysregulated in lung cancer. Moreover, their expression levels are correlated with the clinical features of this disease. These *HOX*-lncRNAs regulate the proliferation, invasion, migration, and chemo-resistance of lung cancer cells through various molecular mechanisms. Although lncRNAs have received much attention lately, the functions of some *HOX*-lncRNAs in the development of cancer are unclear. Thus, *HOX*-embedded lncRNAs should be widely investigated in cancer. Here, we review the functions of *HOX*-lncRNAs in lung cancer.

1. Introduction

Long non-coding RNAs (lncRNAs) are generally defined as RNA products that more than 200 nucleotides in length produced from non-protein-coding RNA genes [1]. LncRNAs can be divided into sense, antisense, intronic, bidirectional, and intergenic forms according to their relationship with adjacent protein-coding genes [2]. They regulate fundamental biochemical and cellular processes via multiple different mechanisms, including but not limited to, direct interaction with mRNAs, micro-RNAs, or proteins [3]. Recently, an increasing number of studies have shown that lncRNAs regulate the initiation and progression of human cancers, as well as the response of these diseases to therapy [4–6]. Lung cancer has the highest death rate among all human cancers [7]. Morphologically, lung cancer is classified into small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) sub-types, and NSCLC accounts for about 85% of total cases and can be further subdivided into lung adenocarcinoma (LUAD), lung squamous cell carcinoma (LUSC), and large cell carcinoma [8,9]. Continued research has discovered the roles of some lncRNAs in the proliferation, invasion, and survival of lung cancer cells, as well as demonstrating the correlation in lncRNA expression to metastasis, advanced pathological stages, and prognosis in lung cancer patients [10].

Homeobox (*HOX*) genes, which have essential functions in embryonic development and tumorigenesis, are characterized by the presence of highly conserved homeodomains. In humans, 39 *HOX* genes are divided into 4 clusters (*HOXA*, *HOXB*, *HOXC*, and *HOXD*), located on different chromosomes (7p15.2, 17q21.32, 12q13.13 and 2q31.1, respectively) [11]. In addition to their roles in normal development and in the determination of cell fate, they also control other cellular processes, which has been demonstrated by descriptions of the congenital [12], metabolic [13], and neoplastic alterations of these genes [14,15]. Based on studies demonstrating the differences in *HOX* gene expression between normal and neoplastic tissues, *HOX* genes may play roles in promoting cancer. Abnormalities of *homeobox* gene expression have been identified in many primary tumors [16], including those of the kidney, colon and even SCLC [17–19]. There is also considerable evidence that the deregulation of *HOX* expression is associated with human acute myeloid leukemia [20–22]. Several *HOX* genes are the targets of chromosomal translocations in leukemia and are thought to be potential oncogenes [23–25]. Thus, the dysregulation of *HOX* genes might be directly related to their abnormal functions in cancers.

Human *HOX* gene clusters harbor non-protein coding genes, the transcription of which yields, besides evolutionarily conserved micro-RNAs [26], numerous lncRNAs [27]. The non-protein-coding RNAs within the *HOX* clusters play important roles in tumor pathogenesis and progression through regulating the *HOX* gene network [28]. In humans,

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Table 1
HOX cluster-embedded antisense lncRNA genes and relevant cancers/tumors reported in previous studies.

