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Emerging role of HOX genes and their related long noncoding RNAs in lung cancer

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ABSTRACT

The transcription factor homeobox (Hox) proteins are the master regulator for the embryonic development. Studies have identified new functions for HOX in the regulation of metabolism and other primary cellular processes in humans. Their dysregulation has been observed in a variety of cancers and accumulating evidence has revealed the crucial role of HOX in cancer progression, metastasis, and resistance to therapy. HOX-related long non-coding RNAs (lncRNAs) became the most attracting lncRNAs recently that play critical role in gene regulation and chromatin dynamics in cancers. In this review, we explore the roles of HOX and their related lncRNAs in lung cancer, indicating HOX genes as potential therapeutic targets in lung cancer.

1. Introduction

Homeobox (*Hox*) genes are a family of homeodomain-containing transcription factors that play essential roles in the determination of cell fate and the development of the body plan. There are 39 *HOX* genes in humans, divided into four groups (A–D) and each localized on different chromosomes (*HOX A* at 7p15.3, *HOX B* at 17q21.3, *HOX C* at 12q13.3 and *HOX D* at 2q31) (Apiou et al., 1996). In addition to their roles in normal development and in the determination of cell fate, they also control primary cellular processes, which have been demonstrated by description of congenital (Mortlock et al., 1996), metabolic (Procino and Cillo, 2013), and neoplastic alterations (Cantile et al., 2009; Bhatlekar et al., 2014). Based on the studies demonstrating the differences in *HOX* gene expression between normal and neoplastic tissue, HOX may play roles in promoting cancer. Abnormalities of homeobox gene expression have been identified in many primary tumors (Grier et al., 2005). For example, differences in HOX expression between normal and tumor samples were observed in kidney and colon (Cillo et al., 1992; De Vita et al., 1993). Tiberio et al reported that most of the *HOX* genes were silent and only 11 *HOX* genes were expressed at low levels in normal lung, while the great majority of *HOX* genes (30/38) were expressed in small-cell lung cancer (SCLC) and most of them at high levels (Tiberio et al., 1994). Flagiello et al demonstrated that retinoic acid treatment of SCLCs resulted in noncontiguous expression patterns in *HOXB* and *HOXC* genes (Flagiello et al., 1997). The *HOX* genes are not regulated collinearly, indicating that the regulatory mechanisms may have been reprogrammed in SCLC. There is considerable evidence that the deregulation of HOX expression is associated with human acute leukemia (Drabkin et al., 2002; Debernardi et al., 2003; Rawat et al., 2008). Several homeobox genes are the targets of chromosomal translocations in leukemia and are thought to be potential oncogenes. For example, four different translocations in acute myeloid leukemia result in the fuse of the nucleoporin domain of NUP98 to the homeobox of a major or divergent HOX protein (Raza-Egilmez et al., 1998; Nakamura et al., 1999; Borrow et al., 1996). Except for the HOX-related fusion genes *HOXA9* was identified as the single gene whose expression was most correlated with treatment failure in acute myeloid leukemia (Golub et al., 1999). Thus, the dysregulation of *HOX* genes might be directly related to their abnormal function in cancers.

Studies have primarily focused on the protein-coding region of *HOX* gene clusters in humans; however, recent studies have revealed another side of the same coin which is the transcribed sense and antisense noncoding sequences located in *HOX* gene clusters or their flanking regions, such as the HOX transcription-antisense intergenic RNA (*HOTAIR*), HOXA13-AS1 (*HOTTIP*) and HOXD antisense growth-associated long non-coding RNA (*HAGLR*). These long non-coding RNAs

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Table 1
Alteration frequency of *HOX* genes in lung cancer. Data were obtained from The Cancer Genome Atlas portal : http://www.cbioportal.org.

