

Recent advances in unraveling the molecular mechanisms and functions of HOXA11-AS in human cancers and other diseases (Review)

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Abstract. A large number of previously published research articles have demonstrated that the expression levels of long noncoding RNAs (lncRNAs) are generally dysregulated, either through overexpression or underexpression, in cancer and other types of disease. As a recently discovered lncRNA, HOXA11 antisense RNA (HOXA11-AS) is able to serve as an oncogenic or tumor-suppressor gene and serves a vital role in the processes of proliferation, invasion, and migration of cancer cells. HOXA11-AS appears to be a major factor contributing to epigenetic modification, and exerts transcriptional, post-transcriptional, translational and post-translational regulatory effects on genes through a variety of mechanisms; for example, by competing endogenous RNA (ceRNA) and a molecular scaffold mechanism. A number of reports have demonstrated that HOXA11-AS functions as a protein scaffold for polycomb repressive complex 2 (PRC2), lysine-specific histone demethylase 1 (LSD1) and DNA methyltransferase 1 (DNMT1) to perform epigenetic modifications on chromosomes in the nucleus. Furthermore, HOXA11-AS is also located in the cytoplasm and can act as a ceRNA, which

sponges miRNAs. In addition, HOXA11-AS may be useful as a biomarker for the diagnosis and prognosis of cancer. In the present review article, the clinical value, phenotype and mechanism of HOXA11-AS in a variety of tumors types are briefly summarized, as well as its clinical value in certain additional diseases. The perspective of the authors is that HOXA11-AS may represent an effective tumor marker and therapeutic target for cancer diagnosis and therapy.

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1. Introduction

With the incidence of cancer and mortality rates rising rapidly worldwide, cancer is anticipated to become both the most significant obstacle to extending life expectancy, and the major cause of death worldwide. Cancer has already become the first or second main cause of mortality in 91 of 172 countries for persons aged 70 or less, and is ranked third or fourth in a further 22 countries, according to data published by the World Health Organization (WHO) in 2015 (1). During 2018, over 18.1 million new cases of cancer and 9.6 million cancer deaths were estimated to have occurred worldwide. For both the sexes, in 2018 Asia accounted for nearly one-half of all cancer cases, and more than one-half of cancer-associated deaths globally (1). Despite improvements in radiotherapy, chemotherapy and surgical treatment technologies, various types of cancer remain very difficult to treat, such as gastric cancer (GC), non-small cell lung cancer (NSCLC) and bladder cancer (BC) (2,3). Therefore, study of the pathogenesis and therapeutic targets of cancer is imperative.

The transcriptional background of all organisms has been shown to be much more complicated than was at first envisioned, since various protein-coding RNAs and noncoding

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RNAs (ncRNAs) are extensively transcribed from large portions of genomic sequences (4,5). Thus, to resolve these problems, a clear understanding of the intracellular transcriptional environment must be obtained. Benefiting from the development of new generation sequencing technologies, it has been shown that, in humans, over 70% of the genome sequence is transcribed. Among these transcripts, less than 2% of the transcripts contain protein-coding RNAs, whereas the remaining transcripts produce ncRNAs (6-9). Previously, it was considered that the products of most non-protein-coding genes were without any function, simply produced during the process of gene transcription. However, with the development of research in this area, there is a new understanding that the products of these non-protein-coding genes are involved in the regulation of a variety of biological processes in cells (6-9). At present, ncRNAs are a hot research topic in the life sciences.

NcRNAs comprise regulatory RNAs (for instance, miRNAs) and structural RNAs [such as small nuclear RNAs (snRNAs), ribosomal RNAs (rRNAs) and transfer RNAs (tRNAs)] (10). Thanks to recent advances in the acquisition of genome and transcriptome sequencing data, the catalogue of regulatory molecules now contains numerous long noncoding RNAs (lncRNAs), a loosely classified group of long RNA transcripts that lack protein-coding function (11,12). As early as 1991, it was found that X-inactive specific transcript (XIST) is involved in regulating X chromosome inactivation, providing an initial insight into lncRNA functionality (13,14). At present, 96,308 lncRNA genes as well as 172,216 lncRNA transcripts, have been identified in humans [data from NONCODE, the ncRNA database including sequence, documentation and analysis (<http://www.bioinfo.org/noncode/>)], which influence a great variety of cellular biological processes. lncRNAs were undervalued for a long time, being considered as merely transcriptional 'garbage' across the entire length of the genome (15). However, the expression of lncRNAs is now known to be dysregulated in a great majority of tumor types, including lung cancer (16), hepatocellular carcinoma (HCC) (17), glioma (18), colorectal cancer (CRC) (19), breast cancer (BC) (20), osteosarcoma (21), ovarian cancer (22), gastric cancer (GC) (23), and esophageal squamous cell carcinoma (ESCC) (24). Emerging studies have now shown that lncRNA has a vital role in a wide variety of cellular biological processes, including cellular differentiation, cell cycle, proliferation, migration, metabolism, as well as apoptosis, especially in tumor cells (25,26). These findings suggest that lncRNA functions as an oncogene or tumor suppressor through interaction with other biomolecules or via chromatin modifications (27).

lncRNAs are able to interfere in numerous cellular processes, including chromatin organization, transcription complex recruitment, post-transcriptional regulation, translation, and post-translational processes (12,28,29). Several of the main mechanisms of lncRNAs are discussed below.

Chromatin organization. The dosage compensation effect of the X chromosome in mammals provides a striking instance of lncRNA-mediated chromatin regulation. Xist, one of the first functionally annotated lncRNAs, regulates dosage compensation in female mammals by localizing to the X chromosome, and recruiting various factors directly or indirectly

to accomplish X chromosome inactivation (XCI) (30). In brief, dosage compensation refers to the process by which the gene expression level of the two X chromosomes in female cells is made equivalent to the one X chromosome in male cells. The expression of lncRNA Xist in female cells is from one of the two X chromosomes, which subsequently changes the chromatin structure of the whole chromosome, whereby most of the genes in the inactive X chromosome are silenced during transcription (31-33). Significantly, Xist can interact with polycomb repressive complex 2 (PRC2) via a structural domain called Repeat A, resulting in PRC2 and its cognate histone marker histone H3 lysine 27 trimethylation (H3K27me3) being located on the inactive X chromosome. lncRNAs can also recruit PRC2 to modulate distal genes throughout the genome (34). In addition, lncRNAs expressed only in embryonic stem cells are able to directly interact with chromatin to regulate gene expression and maintain pluripotency (35). The interaction between DNA and lncRNA is achieved either via sequence complementation or via combination in helical structures (28). Therefore, lncRNAs are associated with organization of the nuclear architecture and the general structuring of the genome, thereby affecting the expression of related genes (36).

Transcriptional regulation. At the transcriptional level, lncRNA is often used as a molecular scaffold to recruit two or more proteins to the promoter regions of their target genes, and modulates the transcription of the target genes (37-39). These proteins include zinc-finger proteins, DNA methyltransferases, transcription factors (TFs), and other transcriptional regulators (40). Furthermore, lncRNA can act as an adaptor to recruit associated proteins into discrete complexes (41). For instance, the lncRNA HOTAIR synchronously binds both PRC2 and LSD1-CoREST complexes through specific structural domains of the RNA (42). This interaction effectively harmonizes the methylation of H3K27 and demethylation of H3K4me2, guaranteeing that gene silencing occurs. Functioning as a molecular scaffold is among the primary mechanisms by which HOXA11-AS functions.

Post-transcriptional regulation. At the post-transcriptional level, lncRNAs operate in diverse ways to affect miRNAs and mRNAs (43,44). First, lncRNAs are hypothesized to act as competing endogenous RNA (ceRNA), or as 'RNA sponges', which are able to interact with miRNAs, thereby blocking the interaction between miRNAs and mRNAs, thus decreasing their regulatory impact on target mRNAs (45,46). For example, HOXA11-AS serves as a ceRNA to modulate the expression level of the transcription factor Sp1 by sequestering miR-124. Findings demonstrated that improvements in cell invasion and proliferation mediated by HOXA11-AS were reversed by miR-124 (47). Secondly, lncRNAs can be precursors of miRNAs, which are able to modulate different processes in miRNA production and have microprocessor activity to complete primary transcripts via a mechanism independent of polyadenylation (48). For instance, lncRNA LOC554202 was shown to be the putative precursor of miR-31, exerting an important role in preventing metastasis of BC (49). In addition, the maturation of miR-145 can be hindered by lncRNA colon cancer-associated transcript 2 (CCAT2) via the repression

of Dicer cleavage and cytoplasmic export (50). Moreover, lncRNAs also affect alternative splicing and the stability of mRNA. For example, first apoptosis signal (Fas)-antisense lncRNA-SAF complex is able to combine with the human splicing factor SPF45, resulting in removal of exon 6 during Fas splicing and the production of a soluble Fas protein that serves to inhibit Fas/Fas ligand (FASL)-mediated apoptosis in different human cell lines (51). In addition, lncRNA PDCD4-AS1 stabilizes programmed cell death 4 (PDCD4) RNA via formation of an RNA duplex that dictates the mutual effect between RNA decay promoting factors and PDCD4 RNA, in human BC (52).