HOX cluster	Antisense RNA gene	HGNC ID	Aliases	Affected cancers/tumors
HOXA	*HOTAIRM1*	37117	*HOXA-AS1, HOXA1-AS1, NCRNA00179*	Acute myeloid leukemia [31–34], colorectal cancer [35], head and neck tumors [36], hepatocellular carcinoma [37], lung cancer [30]
	HOXA-AS2	43745	*HOXA3-AS*	Breast, colorectal, gallbladder carcinoma, gastric and pancreatic cancers, hepatocellular carcinoma, malignant glioma, and promyelocytic leukemia (reviewed in Ref. [95])
	HOXA-AS3	43748	*HOXA6-AS*	Glioma [38], lung adenocarcinoma [39]
	HOXA10-AS	40281	*HOXA-AS4*	Lung adenocarcinoma [40]
	HOXA11-AS	24957	*HOXA-AS5, NCRNA00076*	Breast, cervical, colorectal, gastric and ovarian cancers, glioblastoma, glioma, hepatocellular carcinoma, osteosarcoma, uveal melanoma, and NSCLC (reviewed in Ref. [41]), laryngeal squamous cell carcinoma [42], renal cancer [43]
	HOTTIP	37461	*HOXA-AS6, HOXA13-AS1, NCRNA00213*	Colorectal, gastric, lung, pancreatic and prostate cancers, hepatocellular carcinoma, and osteosarcoma (reviewed in Ref. [49]), breast cancer [50,51], endometrial cancer [52], esophageal squamous carcinoma [53,54], glioma [55,56], periampullary region tumors [57], renal cell carcinoma [58], thyroid carcinoma [59], tongue squamous cell carcinoma [60]
HOXB	*HOXB-AS1*	43744	*HOXB3-AS*	Unknown
	HOXB-AS2	40284		Unknown
	HOXB-AS3	40283		Colon Cancer [96]
	HOXB-AS4	40285		Unknown
	PRAC2	30143	*C17orf93, HOXB-AS5, HOXB13-AS1, NARNA00253*	Breast cancer [97], prostate cancer [98]
HOXC	*HOXC-AS1*	43749		Unknown
	HOXC-AS2	43750		Unknown
	HOXC-AS3	43751		Unknown
	HOTAIR	33510	*HOXAS, HOXC-AS4, HOXC11-AS1, NCRNA00072*	Breast, cervical, colorectal, gastric, lung, head and neck, ovarian and prostate cancers, endometrial carcinoma, esophageal and papillary thyroid carcinoma, glioblastoma, hematologic malignancies, hepatocellular carcinoma, osteosarcoma, and renal carcinoma (reviewed in Ref. [66])
	HOXC13-AS	43753	*HOXC-AS5*	Unknown
HOXD	*HAGLR*	43755	*HOXD-AS1, Mdgt*	Bladder, cervical, colorectal, gastric, liver, ovarian and prostate cancers, glioma, melanoma, neuroblastoma, osteosarcoma, and NSCLC (reviewed in Ref. [80])
	HOXD-AS2	43756		Unknown

HGNC, HUGO Gene Nomenclature Committee (https://www.genenames.org/); NSCLC, non-small cell lung cancer.

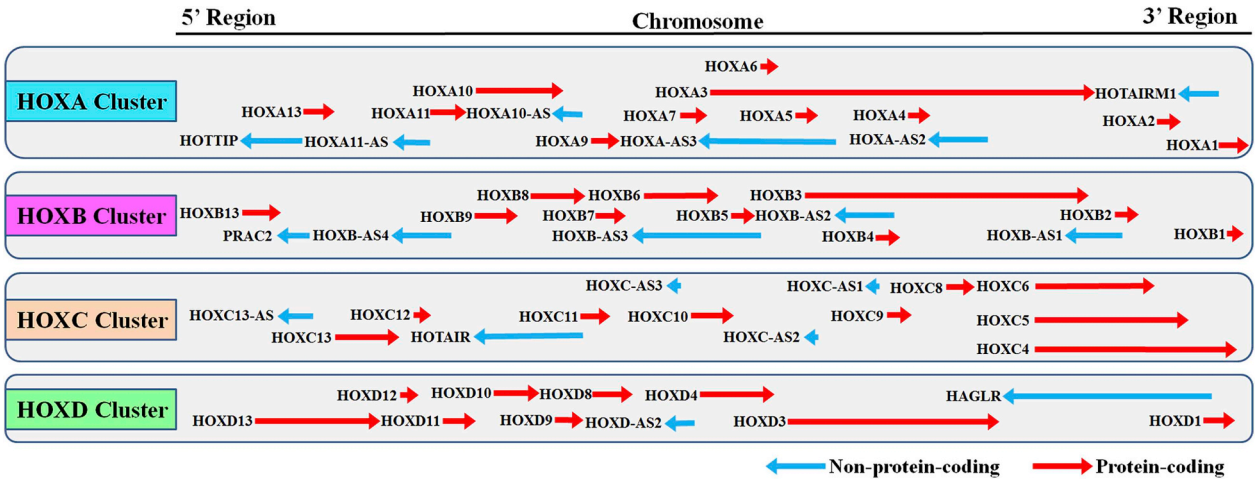

Fig. 1. Diagrams of the locations of antisense lncRNAs and *HOX* genes in the *HOX* clusters.