Database	Alteration	Frequency (case number)								
		HOXA1	*HOXA5*	*HOXA9*	*HOXB3*	*HOXB5*	*HOXB7*	*HOXB9*	*HOXC8*	*HOXD3*
Lung adenocarcinoma, TCGA, Nat Genet 2016 (n = 660)	Mutation	2.73% (18)	3.03%(20)	1.21%(8)	3.33%(22)	0.91%(6)	0.45%(3)	0.3%(2)	0.3%(2)	1.82%(12)
	Amplification	2.42%(16)	2.42%(16)	2.42%(16)	0.45%(3)	0.61%(4)	0.61%(4)	0.61%(4)	1.21%(8)	0.76%(5)
	Deep deletion	0.45%(3)	0.45%(3)	0.45%(3)	–	–	–	–	0.15%(1)	–
	In total	**5.6% (37)**	**5.9%(39)**	**4.09%(27)**	**3.78%(25)**	**1.52%(10)**	**1.06%(7)**	**0.91%(6)**	**1.67%(11)**	**2.58%(17)**
Lung squamous cell carcinoma, TCGA, Nat Genet 2016 (n = 484)	Mutation	1.45% (7)	0.41%(2)	0.41%(2)	1.03%(5)	1.45%(7)	0.41%(2)	1.24%(6)	0.41%(2)	2.27%(11)
	Amplification	1.24%(6)	1.24%(6)	1.24%(6)	–	0.21%(1)	0.41%(2)	0.41%(2)	0.21%(1)	2.07%(10)
	Deep deletion	0.21%(1)	0.21%(1)	0.21%(1)	–	–	–	–	–	–
	In total	**2.9%(14)**	**1.86%(9)**	**1.86%(9)**	**1.03%(5)**	**1.66%(8)**	**0.82%(4)**	**1.65%(8)**	**0.62%(3)**	**4.34%(21)**
Lung adenocarcinoma, TCGA, Provisional(n = 230)	Mutation	3.48%(8)	1.74%(4)	0.87%(2)	3.48%(8)	0.87%(2)	–	0.43%(1)	–	1.74%(4)
	Amplification	3.04%(7)	3.04%(7)	3.48%(8)	1.74%(4)	1.74%(4)	1.74%(4)	1.3%(3)	1.3%(3)	1.74%(4)
	Deep deletion	0.87%(2)	0.87%(2)	0.87%(2)	–	–	–	–	0.43%(1)	–
	mRNA upregulation	3.91% (9)	0.87% (2)	4.78% (11)	5.65% (13)	1.74% (4)	7.83% (18)	3.04% (7)	4.35% (10)	3.48% (8)
	Multiple alterations	0.87%(2)	0.43%(1)	–	0.43%(1)	0.43%(1)	0.43%(1)	0.87% (2)	0.43% (1)	–
	In total	**12.17% (28)**	**6.95% (16)**	**10% (23)**	**11.3% (26)**	**4.78% (11)**	**10% (23)**	**5.64% (13)**	**6.51% (15)**	**6.96% (16)**
Lung squamous cell carcinoma, TCGA, Provisional (n = 178)	Mutation	1.12% (2)	2.25% (4)	–	1.12% (2)	0.56% (1)	1.12% (2)	1.12% (2)	0.56% (1)	2.25% (4)
	Amplification	2.25% (4)	–	2.25% (4)	1.12% (2)	1.12% (2)	1.12% (2)	1.69% (3)	0.56% (1)	2.81% (5)
	Deep deletion	0.56% (1)	0.56% (1)	0.56% (1)	–	–	–	–	0.56% (1)	–
	mRNA upregulation	3.93% (7)	1.69% (3)	1.12% (2)	1.12% (2)	1.69% (3)	5.62% (10)	0.56% (1)	6.74% (12)	5.06% (9)
	In total	**7.86% (14)**	**4.5% (8)**	**3.93% (7)**	**3.36% (6)**	**3.37% (6)**	**7.86% (14)**	**3.37% (6)**	**8.42% (15)**	**10.12% (18)**

(lncRNAs) affect gene regulation through both cis- and trans-mechanisms on HOX and non-HOX genes (Wang and Chang, 2011; Wang et al., 2011; Dasen, 2013; Lee and Bartolomei, 2013). Functionally, several of them have been identified as being linked to human disorders and exerting specific functions in cancers. One example of such an oncogenic lncRNA is *HOTAIR*, and *HOTAIR* over-expression is a hallmark of many human cancers which have been proved in head and neck squamous cell cancer (Sun et al., 2018), breast (Gupta et al., 2010) and hepatocellular cancers (Yang et al., 2011) and so on. Clinically, the over-expression of *HOTAIR* is a strong predictor of overall survival and progression for several cancers, including colon cancer (Kogo et al., 2011), gastrointestinal stromal tumors (Niinuma et al., 2012), pancreatic cancer (Kim et al., 2013), laryngeal squamous cell carcinoma (Li et al., 2013), and nasopharyngeal carcinoma (Nie et al., 2013). Here, we review the important roles of HOX-related noncoding transcripts in the regulation of HOX clusters and HOX/lncRNAs functions in lung cancer.

2. The aberrant expression of *HOX* genes is closely related to their function in lung cancer

2.1. *HOXA* in lung cancer

Homeobox A5 (*HOXA5*) has been implicated as a tumor suppressor gene in breast cancer. A recent study showed that HOXA5 could co-operate with p53 to inhibit tumor cell invasion in non-small cell lung cancer (NSCLC). By immunohistochemical stain for p53 and HOXA5 in primary human NSCLC specimens the authors have seen that there is a poor prognosis in group with non-immunoreactive for p53 and HOXA5 (Chang et al., 2017). Ectopic expression of HOXA5 in lung adenocarcinoma cell lines suppressed cell migration, invasion, and filopodia formation in vitro, and inhibited metastatic potential in vivo. Consistently, knockdown of HOXA5 promoted the invasiveness of lung cancer cells (Wang et al., 2015). Epigenetics play an important role in the regulation of *HOX* gene expression of which methylation is an important mechanism in HOX silencing. Several studies observed that CpG methylation of homeobox genes occurred during breast tumorigenesis (Raman et al., 2000; Rodriguez et al., 2008; Tommasi et al., 2009). In addition, Rauch et al have indicated that multiple CpG islands within Hox clusters and near other homeobox genes are the frequent methylation targets in lung cancer (Rauch et al., 2007). Kim et al have investigated the methylation status of the promoter region of the *HOXA5* gene in NSCLCs which were found in 113 (81.3%) of 139 NSCLCs and 72 (51.8%) in their paired non-cancerous lung tissues (Kim et al., 2009). Though *HOXA5* methylation did not affect survival in all NSCLCs or at stages II—IV, it was significantly associated with a worse survival in the patients with stage I disease (Kim et al., 2009). *HOX* genes are involved in chemoresistance in cancers. For example, HOXA1 expression is significantly correlated with chemotherapy response in SCLC (Xiao et al., 2014). Enforced expression of HOXA1 in resistant H69AR cells increased chemosensitivity by increasing cell apoptosis and cell-cycle arrest. Meanwhile Inhibition of HOXA1 expression using *HOXA1* siRNA in H69 cells reduced drug-induced cell apoptosis and cell cycle arrest. HOXA1-mediated SCLC chemoresistance is under the regulation of *miR-100* supported by the evidence that *miR-100* targeted the predicted sites in 3′-untranslated region of *HOXA1* gene and endogenous *miR-100* was strongly increased in resistant H69AR cells and negatively correlated with HOXA1 expression both in cells and SCLC tissues (Xiao et al., 2014). HOXA9 expression is dysregulated in NSCLC and *miR-196b*-regualted HOXA9 affects cell invasion through nuclear factor-kappa B activity (Yu et al., 2016). More exactly, ectopic expression of HOXA9 led to a suppression of *miR-196b*-induced cell invasion, and enforced expression of HOXA9 increased E-cadherin expression. In addition, HOXA9 strongly attenuated the expression of snail family zinc finger 2 (SNAI2/SLUG) and matrix metallopeptidase 9 (MMP9) by controlling the binding of nuclear factor-kappa B to the promoter of these genes.