Recently, numerous studies (19,53) have reported that exosomes can function as autocrine or paracrine factors to influence the significant biological functions that mediate intercellular interactions. An increasing amount of evidence has shown that cancer cells are able to release exosomes, and exosome-transmitted lncRNAs are able to promote tumor metastasis, angiogenesis and drug resistance. For example, lncRNA-APC1 is able to inhibit the production of exosomes, and reduce their stability by directly binding Rab5b mRNA, thereby inhibiting the growth, metastasis and tumor angiogenesis of CRC cells (19). Additionally, Qu *et al* (53) found that bioactive lncARSR [lncRNA activated in renal cell carcinoma (RCC) with sunitinib resistance] can be integrated into exosomes and delivered to sensitive cells in RCC. When exosomes containing lncARSR reached the sensitive RCC cells, lncARSR was released into the cytoplasm. The expression of the receptor tyrosine kinases AXL and c-MET in RCC cells was promoted by lncARSR competitively binding miR-34/miR-449, thus promoting sunitinib resistance. AXL and c-MET are responsible for lncARSR-mediated sunitinib resistance in RCC (53).

Translational process. In addition to the abovementioned effects, lncRNAs are also able to promote or inhibit the translational process. For example, dopaminergic neurons specifically express ubiquitin carboxy-terminal hydrolase L1 (Uchl1). Uchl1 can be modulated by its antisense transcript (AS Uchl1), which binds polysomes through its repetitive domain termed 'SINEB2' to facilitate cap-independent translation (54). Furthermore, lncRNA-p21, a post-transcriptional modulator, passively modulates translation of the transcripts of the transcription factor JUNB and β -catenin through incomplete complementary base pairing at diverse sites in the coding and non-coding regions [both 5'- and 3'-untranslated regions (UTRs)] of JUNB (8 sites) and β -catenin (15 sites) mRNA, leading to the formation of an lncRNA-p21-mRNA complex. The communication between mRNAs and Fragile X mental retardation protein (FMRP), as well as the translational repressor RCK, may be improved by the lncRNA-p21-mRNA complex, resulting in suppression of the translation target transcripts via the reduction of ribosome drop-off and polysome sizes (54-56).

Post-translational modification. lncRNAs not only regulate the translational process, but also modify proteins produced after translation via mechanisms such as phosphorylation and ubiquitination. The activity and stability of a protein can be altered through these modifications (57). For instance, the

lncRNA SLCO4A1-AS1 interacts with β -catenin to improve its stability through weakening the communication between glycogen synthase kinase β (GSK β) and β -catenin, restricting its phosphorylation and leading to Wnt/ β -catenin signaling activation in CRC (58). In addition, the lncRNA SNHG15 can sustain Slug stability by inhibiting the interaction between Slug and β -transducin repeat containing (BTRC) E3 ubiquitin protein ligase, blocking BTRC-mediated Slug ubiquitination in colon cancer (59).

It may be concluded that, from the chromatin level to transcription, post-transcription, translation and post-translational regulation, lncRNAs fulfill important roles in all aspects of cell physiology.

2. Discovery and description of HOXA11-AS

lncRNA HOXA11-AS, located in the HOXA gene cluster, has been reported to exert an impact on the occurrence of variety of human diseases and their subsequent development (60). HOXA11-AS is located on chromosome 7p15.2, and is referred to as HOXA11AS, HOXA11-AS1, HOXA11S, HOXA-AS5 or NCRNA00076. The chromosomal localization and secondary structure of HOXA11-AS are shown in Fig. 1. The length of the HOXA11-AS gene is 3,885 bp, whereas the HOXA11-AS transcript is 1628 bp in length (61). HOX genes are organized into four clusters (A, B, C and D) on four diverse chromosomes, and HOXA is a member of the homeobox (HOX) family in the human genome (62,63). The HOXA gene has a sense strand and an antisense strand that include protein-coding genes and ncRNA genes, respectively. The 5'-region of the HOXA gene refers to the direction of the sense strand relative to the direction of protein coding genes, and the most abundant protein-coding gene of the 5'-region is HOXA13. Furthermore, a further three protein-coding genes, HOXA9, HOXA10 and HOXA11, and 3 lncRNAs, HOXA10-AS, HOXA11-AS and HOTTIP, are located in the 5'-region (64,65). HOXA11-AS is a novel lncRNA that functions as an oncogene or tumor-suppressor gene in diverse types of tumor. For example, HOXA11-AS can serve as an oncogene in non-small cell lung cancer (NSCLC), HCC, glioma, BC, GC, renal cancer (RC), uveal melanoma (UM), laryngeal squamous cell carcinoma (LSCC), cervical cancer (CC), ESCC and osteosarcoma. By contrast, HOXA11-AS functions as a tumor suppressor in epithelial ovarian cancer (EOC) (7,66,67).

The subsequent sections of this review provide an overview of the clinical significance, biological functions, and molecular mechanisms of HOXA11-AS in tumors and several other diseases types, with the aim of intuitively understanding the role of HOXA11-AS in the occurrence and development of human disease.

HOXA11-AS in cancer

Nonsmall-cell lung cancer (NSCLC). Lung cancer is the primary cause of cancer mortality and the most commonly occurring type of cancer worldwide (68,69). No fewer than 2.1 million people are diagnosed with lung cancer annually (1). Histologically, lung cancer can be divided into small cell lung cancer (SCLC) and NSCLC. Approximately 80-85% of newly diagnosed cases of lung cancer belong to the NSCLC type (70,71). Numerous lncRNAs, including HOXA11-AS,