18 antisense RNA genes are found in the NCBI GeneBank database within the 4 *HOX* gene clusters. The *HOXA* region contains six *HOXA* antisense RNA genes, the *HOXB* and *HOXC* regions have five each, and the *HOXD* region holds two (Table 1). The positions of the antisense RNA genes in *HOX* clusters and their adjacent *HOX* genes are shown in Fig. 1. Half of these antisense RNAs reported to be associated with the development of different cancers (Table 1). Herein, we review the role of *HOX* cluster-embedded antisense lncRNAs (*HOX*-lncRNAs) in lung cancer, focusing on the cellular biological functions, molecular mechanisms of action, and the aberrant expression of these RNAs, as well as delving into the clinical features accompanying the abnormal expression of these lncRNAs in lung cancer patients (Table 2). We also summarize the chemo-resistance related pathways and modification complex network of these lncRNAs in other types of cancers (Tables S1 and S2).

2. *HOX* cluster-embedded antisense lncRNAs in lung cancer

2.1. HOTAIRM1

The human *HOXA transcript antisense RNA myeloid-specific 1* (*HOTAIRM1*) gene is located between *HOXA1* and *HOXA2* in the 3' region of the *HOXA* cluster. The lncRNA HOTAIRM1 has been studied more in leukemia than in solid tumors, possibly because initial findings with it were associated with myelopoiesis [29]. Recently, Tian et al. reported that the expression of HOTAIRM1 in myeloid-derived suppressor cells (MDSCs) from lung cancer tissues was significantly decreased compared with that from adjacent normal tissues and that the overexpression of HOTAIRM1 inhibited the development of MDSCs [30]. Additionally, HOTAIRM1 levels were determined to be lower in the peripheral blood of lung cancer patients than in those of control patients. HOTAIRM1 was also found to be expressed chiefly in LUAD as compared to LUSC or SCLC. This study established that HOTAIRM1 delayed tumor progression and promoted antitumor immune responses in lung cancer by downregulating the immunosuppressive activity of MDSCs via targeting of *HOXA1*. These results demonstrated that the HOTAIRM1/HOXA1 axis downregulates the immunosuppressive function of MDSCs and may be a potential therapeutic target in lung cancers. In addition to lung cancer, HOTAIRM1 has also been reported to be involved in the carcinogenesis and progression of acute myeloid leukemia [31–34], colorectal cancer [35], head and neck tumors [36], and hepatocellular carcinoma [37]. As a novel lncRNA, HOTAIRM1 should be investigated in a larger cancer cohort, due to its prominent role in preventing tumor progression.

2.2. HOXA-AS3

HOXA cluster antisense RNA 3 (HOXA-AS3) is a novel lncRNA transcribed from the *HOXA* cluster; studies on this lncRNA are limited. Wu et al. reported that HOXA-AS3 expression was upregulated in glioma tissues and in cell lines, and a high HOXA-AS3 expression level was associated with a poor prognosis for patients with glioma [38]. In this study, HOXA-AS3 was found to regulate cell-cycle progression, proliferation, apoptosis, and the migration of glioma cells. In the case of lung cancer, it has also been shown that HOXA-AS3 is significantly overexpressed in LUAD tissues and in A549 cells [39]. Moreover, knockdown of HOXA-AS3 has been found to inhibit cancer cell proliferation, migration, and invasion. This work also examined the mechanism of HOXA-AS3 action. The authors found that it promoted the stability of HOXA6 mRNA and became bound to NF110, which determined its sub-cellular location. Furthermore, upregulation of HOXA-AS3 in A549 cells was related to histone acetylation. This study demonstrated the important role of HOXA-AS3 in LUAD progression and indicated that HOXA-AS3 might serve as a potential prognostic biomarker for LUAD.

2.3. HOXA10-AS

Another novel antisense lncRNA is HOXA10-AS, which has its gene located adjacent to *HOXA10* in the *HOXA* cluster. Only a single article thus far has described a role for HOXA10-AS in cancer, which was in LUAD [40]. That paper demonstrated that HOXA10-AS was upregulated in LUAD tissues and cells, and that the upregulation of its expression was correlated with poor prognosis in LUAD patients. Moreover, knockdown of HOXA10-AS inhibited cell proliferation and migration, and enhanced apoptosis in LUAD cells. Furthermore, it was shown that HOXA10-AS expression promoted LUAD progression by activating the Wnt/β-Catenin signaling pathway. Therefore, these results indicate that HOXA10-AS might be a novel prognostic biomarker for LUAD, although further research is necessary to justify this.