2.2. *HOXB* in lung cancer

Homeobox B (*HOXB*) genes have been demonstrated to play an important role in lung cancer. Palakurthy et al reported the oncogenic activity of HOXB3 in lung adenocarcinoma (Palakurthy et al., 2009). The study showed that the tumor suppressor gene *RASSF1A* was silenced by hypermethylation resulted from direct binding of DNMT3B to the *RASSF1A* promoter; while HOXB3 was required for induction of DNMT3B expression. Knockdown of HOXB3 in A549 cells resulted in decreased cell growth in soft agar, and ectopic expression of RASSF1A reduced proliferation of NCI-H1437 cells with HOXB3 overexpression. Mouse xenograft experiments confirmed that the oncogenic activity of

Table 2
The functions of HOXs and their related lncRNAs in lung cancer.

HOX/LncRNA	Description	Functions in lung cancer	Known molecular mechanisms	Ref.
HOXA1	Homeobox A1	Increases cell apoptosis, cell cycle arrest, and chemosensitivity	Down-regulation by miR-100	(Xiao et al., 2014)
HOXA5	Homeobox A5	Inhibits invasion, migration, and metastasis	Cooperation with P53; methylation	(Chang et al., 2017; Wang et al., 2015; Kim et al., 2009)
HOXA9	Homeobox A9	Suppresses invasion	Inhibits nuclear factor-kappa B activity and increases expression of E-cadherin/SNAI2/SLUG/MMP9	(Yu et al., 2016)
HOXB3	Homeobox B3	Increases cell and tumor growth	Epigenetic silencing of RASSF1A	(Palakurthy et al., 2009)
HOXB5	Homeobox B5	Increases cell proliferation, migration, invasion, and EMT	Wnt/β-catenin pathway activation	(Zhang et al., 2018)
HOXB7	Homeobox B7	Correlated with short survival, tumor status, nodal status and advanced tumor stage; Increases cell growth and metastasis; Induces stem cell-like phenotype	Upregulation of several canonical stem cell /induced pluripotent stem cell markers and transcriptional regulation of LIN28B	(Yuan et al., 2014; Monterisi et al., 2018)
HOXB9	Homeobox B9	Increases cell migration, invasion and metastasis	Transcriptional regulation of JMJD6/acetylated by PCAF and de-acetylated by SIRT1/targets of WNT/TCF	(Zhan et al., 2015; Wan et al., 2016; Nguyen et al., 2009)
HOXC8	Homeobox C8	Promotes cell proliferation, migration, chemoresistance and anti-apoptosis	Transcriptional regulation of TGFβ1	(Liu et al., 2018)
HOXD3	Homeobox D3	Increases cell motility, invasion and foci formation	TGFβ1 pathway activation and regulation of EMT related genes	(Miyazaki et al., 2002; Hamada et al., 2001; Ohta et al., 2006)
HOTAIR	HOX transcript antisense RNA	Promotes cell proliferation, migration, metastasis and drug resistance	Negatively regulation of miR-326/positively regulation of tumor stem cell-related biomarkers/interaction with HOXA1/ induction by type 1 collagen	(Liu et al., 2013; Ono et al., 2014; Li et al., 2017; Zhao et al., 2014; Wang et al., 2016; Liu et al., 2016; Fang et al., 2016; Zhuang et al., 2013)
HOTTIP	HOXA distal transcript antisense RNA	Promotes cell proliferation, migration and inhibits apoptosis	Regulation of HOXA13	(Sang et al., 2016)
HOXA11-AS	HOXA11 antisense RNA	Promotes invasion and EMT	Down-regulation of miR-200b	(Chen et al., 2017)
TUG1	Taurine up-regulated 1	Reduced expression of TUG1 promotes cell proliferation	Regulation of HOXB7	(Zhang et al., 2014)