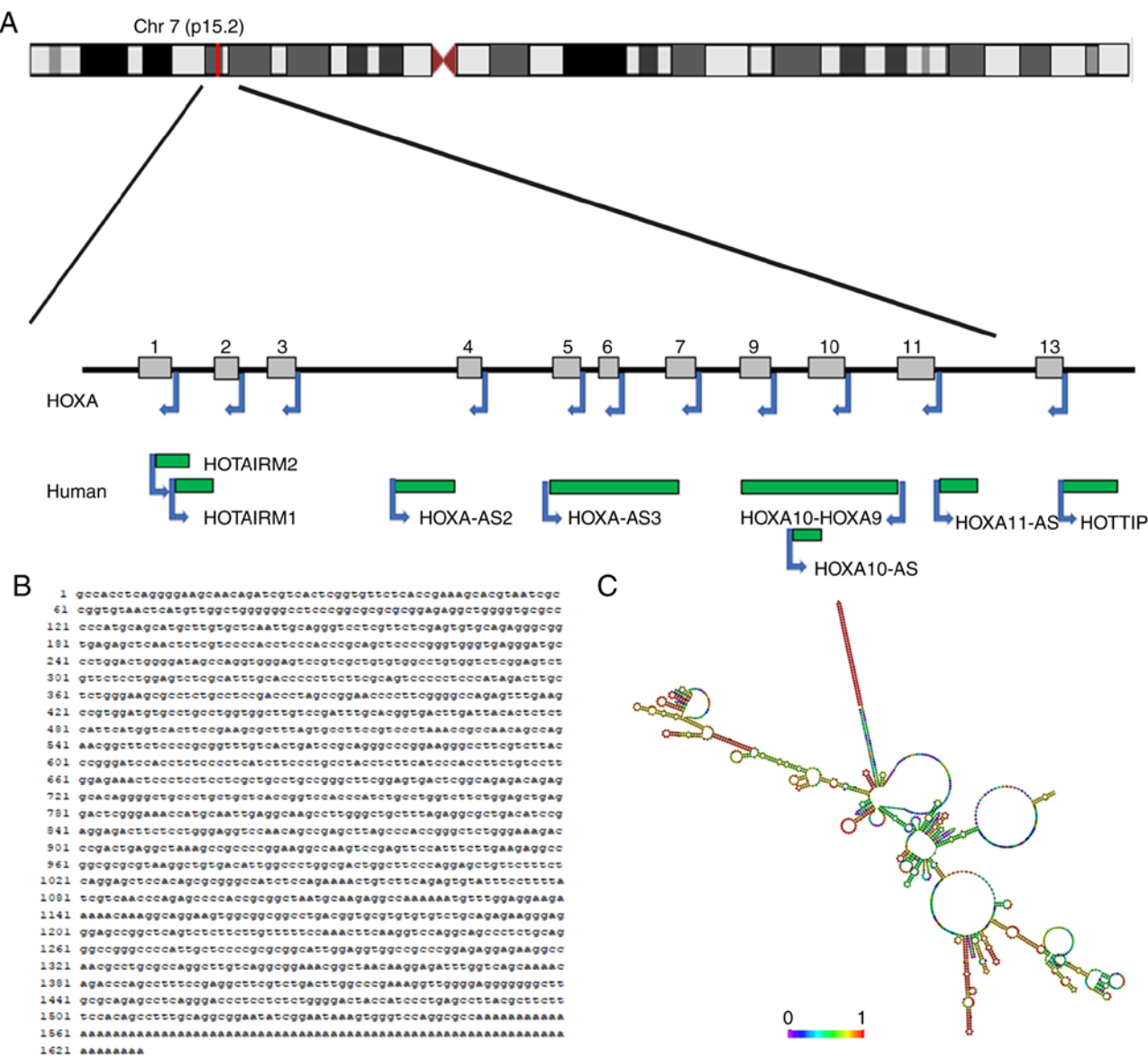


Figure 1. The diagram shows (A) the chromosomal localization of HOXA11-AS and its position in the HOXA family. Also shown are (B) the nucleotide sequence and (C) its secondary structure. HOXA11-AS, HOXA11 antisense RNA.

have been shown to have significant roles in NSCLC. Zhang *et al* (73,74) reported that the expression of HOXA11-AS is higher in both squamous cell carcinoma (SCC) and lung adenocarcinoma (LUAD) compared with that in normal lung tissues, and HOXA11-AS knockdown suppresses tumorigenesis, angiogenesis, proliferation, migration and invasion of NSCLC cells, inducing apoptosis by impeding the cell cycle at the G0/G1 or the G2/M phase. Moreover, Chen *et al* (75) identified that high levels of HOXA11-AS predict poor prognosis in patients with NSCLC. Furthermore, Yu *et al* (48) demonstrated that the expression level of HOXA11-AS is associated with lymph node metastasis and tumor size. Zhao *et al* (76) also reported that high levels of HOXA11-AS are associated with poor prognosis.

Mechanistically, Zhang *et al* (72-74) revealed that HOXA11-AS expression is negatively correlated with dedicator of cytokinesis 8 (DOCK8) in SCC and LUAD. Those authors conjectured that HOXA11-AS could have an oncogenic role in the development and progression

of NSCLC by modulating various pathways, such as the transforming growth factor (TGF)- β pathway, the phosphoinositide 3-kinase (PI3K)-Akt pathway and the Hippo signaling pathway, and genes, such as *DOCK8* gene. In other studies, the same authors demonstrated that the expression of HOXA11-AS co-expressed genes in NSCLC may be partly regulated by the NSCLC pathway and that HOXA11-AS could affect various biological processes of NSCLC via regulation of the expression of miR-642b-3p by targeting the expression of phosphodiesterase 4D (PDE4D) or other target genes (72-74). Additionally, Chen *et al* (75) found that HOXA11-AS interacts with DNA (cytosine-5)-methyltransferase 1 (DNMT1) and enhancer of zeste homolog 2 (EZH2), recruiting these proteins to the promoter regions of miR-200b and mediating methylation silencing of miR-200b in NSCLC cells, a process that promotes both NSCLC cell epithelial-mesenchymal transition (EMT) via regulation of the protein levels of E-cadherin, N-cadherin, Snail1/2 and ZEB1/2 and tumor progression. Yu *et al* (48) revealed

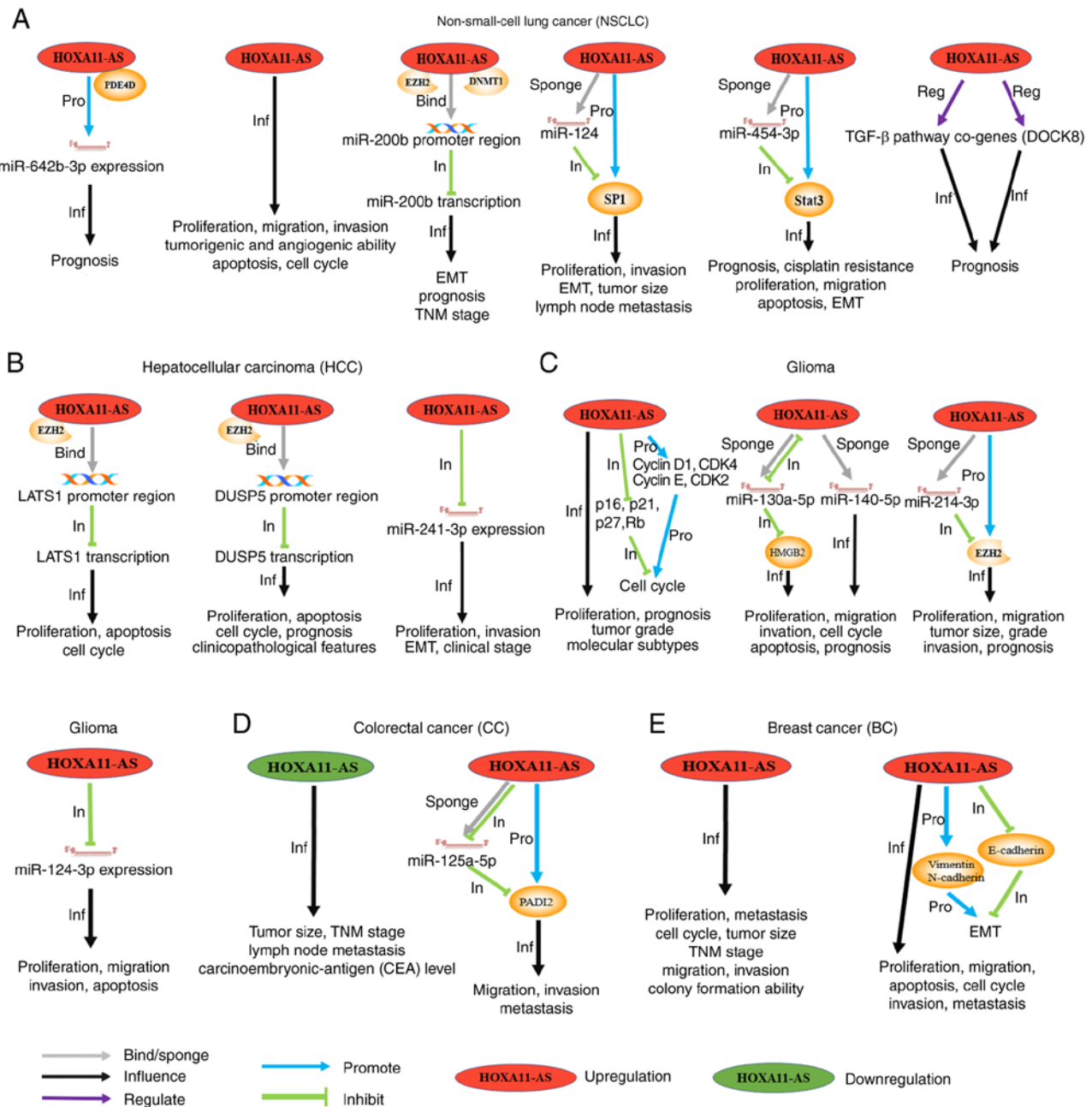


Figure 2. Schematic diagram that introduces in detail the molecular mechanisms, clinical values and cell phenotypes affected by HOXA11-AS in different tumor types, including (A) NSCLC, (B) HCC, (C) glioma, (D) CC, and (E) BC. 'Upregulation'/'downregulation' indicates that the expression level of HOXA11-AS in such a tumor was increased/decreased compared with normal tissues. The gray arrows ('bind'/'sponge') indicate that HOXA11-AS binds to the promoter region of a gene or, as a sponge, binds to a miRNA. The black arrows ('Inf') indicate that HOXA11-AS affects the phenotypes and the clinical characteristics of the cancer under consideration. The blue ('Pro')/green ('In') arrows indicate the promoting or inhibitory effects on the downstream genes, respectively. The purple arrows ('Reg') indicate the regulatory effects on the downstream pathway. NSCLC, non-small cell lung cancer; HCC, hepatocellular carcinoma; CRC, colorectal cancer; BC, breast cancer; HOXA11-AS, HOXA11 antisense RNA.

that HOXA11-AS acts as a ceRNA to positively modulate the expression of transcription factor Sp1 by sequestering miR-124, a process that can inhibit cell proliferation and the invasion-promoting effects of HOXA11-AS. Furthermore, those authors found that HOXA11-AS can serve as an oncogene by promoting EMT via regulation of the protein levels of E-cadherin, β -catenin, vimentin and the EMT-mediating transcription factors Slug and Snail in NSCLC (48). Zhao *et al* (76) discovered that, in human LUAD cells, HOXA11-AS can function as a ceRNA to facilitate cisplatin tolerance through the miR-454-3p/Stat3 pathway (the

abovementioned mechanisms are shown in Fig. 2A). Recent findings (77) have shown that membrane-bound extracellular vesicles, especially exosomes, serve significant roles as mediators for communication among different tissues and organs. Exosomes have a vital role in signal transduction among cells, and a wide range of biological functions. Wu *et al* (77) reported that high expression levels of HOXA11-AS in exosomes are closely associated with smoking and NSCLC in lung tissues. These findings indicate that HOXA11-AS has several functions associated with oncogenesis, regulating various physiological activities in NSCLC. These findings

shed light upon the effects of HOXA11-AS on the progression of NSCLC and indicate that HOXA11-AS is a potential target for future treatment of NSCLC.