2.4. HOXA11-AS

The *HOXA11 antisense RNA* (*HOXA11-AS*) gene is located between *HOXA11* and *HOXA13* in the human genome, and plays a critical role in tumorigenesis and tumor progression [41–43]. Bioinformatics analysis has shown that HOXA11-AS may play pivotal roles in NSCLC development and progression by regulating the expression of various genes and signaling pathways [44]. Several studies have explored the mechanisms of HOXA11-AS action using functional experiments. Zhang et al. reported that the expression of HOXA11-AS was markedly

Table 2
Lung cancer-associated *HOX* cluster-embedded antisense lncRNAs.

LncRNAs (HGNC ID)	Cancer subtypes	Expression in cancer	Associated clinical features	Cellular biological functions	Related molecules and pathways	REF
HOTAIRM1 (37117)	Lung cancer	Downregulated	Smoking history, lymph node metastasis, TNM stage, and histological tumor type	Inhibits the development of MDSCs and downregulates the immunosuppressive activity of MDSCs in lung cancer	HOXA1	[30]
HOXA-AS3 (43748)	LUAD	Upregulated		Promotes cell proliferation, migration, and invasion	HOXA6; NF110 and H3K9ac	[39]
HOXA10-AS (40281)	LUAD	Upregulated	Poor prognosis	Promotes cell proliferation and metastasis, and inhibits cell apoptosis	ELK1 and Wnt/β-catenin signaling	[40]
HOXA11-AS (24957)	NSCLC	Upregulated	Tumor size, lymph node metastasis, advanced clinical stage, TNM stage, and poor prognosis	Promotes cell proliferation, migration, and invasion, tumorigenic and angiogenic ability and inhibits cell apoptosis	miR-124/Sp1; EZH2 and DNMT1/miR-200b; EMT signaling pathway; miR-642b-3p	[45–48]
HOTTIP (37461)	SCLC NSCLC	Upregulated	Clinical stage, chemotherapy response, and poor prognosis of SCLC patients	Promotes cell proliferation, migration, cell cycle, drug-resistance and inhibits cell apoptosis	miR-574-5p/EZH1; HOXA13; miR-216a/BCL-2; AKT signaling pathway	[61–64]
HOTAIR* (33510)	SCLC NSCLC	Upregulated	Histology subtype, TNM stage, clinical stage, lymphatic metastasis, and poor prognosis	Promotes cell proliferation, migration, invasion, and drug-resistance and inhibits cell apoptosis	P53 and H3K27me3; Cav-1; Bax/Caspase-3 and TGF-α/EGFR signaling; miR-613; 14-3-3σ; miR-326/Phox2a; miR-326/SP1	[67–78]
HAGLR (43755)	NSCLC	Upregulated	Tumor size, stage, recurrence, and TNM stage, lymph node metastasis, and poor overall survival	Promotes cell proliferation, migration, invasion, and cell cycle progression, and suppresses cell apoptosis	p21 and MMP9; miR-133b/MMP9; miR-147a/pRB	[81–83]

HGNC, HUGO Gene Nomenclature Committee (https://www.genenames.org/); LUAD, lung adenocarcinoma; MDSCs, myeloid-derived suppressor cells; NSCLC, non-small cell lung cancer; REF, references; SCLC, small cell lung cancer; TNM, tumor lymph node metastasis. *Data from recent studies.

increased in NSCLC tissues as well as in cell lines and that its high expression was correlated with an advanced clinical stage in NSCLC patients [45]. Moreover, knockdown of HOXA11-AS suppressed the proliferation, migration, invasion, tumorigenic, and angiogenic capabilities of NSCLC cells, as well as inducing apoptosis in these cells. Furthermore, inhibition of HOXA11-AS also led to a cell cycle arrest at the G0/G1 transition or at the G2/M phase checkpoint. In addition, Chen et al. found that high expression of HOXA11-AS in NSCLC tissues showed a correlation with lymph node metastasis, tumor node metastasis (TNM) stage, and poor prognosis [46]. Their results in NSCLC cells further indicated that the lncRNA HOXA11-AS promoted cell invasion, in addition to an epithelial to mesenchymal transition (EMT) process by suppressing miR-200b expression through an interaction with EZH2 and DNMT1. Following knockdown of HOXA11-AS in NSCLC cells, miR-642b-3p was also significantly downregulated [47]. Yu et al. confirmed that HOXA11-AS expression was upregulated in NSCLC tissues and in cell lines and that high expression levels of HOXA11-AS in patients were associated with larger tumor size and lymph node metastasis [48]. Analysis of its biological function demonstrated that HOXA11-AS promoted the proliferation and invasion of NSCLC cells by sequestering miR-124, effectively regulating SP1 expression. The lncRNA HOXA11-AS thus plays a pivotal role in NSCLC, and it may be a promising biomarker for the early detection and prognostic evaluation of NSCLC.