HOXB3 is partially due to epigenetic silencing of RASSF1A. Knockdown of HOXB3 in A549 cells decreased tumor growth in mouse model. Conversely, ectopic expression of HOXB3 in NCI-H1437 cells potently increased tumor growth. When double knockdown of HOXB3 and RASSF1A in A549 cells, xenografts generated from these cells grew at a similar rate as that of control A549 cells. The authors provided strong evidence for epigenetic repression of RASSF1A by HOXB3 and MYC/EZH2/DNMT3B proteins in A549 cells. The abnormal expression of HOXB5 and HOXB7 has been detected in lung cancer (Zhang et al., 2018; Yuan et al., 2014). HOXB5 was overexpressed in human NSCLC tissues and HOXB7 expression was elevated in lung adenocarcinomas (LAC) compared to their corresponding normal lung tissues. The functional study found that knockdown of HOXB5 not only decreased the cell proliferation, migration and invasion but also impeded the epithelial to mesenchymal transition (EMT) phenotype in NSCLC cells. In vivo experiments indicated that knockdown of HOXB5 attenuated the growth of NSCLC xenografts. The roles of HOXB5 are partly mediated through the Wnt/β-catenin signaling pathway because knockdown of HOXB5 suppressed the expression level of β-catenin and its downstream targets c-Myc and cyclin D1 in A549 cells (Zhang et al., 2018). By immunohistochemistry analysis Yuan et al demonstrated that elevated expression of HOXB7 was associated with a short survival in LAC patients (Yuan et al., 2014) suggesting that might be used as a prognostic indicator for LAC patients. Furthermore, HOXB7 expression level was correlated with the tumor status, nodal status and tumor stage in lung adenocarcinoma. A new role of HOXB7 in favoring the acquisition of a stem cell-like (SC-like) phenotype in lung cancer has been discovered recently and the expansion of cell subpopulations with SC-like characteristics might contribute to tumor aggressiveness (Monterisi et al., 2018). HOXB9 has been reported to be overexpressed in breast cancer, and functions in tumorigenicity and lung metastasis as well as in EMT (Hayashida et al., 2010; Chiba et al., 2012; Shrestha et al., 2012). In addition to its crucial role in breast cancer, HOXB9 was also found to be up-regulated in lung adenocarcinoma and its high expression predicts poor prognosis in lung adenocarcinoma patients (Zhan et al., 2015). Overexpression of HOXB9 resulted in a significantly increase in cell migration and invasion in H1299 cells (Wan et al., 2016). The regulation of HOXB9 was also investigated in this study and the authors found that HOXB9 was acetylated at residue K27. Acetylation of HOXB9 suppressed lung cancer cell migration and xenografted tumor growth. The suppression role of acetylated HOXB9 in lung adenocarcinoma was through the binding of JMJD6 promoter and subsequently suppressed JMJD6 transcription. Importantly, HOXB9 K27 acetylation is significantly associated with the outcome of patients with lung adenocarcinoma, and the patients with higher HOXB9 K27 acetylation had a better overall survival than those who was tested with lower HOXB9 K27 acetylation. The authors also identified the mechanism for HOXB9 K27 acetylation and demonstrated that HOXB9 was acetylated by PCAF at K27 and was de-acetylated by SIRT1 (Wan et al., 2016). In addition, another important study has reported that HOXB9 and LEF1 are WNT/TCF targets and they are the effectors of the WNT metastasis program in lung adenocarcinoma (Nguyen et al., 2009).

2.3. HOXC and HOXD in lung cancer

Numerous evidences show that *HOXC* and *HOXD* genes are deregulated in multiple cancers. For example, upregulation of HOXC8 was found in breast cancer, cervical cancer, prostate cancer and colorectal cancer and facilitated the migration and metastasis of cancer cells (Axlund et al., 2010; Li et al., 2010, 2011; Li et al., 2014; Alami et al., 1999; Vider et al., 1997; Waltregny et al., 2002). The expression of HOXC8 was also found to be elevated in lung cancer. Liu et al examined HOXC8 expression levels in NSCLC specimens and lung cancer cell lines. Their results showed that HOXC8 expression was significantly elevated and located mainly in cell nucleus in NSCLC clinical specimens, and it was upregulated in NSCLC cell lines compared to normal

human bronchial epithelial cells BEAS-2B (Liu et al., 2018). Previous studies revealed that the TGF-β signaling pathway was associated with functional roles of Hoxa1 in patterning and differentiation and was required for *HOXA1*-mediated cell invasion in melanoma cells (De Kumar et al., 2017; Wardwell-Ozgo et al., 2014). HOXC8 functions as transcription activator to induce the expression of TGF-β1 in NSCLC cells and HOXC8-TGF-β1 pathway promoted the proliferation, anchorage-independent cell growth and migration of NSCLC cells. HOXC8 was involved in chemoresistance and anti-apoptosis in NSCLC (Liu et al., 2018). Similarly, Miyazaki et al found the important role of the TGF-β-regulated pathway in the conversion of the cells to a more motile and invasive phenotype upon HOXD3-overexpression (Miyazaki et al., 2002). The genes differentially expressed between the HOXD3-overexpressing cells and the control cells were examined and some were TGF-β-regulated genes including *TSP-1*, *βig-h3*, *PAI-1* and *MMP-2*. The expression patterns of these genes in A549 cells stimulated with exogenous TGF-β were similar to those in A549 with HOXD3 overexpression. The authors demonstrated that the activation of the TGF-β pathway was resulted from an accelerated conversion of latent TGF-β to an active form in the HOXD3-overexpressing A549 cells (Miyazaki et al., 2002). HOXD3 was found to enhance cell motility and invasiveness in A549 cells (Hamada et al., 2001). HOXD3-overexpressing A549 cells formed much more foci in lungs compared with the control cells in vivo. Overexpression of HOXD3 induced the expression of N-cadherin, integrin, matrix metalloproteinase-2 and urokinase-plasminogen activator, whereas expression of E-cadherin was lost and plakoglobin was strongly repressed (Hamada et al., 2001). Further experiments observed that the elevated expression of integrin alphav beta3 and loss of E-cadherin by HOXD3-overexpression in A549 cells are required for the enhanced motility and dissociation of cells (Ohta et al., 2006).

Table 1 is the summary of copy number alterations, mutations, deletions and mRNA upregulation for the above mentioned *HOX* genes in lung cancer based on cBioPortal database (Gao et al., 2013; Cerami et al., 2012).