Hepatocellular carcinoma. Hepatocellular carcinoma (HCC), which accounts for 90% of cases of liver cancer, is the fifth most frequent cancer in men and the ninth in women worldwide (78,79). The mortality rate of HCC ranks second in the world (80,81). Recently, cancer-associated studies focused on lncRNAs have demonstrated that a considerable number of lncRNAs are involved in the progression of HCC (82-84). Previous studies revealed that HOXA11-AS is overexpressed in HCC cells and tissues (82-84). Liu *et al* (82) found that high expression levels of HOXA11-AS are significantly correlated with vascular invasion, cirrhosis, tumor size and Edmondson grade. The overall survival (OS) rate of patients with high levels of HOXA11-AS expression is markedly shorter compared with those with lower levels of HOXA11-AS expression. Overexpression of HOXA11-AS promotes cell cycle progression, proliferation, invasion, and EMT, as well as repressing apoptosis in HCC cells.

Yu *et al* (83) reported that HOXA11-AS recruits PRC2 to the promoter region of large tumor suppressor 1 (LATS1) to obstruct its transcription, thereby promoting HCC growth and inhibiting apoptosis and cell cycle progression at the G0/G1 phase. The results from flow cytometry experiments indicated that the cell cycle progression of HCC cells was stalled at the G0/G1 phase when HOXA11-AS RNAi was transfected into HCC cells (83). Zhan *et al* (84) showed that the overexpression of HOXA11-AS is able to facilitate HCC proliferation and invasion, and induce EMT by repressing the expression of miR-214-3p. In addition, these authors demonstrated that the expression of miR-214-3p in early clinical stages (I-II) was higher than that in advanced clinical stages (III-IV). Furthermore, Liu *et al* (82) reported that HOXA11-AS recruits EZH2 to the promoter region of dual specificity protein phosphatase 5 (DUSP5), thereby inhibiting the transcription of DUSP5, which is a downstream target of HOXA11-AS and can function as a tumor suppressor gene. HOXA11-AS performs an oncogenic role in HCC by interacting with PRC2 (the abovementioned mechanisms are shown in Fig. 2B). HOXA11-AS may function as an oncogene in HCC development. The interaction between HOXA11-AS and LATS1, DUSP5 or miR-214-3p may supply novel prognostic markers and therapeutic targets for HCC.

Glioma. Glioma, accounting for approximately 80% of primary malignant brain tumors, is the most aggressive primary tumor of the nervous system. Effective treatment of gliomas is very difficult, particularly glioblastomas (GBMs, also known as grade IV astrocytomas), with a median survival time for patients of less than 15 months using standard therapy (85-88). To date, although many studies have been focused on seeking improvements in diagnosis and treatment, the trend of poor prognosis has not been reversed (89). Among the numerous biomolecules involved in the occurrence and development of glioma, lncRNAs have attracted sustained attention due to their abnormal expression during tumorigenesis. Wang *et al* (90) discovered that high levels of HOXA11-AS expression are closely correlated with OS in high-grade glioma, and

HOXA11-AS may be an independent prognostic factor for GBM. HOXA11-AS overexpression might occur during initial gliomagenesis and increased levels might be maintained in higher grades of gliomas. Those authors reported that the expression levels of HOTTIP, HOXA9, HOXA10, and HOXA13 are prominently correlated with HOXA11-AS expression, and HOXA11-AS can alter the expression of cell cycle-associated proteins, thus regulating cell cycle progression. Moreover, Cui *et al* (91) and Xu *et al* (92) found that high expression levels of HOXA11-AS are correlated with decreased survival time and poorer prognosis compared with patients with lower HOXA11-AS expression. In addition, Xu *et al* (93) found that the overexpression of HOXA11-AS is associated with advanced stages of glioma and poor prognosis. Authors of that study reported that knocking down the expression of HOXA11-AS leads to suppression of the proliferation, migration, and invasion rates of glioma cells *in vitro*, with the consequent further enhancement of cell cycle arrest at the G0/G1 stage and improved apoptotic responses.

Cui *et al* (91) showed that miR-140-5p is able to directly target the 3'-UTR of HOXA11-AS, and the effects of HOXA11-AS knockdown are shown to be reversed by an miR-140-5p inhibitor, as determined by its effects on cell cycle arrest, proliferation and apoptosis. Xu *et al* (92) demonstrated that HOXA11-AS functions as a ceRNA by sponging miR-214-3p, which can directly target EZH2 and suppress its mRNA transcriptional level. It was thereby confirmed that HOXA11-AS may serve in an oncogenic role by regulating the miR-214-3p/EZH2 pathway. Yang *et al* (94) found that HOXA11-AS leads to a marked increase in proliferation, invasion and migration rates, while inhibiting apoptosis by absorbing miR-124-3p in glioma cells. Furthermore, Xu *et al* (93) found that HOXA11-AS can exert its oncogenic role by directly binding to miR-130a-5p as a ceRNA, which inhibits the inhibitory effect of miR-130a-5p on HMGB2 expression. HMGB2 has been demonstrated to be involved in several diseases, such as sepsis, arthritis and cancer (the abovementioned mechanisms are shown in Fig. 2C). The above results suggest that HOXA11-AS may be an oncogene participating in the prognosis and treatment response of specific GBM subtypes.

Colorectal cancer. Colorectal cancer (CRC) ranks third among the most common types of cancer in men, and second among women worldwide, with ~55% of CRC cases occurring in developed countries (95,96). The incidence of CRC has rapidly increased in China, and in 2011, it was shown to be the second most common cause of cancer-associated mortality (97). Although recent advances have been made in the diagnosis and treatment of CRC in recent years, the prognosis of patients diagnosed with CRC remains poor; in fact, the 5-year survival rate in patients with metastatic CRC has been shown to be less than 20% (98,99). Li *et al* (100) reported that HOXA11-AS is downregulated in CRC cell lines and tissues, and low expression levels of HOXA11-AS are associated with advanced tumor-lymph node-metastasis (TNM) stages, lymphatic metastasis, large tumor size and elevated levels of carcinoembryonic antigen (CEA). Authors of that study also showed that the lncRNA HOXA11-AS may distinguish CRC tissue from noncancerous tissue, and they further explored the correlation between HOXA11-AS and lymph node

metastasis. Moreover, Chen *et al* (101) reported that the level of HOXA11-AS was markedly upregulated in CRC patients with liver metastasis, and the migration and invasion of CRC cells was facilitated by HOXA11-AS. In addition, Chen *et al* (101) found that HOXA11-AS can act as a ceRNA sequestering miR-125a-5p to modulate the expression of protein-arginine deiminase type-2 (PADI2), which was shown to facilitate metastasis and the invasion of CRC (the abovementioned mechanisms are shown in Fig. 2D). Consequently, a novel HOXA11-AS/miR-125a-5p/PADI2 pathway, involved in CRC liver metastasis, was identified. Taken together, these results demonstrated that HOXA11-AS is a potential biomarker and molecular therapy target in CRC.