2.5. HOTTIP

The *HOXA transcript at the distal tip* (*HOTTIP*) gene is located at the 5' end of the HOXA cluster in the human genome and is transcribed into a functional lncRNA. The lncRNA HOTTIP has been reported to be dysregulated in various cancers, including lung cancer [49–60]. In SCLC, HOTTIP is upregulated in tissues and cells, and its expression is correlated with the clinical stage, survival and chemotherapy response of SCLC patients [61,62]. HOTTIP overexpression promotes SCLC cell proliferation and the progression of the cell cycle through the regulation of miR-574-5p/EZH1 [61]. In addition, HOTTIP regulates apoptosis and chemo-resistance of SCLC cells by binding to miR-216a, thereby enhancing the expression of BCL-2, which suppresses apoptosis [62]. In addition to SCLC, HOTTIP is also highly expressed in NSCLC tissues and cells, and overexpression of HOTTIP significantly promotes cell proliferation and migration. HOTTIP overexpression also inhibits cell apoptosis by suppressing the expression of HOXA13 [63]. Moreover, overexpression of HOTTIP promotes the drug resistance of LUAD by regulating the AKT signaling pathway [64]. These findings suggest that the lncRNA HOTTIP also may be a valuable biomarker for lung cancer progression.

2.6. HOTAIR

One of the most studied HOX cluster-embedded lncRNAs is the HOX transcript antisense RNA (HOTAIR); its gene resides between the *HOXC11* and *HOXC12* genes in the HOXC cluster on human chromosome 12q13.13 [65]. HOTAIR has been reported to play oncogenic roles in various cancers, including lung cancer [66]. Indeed, the functions of the lncRNA HOTAIR have been widely studied in lung cancer; a review [10] has summarized the results from those studies. HOTAIR expression was significantly upregulated in cell lines, tissues and even the plasma of NSCLC patients [67–72], and this upregulation of HOTAIR showed a correlation with histology subtype, high TNM and clinical stage, lymphatic metastasis, and poor prognosis in NSCLC patients [69,73]. Functionally, HOTAIR affected tumorigenesis and progression in NSCLC by enhancing the proliferation, migration, and invasion of NSCLC cells, and inhibiting apoptosis in NSCLC cells [68,70,73]. Mechanistically, HOTAIR promoted the expression of 14-3-3σ [71] and negatively regulated the expression of p53 through enhancing H3K27me3 levels at the p53 promoter [67] in NSCLC.

Moreover, the expression of HOTAIR was increased by CAV-1 [68], and knockdown of HOTAIR expression increased the expression of miR-613 [70] and miR-326/Phox2a [74] to induce oncogenesis and tumor progression. The ratio of FOXA1 to FOXA2 was also increased, which at a moderate level is involved in carcinogenesis and disease evolution [73]. Thus, HOTAIR can be considered a promising biomarker for the diagnosis and monitoring of NSCLC.

In addition, aberrant expression of HOTAIR is also associated with drug-resistance in SCLC and NSCLC patients [72,75–78]. It has been reported that HOTAIR may mediate the chemo-resistance of SCLC cells by regulating the methylation of the *HOXA1* gene by affecting DNMT1 and DNMT3b protein expression [77]. In drug-resistant NSCLC patients, the expression of HOTAIR was also elevated, and overexpression of HOTAIR increased the resistance to Cisplatin in NSCLC cells [75]. The study demonstrated that the drug resistance induced by elevated HOTAIR expression might be caused by an upregulation in the expression of Klf4, a tumor stem cell biomarker. Liu et al. reported that the knockdown of HOTAIR restored Gefitinib sensitivity through activation of Bax/Caspase3 and suppression of TGFα/EGFR signaling in LUAD [78]. Silencing of HOTAIR expression was shown to decrease the resistance of NSCLC cells to Crizotinib by inactivating autophagy through suppression of the activation of the ULK1 pathway [72]. Silencing of the *HOTAIR* gene enhanced the sensitivity of LUAD cells to Cisplatin by increasing miR-326 expression and synergistically reducing SP1 expression [76]. In summary, the lncRNA HOTAIR may be a potential therapeutic target for chemo-resistance in SCLC and NSCLC.