3. Mechanisms and functions of HOX-related lncRNAs in lung cancer

3.1. Functions of HOTAIR in lung cancer

Increasing evidences show that lncRNAs play crucial roles in the development and progression of a variety of carcinomas. One of the most studied lncRNAs is *HOTAIR*, which is located in the intergenic region between *HOXC11* and *HOXC12* (Rinn et al., 2007). The expression pattern of *HOTAIR* and its function in lung cancer have been wildly studied. *HOTAIR* was highly expressed both in NSCLC samples and SCLC specimens (Liu et al., 2013; Ono et al., 2014). The high expression of *HOTAIR* was associated with advanced pathological stage and lymph-node metastasis and is expected to serve as a potential biomarker for patients with lung cancer (Liu et al., 2013; Li et al., 2017). Several studies identified the requirement of *HOTAIR* for cell proliferation and metastasis in NSCLC supported by the evidence that knockdown of *HOTAIR* inhibited cell proliferation and invasiveness of lung cancer cells (Liu et al., 2013; Ono et al., 2014; Zhao et al., 2014). In addition, silencing of *HOTAIR* led to increased *miR-326* expression which decreased cell proliferation and migration in lung cancer by targeting Phox2a (Wang et al., 2016). Drug resistance is an obstacle affecting the effectiveness of treatment. *HOTAIR* is up-regulated in tissues of drug-resistant NSCLC patients and multidrug-resistant lung cancer cell lines (Liu et al., 2016; Fang et al., 2016). Elevated expression of *HOTAIR* decreased the sensitivity of cells to cisplatin by upregulation of tumor stem cell-related biomarkers (Nanog, Oct3/4, Sox2, c-Myc, β-catenin, and Klf4) (Liu et al., 2016), conversely, downregulation of *HOTAIR* increased cell sensitivity to anticancer drugs (cisplatin, adriamycin, etoposide) through increasing cell apoptosis and cell cycle arrest (Fang et al., 2016). *HOTAIR* interacts with HOXA1 and depletion of *HOTAIR* reduced HOXA1 methylation by decreasing DNMT1 and DNMT3b expression. These findings have provided clues that *HOTAIR* might mediate chemoresistance of SCLC by regulating HOXA1 methylation (Fang et al., 2016). The tumor microenvironment is a crucial determinant in tumor initiation and tumor maintenance. A study has shown that type I collagen (Col-1) and *HOTAIR* was concurrently upregulated in human NSCLC and Col-1 induced the expression of *HOTAIR*, and the induction of *HOTAIR* was repressed by a neutralizing antibody against the Col-1 receptor α2β1 integrin (Zhuang et al., 2013). In conclusion, these studies have identified *HOTAIR* as an oncogenic lncRNA that is involved in cancer cell proliferation, motility and invasion and acts as a negative prognostic biomarker in lung cancer, indicating *HOTAIR* as a potential therapeutic target in lung cancer.

3.2. Functions of HOTTIP and other lncRNAs in lung cancer

LncRNA *HOTTIP* (HOXA transcript at the distal tip) located in physical contiguity (chr 7p15.2) with the *HOXA13* gene has been functionally characterized (Wang et al., 2011). To date, *HOTTIP* has been identified as a significant up-regulation gene in several solid tumors, such as non-small cell lung cancer, esophageal squamous carcinoma and hepatocellular carcinoma (Sang et al., 2016; Lin et al., 2017; Quagliata et al., 2014). Furthermore, *HOTTIP* was verified to promote lung cell proliferation, migration, and inhibited apoptosis partly by regulating HOXA13 expression (Sang et al., 2016). A similar result was identified in esophageal squamous cell carcinoma (ESCC) cells that *HOTTIP* modulated HOXA13 at both the transcriptional and post-transcriptional levels, and promoted cell proliferation and metastasis. Additionally, *HOTTIP* competitively bound to *miR-30b* leading to the increased expression of snail1, thus promoted EMT and invasion in ESCC cells (Lin et al., 2017). Interestingly, a novel bidirectional regulatory loop between *HOTTIP*/HOXA13 was uncovered in liver cancer cells, and the expression levels of *HOTTIP* and HOXA13 are associated with metastasis and survival in hepatocellular carcinoma (HCC) patients (Quagliata et al., 2014). Another lncRNA named *HOXA11-AS* has also gained increasing attention in cancers. The up-regulation of *HOXA11-AS* has been indicated as a poor prognosis biomarker in NSCLC. Besides its role in cell invasion, *HOXA11-AS* promoted cell EMT by inhibiting *miR-200b* expression in NSCLC (Chen et al., 2017). Lastly, lncRNA taurine-upregulated gene 1 (*TUG1*), a direct transcriptional target of p53, has been reported that it was downregulated in NSCLC tissues and its reduced expression significantly promoted the proliferation via regulation of HOXB7 (Zhang et al., 2014).

Table 2 is the summary of functions and related mechanisms for lung cancer-associated HOXs and lncRNAs.