Breast cancer. Breast cancer (BC) is one of the most frequent causes of cancer-associated mortality in women worldwide (102,103). Although great progress has been made in earlier diagnosis of this disease and in the effective of systemic therapies, the overall prognosis of BC remains unsatisfactory. In particular, distant metastasis is a barrier for successful treatment (104-106). Su and Hu (107) discovered that lncRNA HOXA11-AS is overexpressed in human BC, and the expression of HOXA11-AS is markedly associated with metastasis, tumor size and TNM staging. Clinical statistics revealed that the expression of HOXA11-AS was correlated with Ki-67 protein and human epidermal growth factor receptor (HER2), but not with estrogen receptor (ER) or progesterone receptor (PR). Their results indicated that decreased expression levels of HOXA11-AS in human BC led to suppression in the rates of cell proliferation, migration and invasion, and cell cycle arrest at the G0/G1 phase. Li *et al* (108) also reported that low levels of HOXA11-AS expression inhibited cell proliferation and induced tumor cell apoptosis by inducing cell cycle arrest at the G0/G1 stage. By contrast, high levels of HOXA11-AS expression facilitated metastasis and invasion both *in vitro* and *in vivo* by exerting an influence on EMT in BC (the abovementioned mechanisms are shown in Fig. 2E). Note that the above articles (107,108) only determined the involvement of HOXA11-AS in these processes; the specific mechanisms have yet to be properly elucidated. These studies, however, have confirmed that HOXA11-AS exerts carcinogenic effects in BC, thereby providing some novel insights for even earlier diagnosis in the future, and for the therapy of BC.

Gastric cancer. Gastric cancer (GC) ranks the fifth among the most common types of cancer, and is the third leading cause of cancer mortality (109). GC is more common in men: The mortality rate in men is 2-fold higher compared with women (1). In men, GC is the most commonly occurring gastrointestinal malignancy in East Asia, the most common cancer in several Western Asian countries and the main cause of cancer deaths (110,111). Despite advances in surgical techniques and the successful development of targeted drugs, the 5-year OS rate, however, remains unsatisfactory, and the majority of patients are diagnosed with advanced cancer along with lymphatic metastasis (98). Sun *et al* (112) reported that HOXA11-AS is significantly upregulated in GC tissues. High levels of HOXA11-AS expression are closely related to poor differentiation, larger tumor size, lymph node metastasis and advanced pathological stage in GC. Researchers also found

that progression-free survival (PFS) and OS rates in excess of 3 years in the group with high levels of HOXA11-AS expression were lower compared with the group with low levels of HOXA11-AS expression. HOXA11-AS overexpression leads to increased rates of cell growth, migration and invasion, and inhibition of apoptosis in GC. By contrast, Liu *et al* (113) reported that HOXA11-AS knockdown induces G0/G1 phase arrest in GC cells and decreases GC cell metastasis, migration and invasion, both *in vitro* and *in vivo*.

In terms of the underlying mechanism, Sun *et al* (112) demonstrated that HOXA11-AS acts as a protein scaffold to recruit EZH2, accompanied by DNMT1 or LSD1. In addition, HOXA11-AS functions as a miR-1297 sponge, thereby regulating the translation of EZH2, a direct miR-1297 target. Knockdown of HOXA11-AS increases the expression of the tumor suppressors, serine protease 8 (PRSS8) and Krüppel-like Factor 2 (KLF2), leading to the promotion of cell proliferation and invasion and inhibiting apoptosis in GC cells. Those authors reported that EZH2 can directly bind to the promoter regions of PRSS8 and KLF2 and DNMT1 can directly bind to the promoter region of KLF2 to stimulate H3K27me3 modifications. LSD1 is also able to directly bind to the promoter region of PRSS8 to mediate H3K4 demethylation. Knockdown of HOXA11-AS suppresses the binding capability of DNA with several chromatin modification factors (namely, PRC2, LSD1 and DNMT1). Moreover, Sun *et al* (112) identified the potential regulator E2F1, which can directly bind to the promoter region of HOXA11-AS and regulate the transcription of HOXA11-AS. In addition, HOXA11-AS can function as an oncogene by regulating the miR-1297/EZH2 and HOXA11-AS-EZH2/DNMT1/LSD1-KLF2/PRSS8 pathways to promote GC cell proliferation, migration and invasion and inhibit apoptosis. Liu *et al* (113) identified that HOXA11-AS enhances β -catenin transcription by interacting with WD repeat-containing protein 5 (WDR5), and p21 transcription is subsequently inhibited via binding with EZH2. In addition, HOXA11-AS can interact with double-stranded RNA-binding protein staufen homolog 1 (STAU1) to promote KLF2 mRNA degradation. These findings revealed that HOXA11-AS may serve as an oncogene by modulating the HOXA11-AS-WDR5/EZH2/STAU1- β -catenin/p21/KLF2 pathway (Fig. 3A). Taken together, these results have revealed that HOXA11-AS can function as an oncogene in GC cells, further elucidating the role of HOXA11-AS in promoting better diagnosis of the disease, and developing further how lncRNA may be used in treatments of GC.

Renal cancer. Clear cell renal cell carcinoma (ccRCC) is a common malignant tumor of the urinary system, accounting for >80% of all types of RC (114). No fewer than 209,000 new cases of ccRCC are reported each year, and among these cases, approximately 25-30% of the patients present with distant metastasis and 40% of patients have local recurrence after the initial diagnosis (115,116). The biological behavior of ccRCC is extremely complex and the underlying molecular mechanisms have yet to be fully elucidated, factors which explain how prognosis is both poor and difficult to predict (117). Recently, Yang *et al* (118) found that HOXA11-AS was clearly upregulated in ccRCC cell lines and tissues, and high HOXA11-AS expression levels were very closely correlated with lymph node metastasis, tumor stage and advanced clinical stage. Downregulation of the HOXA11-AS transcript