2.7. HAGLR

The *HAGLR* (*HOXD antisense growth-associated long noncoding RNA*, also known as *HOXD-AS1* and *Mdgt*) gene is located in the intergenic region between *HOXD1* and *HOXD3*. It has been reported to play essential roles in gut development [79] and also in various cancers [80]. In NSCLC, HAGLR was upregulated in tissues and cells, and this upregulation was associated with large tumor size, advanced tumor stage, recurrence, lymph node metastasis, high TNM stage, and reduced overall survival of patients [81–83]. Moreover, HAGLR promoted NSCLC cell proliferation and cell cycle progression while suppressing cell apoptosis [81]; HAGLR stimulated NSCLC cell growth by targeting miR-147a/pRB. Lu et al. have reported that the knockdown of HAGLR suppressed cell invasion and decreased levels of fatty acid synthase in NSCLC cells [82]. They also showed that the free fatty acid content in cancer cells was decreased and the expression levels of the tumor suppressor p21 and a matrix metalloproteinase (MMP9) were dysregulated following inhibition of HAGLR. Additionally, it was demonstrated that HAGLR promoted NSCLC cell migration and invasion by regulating the miR-133b/MMP9 pathway [83]. In conclusion, these data suggested that HAGLR may be a novel prognostic biomarker and a promising therapeutic target for treating NSCLC.

3. Conclusions and future perspectives

LncRNAs, including the *HOX* cluster-embedded antisense lncRNAs, play a vital role in tumorigenesis and tumor progression by affecting multiple pathways. They are dysregulated in many different types of cancers, including solid tumors and hematologic malignancies. In lung cancer, the *HOX* cluster-embedded antisense lncRNAs participate in the initiation and progression of tumor formation and development of drug-resistance by regulating the expression of *HOX* genes or other genes (Fig. 2). In summary, HOTTIP regulates the growth of SCLC cells by modulating miR-574-5p/EZH1 and mediates chemo-resistance through miR-216a/BCL-2. HOTTIP promotes the proliferation and migration of NSCLC cells by suppressing HOXA13 expression and is involved in drug resistance by regulating the AKT signaling pathway in NSCLC. HOTAIRM1 enhances HOAX1 expression to regulate the immunosuppressive activity of MDSCs in lung cancer. HOTAIR promotes tumorigenesis and metastasis in NSCLC by reducing the expression of miR-613. HOTAIR also regulates the growth and chemo-resistance of lung cancer cells by sponging miR-326. HOXA10-AS promotes lung cancer progression by increasing Wnt/β-catenin signaling pathway. HOXA11-AS promotes proliferation and invasion of NSCLC cells by targeting miR-124/Sp1. HOXA11-AS promotes lung cancer progression by recruiting EZH2 and DNMT1 to suppress miR-200b expression and regulating EMT signaling pathway. HOXA-AS3 promotes lung cancer cells proliferation through binding with NF110 to increase HOXA6 expression. HAGLR promotes NSCLC progression by regulating miR-133b/MMP9 and miR-147a/pRB. Therefore, most HOX cluster-embedded antisense lncRNAs may serve as potential biomarkers and therapeutic targets for lung cancer.