4. Conclusion and prospects

Emerging evidence reveals that *HOX* genes play significant roles in tumor progression and metastasis. Despite the research advances in biological function and insight into the mechanisms of regulating *HOX* expression (De Kumar et al., 2015; De Kumar and Krumlauf, 2016), their precise regulatory mechanisms in cancer progression remain to be further explored. Deregulation of HOX may result from transcriptional regulation, post-transcriptional regulation as well as epigenetic modification. HOX methylation has been noted in oral squamous cell carcinoma, mantle cell lymphoma and breast cancer (Xavier et al., 2014; Kanduri et al., 2013; Avraham et al., 2010). Interestingly, HOXA7 methylation was detected more frequently in lung squamous, lung adenocarcinoma, sputum and plasma of lung cancer patient, but not in normal lung tissue and control samples (Diaz-Lagares et al., 2016; Hulbert et al., 2017). DNA methylation in specific genes has the potential to work as biomarker to identify early-stage lung tumors especially those highly sensitive and specific methylation signatures in patient bodily fluids. Except for the early detection of lung cancer,

methylation-based liquid biopsy biomarkers have unique advantages such as their potential for tracking disease progression and response to treatment. Thus, it is promising to explore epigenetic regulatory mechanisms of *HOX* genes in lung cancer. As discussed above, several HOX-related lncRNAs are involved in cancer cell proliferation, motility and invasion and act as HOX regulators in lung cancer. However, more HOX-related lncRNAs need further study and the critical effects exerted by lncRNAs on the HOX expression in lung cancer remain to be elucidated.

Conflicts of interest

The authors have no conflict of interests to disclose.