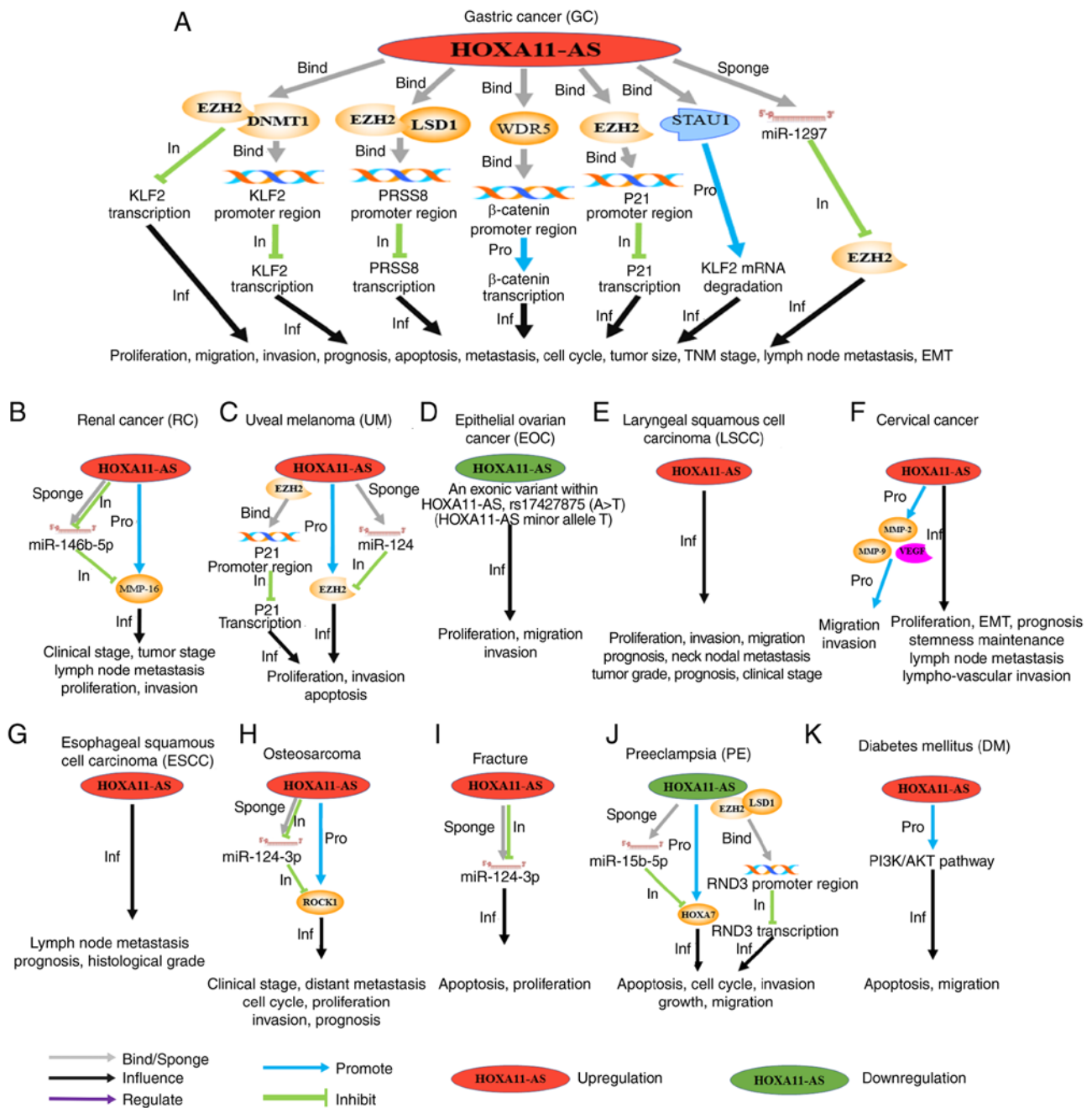


Figure 3. Schematic diagram, introducing in detail the molecular mechanisms, clinical values and cell phenotypes affected by HOXA11-AS in different types of tumors, including (A) GC, (B) RC, (C) UM, (D) EOC, (E) LSCC, (F) CC, (G) ESCC, (H) osteosarcoma, (I) fracture, (J) PE and (K) DM. 'Upregulation'/'downregulation' indicates that the expression level of HOXA11-AS in such a tumor was increased/decreased compared with normal tissues. The gray arrows ('bind/sponge') indicate that HOXA11-AS binds to the promoter region of a gene or, as a sponge, binds to a miRNA. The black arrows ('Inf') indicate that HOXA11-AS affects the phenotypes and the clinical characteristics of the cancer under consideration. The blue ('Pro') and green ('In') arrows indicate the promoting or inhibitory effects on the downstream genes, respectively. The purple arrows ('Reg') indicate the regulatory effects on the downstream pathway. GC, gastric cancer; RC, renal cancer; UM, uveal melanoma; EOC, epithelial ovarian cancer; LSCC, laryngeal squamous cell carcinoma; ESCC, esophageal squamous cell carcinoma; PE, pre-eclampsia; DM, diabetes mellitus; HOXA11-AS, HOXA11 antisense RNA.

led to a marked decrease in the growth, proliferation, invasion, and EMT of the ccRCC cells. Regarding the mechanism, Yang *et al* (118) discovered that HOXA11-AS functions as a ceRNA to suppress the expression of miR-146b-5p, which subsequently modulates the expression of its downstream target, matrix metalloproteinase-16 (MMP16) in RC. Therefore, HOXA11-AS promotes RC cell invasion and proliferation by regulating the miR-146b-5p/MMP16 pathway (Fig. 3B). During this process, HOXA11-AS may

function as an oncogene in ccRCC and may therefore represent an efficient therapeutic target for RCC.

Uveal melanoma. Uveal melanoma (UM) ranks first among primary intraocular malignant tumors in adults, and the uvea ranks second among the common sites of primary melanoma (119,120). The metastatic rate of UM is very high, and UM ultimately spreads to the liver in up to 50% of patients (121). Lu *et al* (122) discovered that HOXA11-AS is overexpressed in

UM, and HOXA11-AS is shown to enhance the rates of UM cell proliferation and invasion, while repressing apoptosis. Authors of that study also reported that HOXA11-AS recruits EZH2 to the promoter region of p21 and mediates H3K27me3 to suppress its transcription. Furthermore, HOXA11-AS acts as a ceRNA for miR-124, which directly targets EZH2, and the cell proliferation and invasion-increasing effects of HOXA11-AS were attenuated upon miR-124 overexpression (Fig. 3C). Taken together, these studies indicate that HOXA11-AS has an oncogenic role through regulating the HOXA11-AS/EZH2/p21 and miR-124/EZH2 pathways in UM tumorigenesis, and HOXA11-AS may also represent a potential therapeutic target for treatment of UM.

Epithelial ovarian cancer. Ovarian malignancies are among the most commonly occurring malignancies in female reproductive organs. The most frequent ovarian malignancy type is cutaneous carcinoma, followed by malignant germ cell tumor. Among these malignant gynecological tumors, the mortality rate of epithelial ovarian cancer (EOC) is the highest, posing a serious threat to women's health (1). A large number of studies have shown that not only HOXA11-AS, but also many other lncRNAs act as oncogenes or tumor suppressor genes in different cancers. Ignarski *et al* (123) reported that the expression pattern of lncRNA genes is far more tissue- and cell-type specific than is the case for protein coding genes. HOXA11-AS exerts opposing effects in different types of cancer. Such expressional and functional discrepancies of HOXA11-AS in different types of cancer could be caused by distinct gene expression backgrounds in different tumors (124). For example, in EOC, HOXA11-AS can act as a tumor suppressor gene, which is different from the tumor mentioned above.

It has been reported that common germline genetic variants or single nucleotide polymorphisms (SNPs) affecting lncRNAs are conducive to the development of various types of cancer (125), such as EOC (126). Richards *et al* (126) reported that overexpression of HOXA11-AS results in a clear reduction in cell proliferation and survival, which are two main cellular processes associated with EOC development in both common and minor allele constructs. In particular, the existence of minor allele constructs markedly reduced the proliferation and survival of EOC cells compared with the common allele, and the expression of both alleles served to diminish cell migration and invasion. However, compared with the common allele, the minor allele exerted a more pronounced suppressive effect in both assays. Richards *et al* (126) found that the minor allele repressed the carcinogenic phenotypes to a greater extent compared with the common allele in EOC cells. The finding has identified a greatly decreased risk of EOC among women who have the HOXA11-AS rs17427875 T allele (126). In EOC tumor tissue, HOXA11-AS expression was reduced by over 60% on average compared with normal ovarian tissue. Richards *et al* (126) also found HOXA11-AS cannot exert any influence upon HOXA11 and HOXA13 (Fig. 3D). Thus, these studies suggest that HOXA11-AS may function as a tumor suppressor gene in EOC.

Laryngeal squamous cell carcinoma. Laryngeal squamous cell carcinoma (LSCC) is a commonly occurring malignant tumor of the upper respiratory tract. Laryngeal carcinoma is ranked

second in terms of the most frequently occurring malignant tumors in the head and neck (127). Qu *et al* (128) found that the expression levels of HOXA11-AS are closely correlated with pathological grade, T (tumor) grade, clinical stage, neck nodal metastasis and advanced tumors of grade T3 to T4 in LSCC. Furthermore, advanced clinical stages, poor prognosis, poor differentiation and lymph node metastasis were identified in patients who expressed higher levels of HOXA11-AS. Authors of that study also found that HOXA11-AS was able to promote LSCC cell proliferation, invasion and migration (Fig. 3E). Notably, only the general effects attributable to HOXA11-AS were identified in the study of Qu *et al* (128), and the specific mechanism involved requires further investigation. However, their results have demonstrated that HOXA11-AS may function as an oncogene, suggesting that it is a potential novel biomarker and an efficient therapeutic target in LSCC.

Cervical cancer. It is estimated that CC is the fourth leading cause of cancer mortality, and ranks fourth out of the most commonly diagnosed cancers among women. In 2018, there were approximately 570,000 CC cases and 311,000 cancer-associated deaths worldwide (1). In fact, in terms of its incidence and the mortality rates, CC is ranked second behind BC (1). Kim *et al* (129) reported that the expression of HOXA11-AS is specifically upregulated in CC, and OS and 5-year survival rates are both reduced in CC patients with HOXA11-AS overexpression. Cox multivariate proportional hazards analysis revealed that nodal metastasis, tumor stage, and HOXA11-AS are independent prognosticators of OS. Those authors found that HOXA11-AS is associated with enhanced cell proliferation, also leading to increased rates of cell migration and invasion in CC. In terms of the underlying mechanism, HOXA11-AS promotes CC cell migration and invasion by upregulating the levels of MMP-9, MMP-2, and vascular endothelial growth factor (VEGF), and disordering of the EMT-associated genes suggested that HOXA11-AS may be involved in cell migration and invasion in CC (Fig. 3F). Kim *et al* (129) also showed that HOXA11-AS can promote activation of the genetic program that supports the cancer stem cell (CSC) phenotype and improves EMT, suggesting that HOXA11-AS may function as an oncogene in CC. Thus, HOXA11-AS may be a therapeutic target in the search for improved treatments for CC.

Esophageal squamous cell carcinoma. Among the different types of cancer, ESCC is ranked seventh in terms of its incidence and sixth in terms of overall mortality, which means that 1 out of every 20 cases of cancer-associated mortality in 2018 was estimated to have been caused by ESCC (1). Sun *et al* (130) found that high expression levels of HOXA11-AS are correlated with lymph node metastasis and histological grade in patients with ESCC. Compared with those patients with HOXA11-AS overexpression, patients with low HOXA11-AS expression exhibited both increased median disease-free survival (DFS) and median OS. Sun *et al* (130) found that lymph node metastasis and the expression of HOXA11-AS were independent poor prognosis factors in patients with ESCC (Fig. 3G). Taking all these findings into consideration, HOXA11-AS may have an oncogenic role in ESCC, and therefore HOXA11-AS may also represent a predictive marker in postoperative ESCC patients.