In addition to lung cancer, HOTTIP, HOXA11-AS, HOTAIR, and HAGLR have been reported in many other common cancers. Fu et al. have reported that HOTTIP is upregulated in pancreatic cancer stem cells (PCSCs) [84], the same finding as in lung cancer. HOTTIP alterations affect the stem cell characteristics of PCSCs by modulating HOXA9 to enhance the Wnt/β-catenin pathway. In prostate cancer, TWIST1-WDR5-HOTTIP increases H3K4me3 chromatin at the HOXA9 promoter to facilitate metastasis [85]. HOTTIP also regulates tumorigenesis of gastric cancer and esophageal squamous carcinoma through regulating HOXA13 at the transcriptional and posttranscriptional level [53,86]. HOXA11-AS promotes the progression of hepatocellular carcinoma through repressing miR-214-3p [87]. In gastric cancer, HOXA11-AS promotes proliferation and invasion by scaffolding the chromatin modification factors PRC2, LSD1, and DNMT1 [88]. Moreover, overexpression of HOXA11-AS promotes cell cycle progression and metastasis in gastric cancer by interacting with WDR5 and promoting β-catenin transcription, and through binding with EZH2 and repressing p21 transcription, and HOXA11-AS induces KLF2 mRNA degradation via interacting with STAU1 [89]. HOTAIR expression is high in ovarian cancer, and it regulates the expression of CCND1 and CCND2 by sponging miR-206 in cancer cells [90]. HOTAIR is a prognostic biomarker for the proliferation and chemo-resistance of colorectal cancer through miR-203a-3p-mediated Wnt/β-catenin pathway [91]. The STAT3/HOTAIR signaling axis regulates head and neck squamous cell cancer growth with an EZH2-dependent manner [92]. HAGLR expression is increased in bladder cancer tissues and cells, and it regulates the progression of this cancer [93]. STAT3-mediated upregulation of HAGLR facilitates liver cancer metastasis through binding with miR-130a-3p and regulation of SOX4 [94]. HOXA-AS2 has been studied in many kinds of tumors, but not in lung cancer [95]. HOTAIRM1, HOXA-AS3, HOXA10-AS, HOXB-AS3 [96] and PRAC2 [97,98] have only been explored in a limited number of cancer types. Furthermore, the roles of about half of the *HOX*-lncRNAs in cancer are unclear, namely, HOXB-AS1, HOXB-AS2, HOXB-AS4, HOXC-AS1, HOXC-AS2, HOXC-AS3, HOXC13-AS, and HOXD-AS2. Therefore, an investigation of *HOX* cluster-embedded antisense lncRNAs in cancer is a promising area for future research.

Conflicts of interest

The authors declare that they do not have any conflicts of interest for this article.

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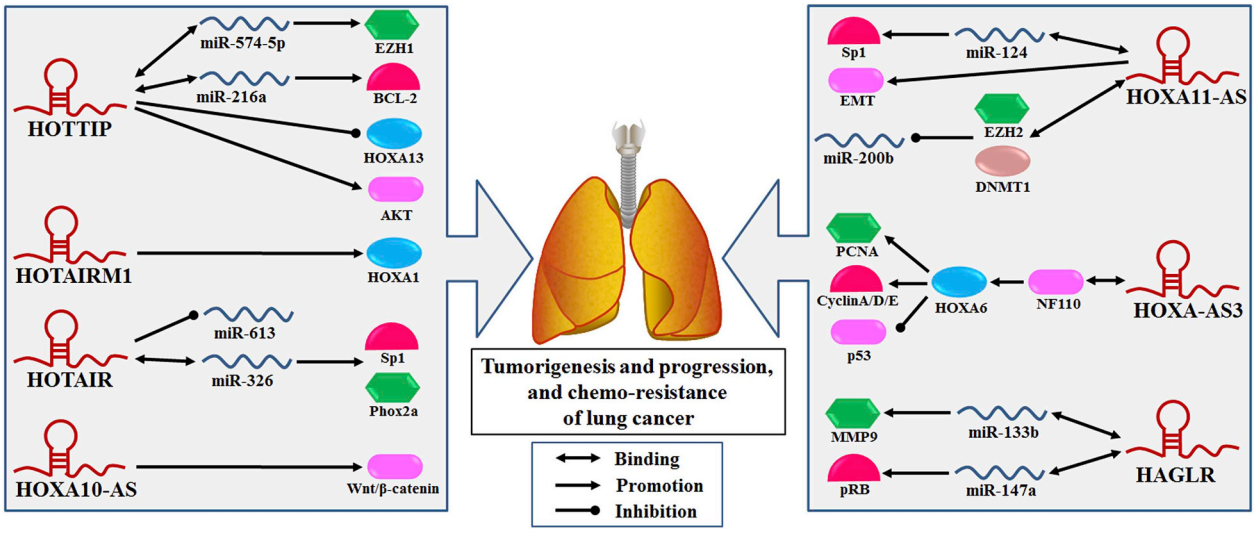

Fig. 2. The network of *HOX*-lncRNAs and other regulatory factors in lung cancer.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.canlet.2019.02.036.

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