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References

Alami, Y., et al., 1999. HOXC5 and HOXC8 expression are selectively turned on in human cervical cancer cells compared to normal keratinocytes. Biochem. Biophys. Res. Commun. 257, 738–745.
Apiou, F., et al., 1996. Fine mapping of human HOX gene clusters. Cytogenet. Cell Genet. 73, 114–115.
Avraham, A., et al., 2010. A similar cell-specific pattern of HOXA methylation in normal and in cancer tissues. Epigenetics 5, 41–46.
Axlund, S.D., et al., 2010. HOXC8 inhibits androgen receptor signaling in human prostate cancer cells by inhibiting SRC-3 recruitment to direct androgen target genes. Mol. Cancer Res. 8, 1643–1655.
Bhatlekar, S., et al., 2014. HOX genes and their role in the development of human cancers. J. Mol. Med. 92, 811–823.
Borrow, J., et al., 1996. The t(7;11)(p15;p15) translocation in acute myeloid leukaemia fuses the genes for nucleoporin NUP98 and class I homeoprotein HOXA9. Nat. Genet. 12, 159–167.
Cantile, M., et al., 2009. HOX D13 expression across 79 tumor tissue types. Int. J. Cancer 125, 1532–1541.
Cerami, E., et al., 2012. The cBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data. Cancer Discov. 2, 401–404.
Chang, C.J., et al., 2017. HOXA5 and p53 cooperate to suppress lung cancer cell invasion and serve as good prognostic factors in non-small cell lung cancer. J. Cancer 8, 1071–1081.
Chen, J.H., et al., 2017. Overexpression of lncRNA HOXA11-AS promotes cell epithelial-mesenchymal transition by repressing miR-200b in non-small cell lung cancer. Cancer Cell Int. 17, 64.
Chiba, N., et al., 2012. Homeobox B9 induces epithelial-to-mesenchymal transition-associated radioresistance by accelerating DNA damage responses. Proc. Natl. Acad. Sci. U.S.A. 109, 2760–2765.
Cillo, C., et al., 1992. HOX gene expression in normal and neoplastic human kidney. Int. J. Cancer 51, 892–897.
Dasen, J.S., 2013. Long noncoding RNAs in development: solidifying the Lncs to Hox gene regulation. Cell Rep. 5, 1–2.
De Kumar, B., Krumlauf, R., 2016. HOXs and lincRNAs: two sides of the same coin. Sci. Adv. 2, e1501402.
De Kumar, B., et al., 2015. Analysis of dynamic changes in retinoid-induced transcription and epigenetic profiles of murine Hox clusters in ES cells. Genome Res. 25, 1229–1243.
De Kumar, B., et al., 2017. Hoxa1 targets signaling pathways during neural differentiation of ES cells and mouse embryogenesis. Dev. Biol. 432, 151–164.
De Vita, G., et al., 1993. Expression of homeobox-containing genes in primary and metastatic colorectal cancer. *Eur J Cancer* 29A 887–893.
Debernardi, S., et al., 2003. Genome-wide analysis of acute myeloid leukemia with normal karyotype reveals a unique pattern of homeobox gene expression distinct from those with translocation-mediated fusion events. Genes Chromosomes Cancer 37, 149–158.
Diaz-Lagares, A., et al., 2016. A novel epigenetic signature for early diagnosis in lung Cancer. Clin. Cancer Res. 22, 3361–3371.
Drabkin, H.A., et al., 2002. Quantitative HOX expression in chromosomally defined subsets of acute myelogenous leukemia. Leukemia 16, 186–195.
Fang, S., et al., 2016. Long noncoding RNA-HOTAIR affects chemoresistance by regulating HOXA1 methylation in small cell lung cancer cells. Lab. Invest. 96, 60–68.
Flagiello, D., et al., 1997. Distinct patterns of all-trans retinoic acid dependent expression of HOXB and HOXC homeogenes in human embryonal and small-cell lung carcinoma cell lines. FEBS Lett. 415, 263–267.
Gao, J., et al., 2013. Integrative analysis of complex cancer genomics and clinical profiles using the cBioPortal. Sci. Signal. 6, pl1.
Golub, T.R., et al., 1999. Molecular classification of cancer: class discovery and class prediction by gene expression monitoring. Science 286, 531–537.
Grier, D.G., et al., 2005. The pathophysiology of HOX genes and their role in cancer. J. Pathol. 205, 154–171.
Gupta, R.A., et al., 2010. Long non-coding RNA HOTAIR reprograms chromatin state to promote cancer metastasis. Nature 464, 1071–1076.
Hamada, J., et al., 2001. Overexpression of homeobox gene HOXD3 induces coordinate expression of metastasis-related genes in human lung cancer cells. Int. J. Cancer 93, 516–525.
Hayashida, T., et al., 2010. HOXB9, a gene overexpressed in breast cancer, promotes tumorigenicity and lung metastasis. Proc. Natl. Acad. Sci. U.S.A. 107, 1100–1105.
Hulbert, A., et al., 2017. Early detection of lung Cancer Using DNA promoter hypermethylation in plasma and sputum. Clin. Cancer Res. 23, 1998–2005.
Kanduri, M., et al., 2013. A key role for EZH2 in epigenetic silencing of HOX genes in mantle cell lymphoma. Epigenetics 8, 1280–1288.
Kim, D.S., et al., 2009. Epigenetic inactivation of Homeobox A5 gene in nonsmall cell lung cancer and its relationship with clinicopathological features. Mol. Carcinog. 48, 1109–1115.
Kim, K., et al., 2013. HOTAIR is a negative prognostic factor and exhibits pro-oncogenic activity in pancreatic cancer. Oncogene 32, 1616–1625.
Kogo, R., et al., 2011. Long noncoding RNA HOTAIR regulates polycomb-dependent chromatin modification and is associated with poor prognosis in colorectal cancers. Cancer Res. 71, 6320–6326.
Lee, J.T., Bartolomei, M.S., 2013. X-inactivation, imprinting, and long noncoding RNAs in health and disease. Cell 152, 1308–1323.
Li, Y., et al., 2010. Ratio of miR-196s to HOXC8 messenger RNA correlates with breast cancer cell migration and metastasis. Cancer Res. 70, 7894–7904.
Li, Y., et al., 2011. HOXC8-dependent cadherin 11 expression facilitates breast Cancer cell migration through trio and rac. Genes Cancer 2, 880–888.
Li, D., et al., 2013. Long intergenic noncoding RNA HOTAIR is overexpressed and regulates PTEN methylation in laryngeal squamous cell carcinoma. Am. J. Pathol. 182, 64–70.
Li, Y., et al., 2014. HOXC8 promotes breast tumorigenesis by transcriptionally facilitating cadherin-11 expression. Oncotarget 5, 2596–2607.
Li, N., et al., 2017. Identification of circulating long noncoding RNA HOTAIR as a novel biomarker for diagnosis and monitoring of non-small cell lung Cancer. Technol. Cancer Res. Treat., 1533034617723754.
Lin, C., et al., 2017. Transcriptional and posttranscriptional regulation of HOXA13 by lncRNA HOTTIP facilitates tumorigenesis and metastasis in esophageal squamous carcinoma cells. Oncogene 36, 5392–5406.
Liu, X.H., et al., 2013. The long non-coding RNA HOTAIR indicates a poor prognosis and promotes metastasis in non-small cell lung cancer. BMC Cancer 13, 464.
Liu, M.Y., et al., 2016. Elevated HOTAIR expression associated with cisplatin resistance in non-small cell lung cancer patients. J. Thorac. Dis. 8, 3314–3322.
Liu, H., et al., 2018. HOXC8 promotes proliferation and migration through transcriptional up-regulation of TGFbeta1 in non-small cell lung cancer. Oncogenesis 7, 1.
Miyazaki, Y.J., et al., 2002. HOXD3 enhances motility and invasiveness through the TGF-beta-dependent and -independent pathways in A549 cells. Oncogene 21, 798–808.
Monterisi, S., et al., 2018. HOXB7 overexpression in lung cancer is a hallmark of acquired stem-like phenotype. Oncogene 37, 3575–3588.
Mortlock, D.P., et al., 1996. The molecular basis of hypodactyly (Hd): a deletion in Hoxa 13 leads to arrest of digital arch formation. Nat. Genet. 13, 284–289.
Nakamura, T., et al., 1999. NUP98 is fused to PMX1 homeobox gene in human acute myelogenous leukemia with chromosome translocation t(1;11)(q23;p15). Blood 94, 741–747.
Nguyen, D.X., et al., 2009. WNT/TCF signaling through LEF1 and HOXB9 mediates lung adenocarcinoma metastasis. Cell 138, 51–62.
Nie, Y., et al., 2013. Long non-coding RNA HOTAIR is an independent prognostic marker for nasopharyngeal carcinoma progression and survival. Cancer Sci. 104, 458–464.
Niinuma, T., et al., 2012. Upregulation of miR-196a and HOTAIR drive malignant character in gastrointestinal stromal tumors. Cancer Res. 72, 1126–1136.
Ohta, H., et al., 2006. HOXD3-overexpression increases integrin alpha v beta 3 expression and deprives E-cadherin while it enhances cell motility in A549 cells. Clin. Exp. Metastasis 23, 381–390.
Ono, H., et al., 2014. Long noncoding RNA HOTAIR is relevant to cellular proliferation, invasiveness, and clinical relapse in small-cell lung cancer. Cancer Med. 3, 632–642.
Palakurthy, R.K., et al., 2009. Epigenetic silencing of the RASSF1A tumor suppressor gene through HOXB3-mediated induction of DNMT3B expression. Mol. Cell 36, 219–230.
Procino, A., Cillo, C., 2013. The HOX genes network in metabolic diseases. Cell Biol. Int. 37, 1145–1148.
Quagliata, L., et al., 2014. Long noncoding RNA HOTTIP/HOXA13 expression is associated with disease progression and predicts outcome in hepatocellular carcinoma patients. Hepatology 59, 911–923.
Raman, V., et al., 2000. Compromised HOXA5 function can limit p53 expression in human breast tumours. Nature 405, 974–978.
Rauch, T., et al., 2007. Homeobox gene methylation in lung cancer studied by genome-wide analysis with a microarray-based methylated CpG island recovery assay. Proc. Natl. Acad. Sci. U.S.A. 104, 5527–5532.
Rawat, V.P., et al., 2008. Overexpression of CDX2 perturbs HOX gene expression in murine progenitors depending on its N-terminal domain and is closely correlated with deregulated HOX gene expression in human acute myeloid leukemia. Blood 111, 309–319.
Raza-Egilmez, S.Z., et al., 1998. NUP98-HOXD13 gene fusion in therapy-related acute myelogenous leukemia. Cancer Res. 58, 4269–4273.