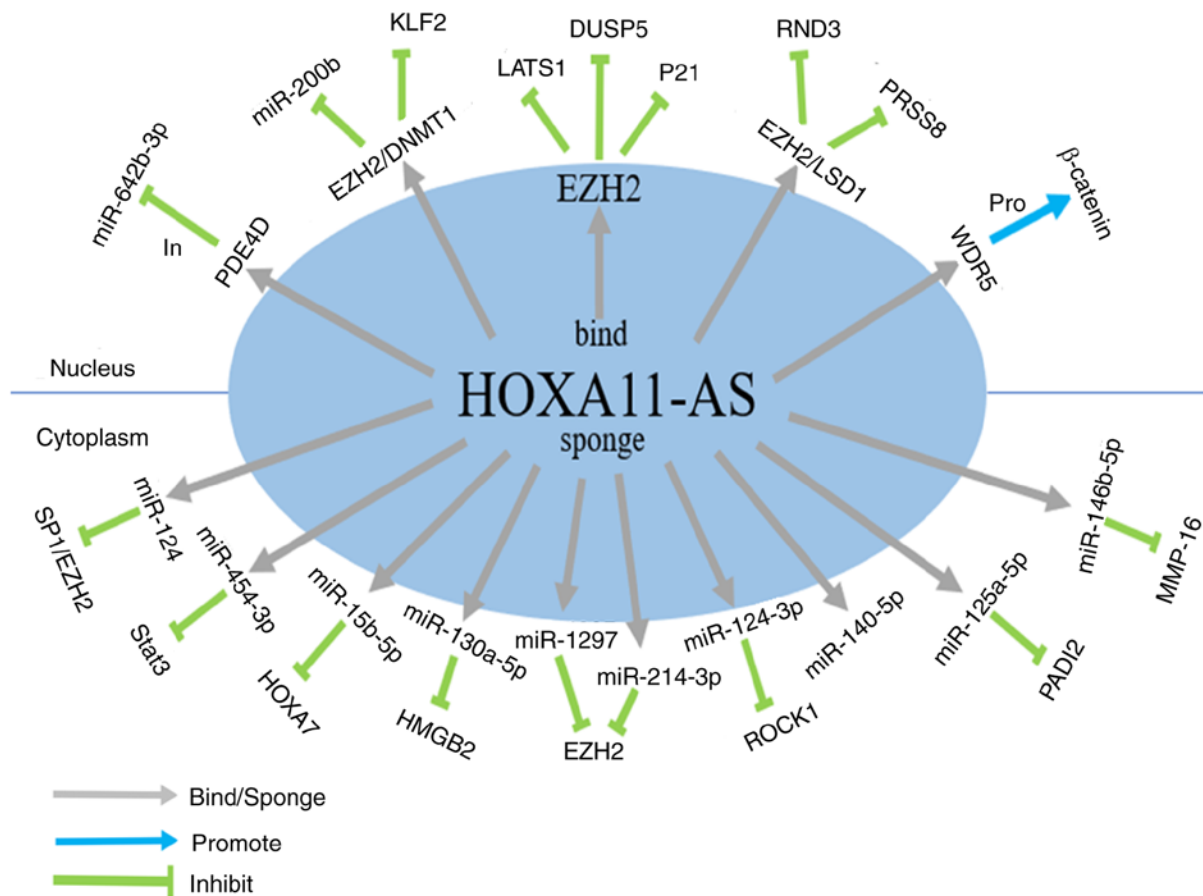


Figure 4. Schematic diagram summarizing the major molecular mechanisms of HOXA11-AS involved in different types of disease. The molecular mechanisms depicted can be divided into two categories: i) HOXA11-AS functions as molecular scaffold in the nucleus and ii) functions as ceRNA in the cytoplasm. The gray arrows ('bind'/'sponge') indicate that HOXA11-AS binds to the promoter region of genes or, as a sponge, binds to miRNAs. The blue ('Pro')/green ('In') arrows indicate the promotion or inhibition effects on the downstream genes, respectively. HOXA11-AS, HOXA11 antisense RNA.

Osteosarcoma. Osteosarcoma is ranked the first among the most commonly occurring types of primary malignant bone cancer, and is placed second in terms of cancer-associated deaths in pediatrics (131). lncRNAs are well known to be involved in the development of most tumors. Cui *et al* (60) found that a high level of HOXA11-AS expression is correlated with distant metastasis, reduced OS and advanced clinical stage in patients with osteosarcoma. Their study suggested that HOXA11-AS knockdown in osteosarcoma induces cell cycle arrest at the G0/G1 phase, and HOXA11-AS overexpression led to a substantial improvement in cell invasion and growth rates in osteosarcoma cells via the competitive binding of miR-124-3p, which targets Rho-associated, coiled-coil-containing protein kinase 1 (ROCK1) (Fig. 3H). In this manner, HOXA11-AS may exert oncogenic functions by regulating the miR-124-3p/ROCK1 pathway. Investigating the underlying mechanistic roles of the HOXA11-AS/miR-124-3p/ROCK1 pathway may be an important step in developing novel osteosarcoma therapeutic strategies.

Other diseases

Fracture. Given the ever-increasing aging population, fractures have become a serious health problem, constituting the most common injuries sustained worldwide. Despite the body being capable of healing fractures, many risk factors have substantially delaying effects on the process of fracture healing,

including advanced age, smoking, diabetes mellitus (DM) and anti-cancer drugs (132). Therefore, it is imperative to explore the mechanisms underlying fracture healing, notably in patients with these factors, is an urgent requirement. Numerous studies have been published that demonstrate how lncRNAs are able to participate in the occurrence and development of many diseases, including fracture healing (133). Wang *et al* (133) found that HOXA11-AS overexpression led to a suppression of OS-732 osteoblast proliferation and improved apoptosis. In addition, HOXA11-AS can act as a ceRNA by sequestering miR-124-3p to inhibit cell proliferation and enhance apoptosis (Fig. 3I). These results may provide a novel perspective for deciphering the mechanism of fracture healing.

Preeclampsia. Preeclampsia (PE) is the leading cause of pregnancy-associated death and fetal defects (134). PE is characterized as having a blood pressure exceeding 140/90 mmHg from the 20th week of pregnancy onwards. Between 3 and 5% of pregnant women experience PE, especially in developing countries (135). Xu *et al* (136) found that HOXA11-AS expression was markedly downregulated in pre-eclamptic placental tissues, and reducing HOXA11-AS expression led to a clear inhibition of trophoblast cell growth and migration. Mechanistically, those authors revealed that HOXA11-AS recruits LSD1 and EZH2 proteins to the RND3 gene promoter region in the nucleus to repress its expression in trophoblast

Table I. HOXA11-AS expression pattern, function and clinical value in human.

Cancer types	Expression level	Gene types	Number of cases	Cell lines involved	Genes, RNAs and proteins interact with HOXA11-AS	Signaling pathways	HOXA11-AS molecular mechanisms	HOXA11-AS binding sites (5'→3')	Affected phenotypes	Association with patients' outcome	(Refs.)
Lung cancer	Up	Oncogene	Three pairs NSCLC tissues (HOXA11-AS and HOXA11-AS RNAi)	A549	DOCK8	TGF-beta pathway					Zhang <i>et al</i> (2016) (72)
	Up	Oncogene	287 lung adenocarcinoma cases vs. 12 non-cancerous lung cases and 463 lung squamous cell carcinoma cases vs. 12 non-cancerous lung cases	PC9, A549, H460 and H1299		ErbB, MAPK, Calcium, PI3K-Akt and P53 signaling pathways			Proliferation, migration, invasion, apoptosis, tumorigenic angiogenic ability		Zhang <i>et al</i> (2017) (73)
	Up	Oncogene	78 pairs NSCLC tissues and corresponding adjacent normal tissues	A549, H1299	miR-124	HOXA11-AS/miR-124/Sp1 pathway	ceRNA	509-515 (NR_002795.2) (GTGCCCTT)	Proliferation, invasion, EMT	Tumor size, lymph node metastasis	Yu <i>et al</i> (2017) (47)
	Up	Oncogene	78 pairs NSCLC tissues and adjacent normal tissue samples	A549, H1299, 95D, 16HBE	EZH2, DNMT1, miR-200b		Scaffold		Invasion, EMT	Prognosis, lymph node metastasis, TNM stage	Chen <i>et al</i> (2017) (75)
	Up	Oncogene	Cell line study	A549, H157, A549-CR, H157-CR (cisplatin-Resistant cells), HEK-293T	miR-454-3p	HOXA11-AS/miR-454-3p/Stat3 pathway	ceRNA	1057-1075 (ENST00000520395.2) (CTAXXXXXXTATT-GCACT)	Proliferation, migration, apoptosis, EMT	Prognosis	Zhao <i>et al</i> (2018) (76)
	Up	Oncogene	Cell line study	A549	miR-642b-3p, PDE4D	HOXA11-AS/miR-642b-3p/PDE4D axis			ENST00000-520395.2		Zhang <i>et al</i> (2018) (74)
Liver cancer	Up	Oncogene	72 pairs HCC tissues and its adjacent tissue specimens	HepG2, Hep3B, MHCC-97H	LAST1, EZH2		Scaffold		Proliferation, apoptosis, cell cycle progression, tumor formation ability		Yu <i>et al</i> (2017) (83)
	Up	Oncogene	66 pairs HCC tissues and adjacent normal tissues	HepG2, Hep3B	DUSP5, EZH2		Scaffold		Proliferation, apoptosis, cell cycle	Vascular invasion, cirrhosis, tumor size and edmondson grade, prognosis	Liu <i>et al</i> (2017) (82)
	Up	Oncogene	40 pairs of HCC samples and the adjacent noncancerous samples	Hep3B, MHCC97-H	miR-214-3p	HOXA11-AS/miR-214-3p axis			Proliferation, invasion, EMT		Zhan <i>et al</i> (2018) (84)