Rinn, J.L., et al., 2007. Functional demarcation of active and silent chromatin domains in human HOX loci by noncoding RNAs. Cell 129, 1311–1323.
Rodriguez, B.A., et al., 2008. Epigenetic repression of the estrogen-regulated Homeobox B13 gene in breast cancer. Carcinogenesis 29, 1459–1465.
Sang, Y., et al., 2016. Up-regulation of long non-coding HOTTIP functions as an oncogene by regulating HOXA13 in non-small cell lung cancer. Am. J. Transl. Res. 8, 2022–2032.
Shrestha, B., et al., 2012. Homeodomain-containing protein HOXB9 regulates expression of growth and angiogenic factors, facilitates tumor growth in vitro and is over-expressed in breast cancer tissue. FEBS J. 279, 3715–3726.
Sun, S., et al., 2018. STAT3/HOTAIR signaling Axis Regulates HNSCC growth in an EZH2-dependent manner. Clin. Cancer Res. 24, 2665–2677.
Tiberio, C., et al., 1994. HOX gene expression in human small-cell lung cancers xenografted into nude mice. Int. J. Cancer 58, 608–615.
Tommasi, S., et al., 2009. Methylation of homeobox genes is a frequent and early epigenetic event in breast cancer. Breast Cancer Res. 11, R14.
Vider, B.Z., et al., 1997. Human colorectal carcinogenesis is associated with deregulation of homeobox gene expression. Biochem. Biophys. Res. Commun. 232, 742–748.
Waltregny, D., et al., 2002. Overexpression of the homeobox gene HOXC8 in human prostate cancer correlates with loss of tumor differentiation. Prostate 50, 162–169.
Wan, J., et al., 2016. PCAF-mediated acetylation of transcriptional factor HOXB9 suppresses lung adenocarcinoma progression by targeting oncogenic protein JMJD6. Nucleic Acids Res. 44, 10662–10675.
Wang, K.C., Chang, H.Y., 2011. Molecular mechanisms of long noncoding RNAs. Mol. Cell 43, 904–914.
Wang, K.C., et al., 2011. A long noncoding RNA maintains active chromatin to coordinate homeotic gene expression. Nature 472, 120–124.
Wang, C.C., et al., 2015. HOXA5 inhibits metastasis via regulating cytoskeletal remodelling and associates with prolonged survival in non-small-cell lung carcinoma. PLoS One 10, e0124191.
Wang, R., et al., 2016. MiR-326 regulates cell proliferation and migration in lung cancer by targeting phox2a and is regulated by HOTAIR. Am. J. Cancer Res. 6, 173–186.
Wardwell-Ozgo, J., et al., 2014. HOXA1 drives melanoma tumor growth and metastasis and elicits an invasion gene expression signature that prognosticates clinical outcome. Oncogene 33, 1017–1026.
Xavier, F.C., et al., 2014. Epigenetic repression of HOXB cluster in oral cancer cell lines. Arch. Oral Biol. 59, 783–789.
Xiao, F., et al., 2014. Downregulation of HOXA1 gene affects small cell lung cancer cell survival and chemoresistance under the regulation of miR-100. Eur. J. Cancer 50, 1541–1554.
Yang, Z., et al., 2011. Overexpression of long non-coding RNA HOTAIR predicts tumor recurrence in hepatocellular carcinoma patients following liver transplantation. Ann. Surg. Oncol. 18, 1243–1250.
Yu, S.L., et al., 2016. Homeobox A9 directly targeted by miR-196b regulates aggressiveness through nuclear Factor-kappa B activity in non-small cell lung cancer cells. Mol. Carcinog. 55, 1915–1926.
Yuan, W., et al., 2014. Role of HOXB7 in regulation of progression and metastasis of human lung adenocarcinoma. Mol. Carcinog. 53, 49–57.
Zhan, J., et al., 2015. High expression of transcriptional factor HoxB9 predicts poor prognosis in patients with lung adenocarcinoma. Histopathology 66, 955–965.
Zhang, E.B., et al., 2014. P53-regulated long non-coding RNA TUG1 affects cell proliferation in human non-small cell lung cancer, partly through epigenetically regulating HOXB7 expression. Cell Death Dis. 5, e1243.
Zhang, B., et al., 2018. Knockdown of homeobox B5 (HOXB5) inhibits cell proliferation, migration, and invasion in non-small cell lung Cancer cells through inactivation of the Wnt/beta-Catenin pathway. Oncol. Res. 26, 37–44.
Zhao, W., et al., 2014. Role of HOTAIR long noncoding RNA in metastatic progression of lung cancer. Eur. Rev. Med. Pharmacol. Sci. 18, 1930–1936.
Zhuang, Y., et al., 2013. Induction of long intergenic non-coding RNA HOTAIR in lung cancer cells by type I collagen. J. Hematol. Oncol. 6, 35.