Table I. Continued.

Cancer types	Expression level	Gene types	Number of cases	Cell lines involved	Genes, RNAs and proteins interact with HOXA11-AS	Signaling pathways	HOXA11-AS molecular mechanisms	HOXA11-AS binding sites (5'→3')	Affected phenotypes	Association with patients' outcome	(Refs.)
Glioma	Up	Oncogene	220 glioma cases and 5 normal brain samples	U87 (ATCC), LN229, U251, HA					Proliferation, cell cycle	Grade, prognosis, molecular, subtypes	Wang <i>et al</i> (2016) (90)
	Up	Oncogene	43 cases of glioma tissues and normal brain tissues	SHG44, U251, HA	miR-140-5p	HOXA11-AS/ miR-140-5p axis	ceRNA	(HGNC 24957) (AAACCACT)	Proliferation, apoptosis, cell cycle	Prognosis	Cui <i>et al</i> (2017) (91)
	Up	Oncogene	45 pairs glioma tissues and the adjacent normal brain tissues	U251, U87 (ATCC), LN229, A172, NHA, HEK-293T, SHG-44	miR-214-3p, EZH2	HOXA11-AS/ miR-214-3p/ EZH2 axis	ceRNA	502-515 (NR_002795.2) (CXCXXXGTT-GCCTT)	Proliferation, migration, invasion, tumor growth	Prognosis, tumor size, grade	Xu <i>et al</i> (2017) (92)
	Up	Oncogene	43 pairs of glioma tissues and noncancerous tissues	U251, U87 (ATCC)	miR-130a-5p, HMGB2	miR-130a-5p/ HMGB2 pathway	ceRNA	1487-1494 (ENST0000520395.2) (ATTGCACT)	Proliferation, migration, invasion, apoptosis	Prognosis, advanced stage	Xu <i>et al</i> (2019) (93)
Colorectal cancer	Down	Suppressor gene	84 CRC tissues and adjacent non-cancerous tissues, in addition to 3 CRC cell lines and 1 human normal colorectal cell line.	CCD-18Co, HCT8, HCT116, RKO					Tumor size, TNM stage, lymph node metastasis, carcinoembryonic antigen level	Tumor size, TNM stage, lymph node metastasis, carcinoembryonic antigen level	Li <i>et al</i> (2016) (100)
	Up	Oncogene	30 primary CRC samples (15 patients with CRC) and liver metastasis and 15 patients with CRC without metastasis)	Colo205, Lovo, HCT116, SW620, Caco-2, SW480	miR-125a-5p, PADI2	HOXA11-AS/ miR-125a-5p/ PADI2 regulatory network	ceRNA	1482-1487 (NR_002795.2) (CCTGAG)	Migration, invasion	Liver metastasis	Chen <i>et al</i> (2017) (101)
Breast cancer	Up	Oncogene	100 pairs BC tissues and adjacent non-cancerous tissues	MCF10A, MDA-MB-231, MDA-MB-436, MCF7, T47D					Proliferation, migration, invasion, colony formation, cell cycle progression	Tumor size, metastasis, TNM stage, molecular subtypes	Su and Hu (2017) (107)
	Up	Oncogene	68 pairs breast cancer tissues and adjacent normal tissue specimens	MDA-MB-468, MDA-MB-231, SKBR3, MCF-10A					Migration, invasion, apoptosis, cell cycle progression, EMT	Metastasis	Li <i>et al</i> (2017) (108)

Table I. Continued.

Cancer types	Expression level	Gene types	Number of cases	Cell lines involved	Genes, RNAs and proteins interact with HOXA11-AS	Signaling pathways	HOXA11-AS molecular mechanisms	HOXA11-AS binding sites (5'→3')	Affected phenotypes	Association with patients' outcome	(Refs.)
Gastric cancer	Up	Oncogene	85 pairs gastric cancer and adjacent nontumor tissues	GES1, AGS	miR-1297, EZH2, LSD1, DNMT1	Cell-cell adhesion pathways, HOXA11-AS/miR-1297/EZH2 cross-talk	Scaffold ceRNA	457-469 (NR_002795.2) (CXXXXTXACTTGA) 5' region bind with EZH2 3' region bind with LSD1	Growth, proliferation, migration, invasion, apoptosis, tumorigenesis, tumor progression	Prognosis, tumor size, differentiation, pathologic stage, lymph node metastasis	Sun <i>et al</i> (2016) (112)
	Up	Oncogene	Cell line study	AGS	WDR5, STAU1, EZH2		Scaffold		Proliferation, migration, invasion, cell cycle progression, EMT	Metastasis	Liu <i>et al</i> (2017) (113)
Renal cancer	Up	Oncogene	103 pairs ccRCC specimens and adjacent nontumor tissues	ACHN, 786-O, A498, OSRC-2, HK-2	miR-146b-5p	miR-146b-5p/MMP16 axis.	ceRNA	15-42 (ENST00000522674.1) (AGCXXXGAXX XTCAXXXXGTT CTCA)	Growth, proliferation, invasion, EMT	Advanced clinical stage, tumor stage, lymph	Yang <i>et al</i> (2018) (118)
Uveal melanoma	Up	Oncogene	Five primary UM samples	C918, MUM-2B and D78	EZH2, miR-124		Scaffold ceRNA	509-515 (NR_002795.2) (GTGCCTT)	Growth, proliferation, invasion, apoptosis		Lu <i>et al</i> (2017) (122)
Epithelial ovarian cancer	Down	Suppressor gene	Case control study		HOXA11-AS minor allele T and common allele A				Proliferation, growth migration, invasion	Prognosis	Richards <i>et al</i> (2015) (126)
Laryngeal squamous cell carcinoma	Up	Oncogene	25 pairs cancerous and adjacent nontumor tissues	AMC-HN-8					Proliferation, growth migration, invasion	Grade, neck nodal metastasis, clinical stage, prognosis	Qu <i>et al</i> (2018) (128)
Cervical cancer	Up	Oncogene	92 cervical cancer tissues and 30 normal cervix samples	SiHa, HeLa, CaSki, ME-180, C33A and HOSE	MMP-9, MMP-2, and VEGF				Proliferation, growth, migration, invasion, sphere formation, EMT, stemness maintenance	Prognosis	Kim <i>et al</i> (2016) (129)

Table I. Continued.

Cancer types	Expression level	Gene types	Number of cases	Cell lines involved	Genes, RNAs and proteins interact with HOXA11-AS	Signaling pathways	HOXA11-AS molecular mechanisms	HOXA11-AS binding sites (5'→3')	Affected phenotypes	Association with patients' outcome	(Refs.)
Esophageal squamous cell carcinoma	Up	Oncogene	73 pairs ESCC tissues and adjacent tissue samples	HET-1A, EC109, EC9706						Histological grade, lymph node metastasis, prognosis	Sun <i>et al</i> (2018) (130)
Osteosarcoma	Up	Oncogene	51 pairs OS tissues and adjacent tissue samples	U2OS, MG-63, KHOS and NHost	ROCK1, miR-124-3p	HOXA11-AS/miR-124-3p/ROCK1 signaling axis	ceRNA	502-515 (NR_002795.2) (CXCXXXGTGCCTT)	Proliferation, invasion, cell cycle progression	Clinical stage, distant metastasis, prognosis	Cui <i>et al</i> (2017) (60)

cells. When the level of HOXA11-AS expression was reduced in trophoblast cells, its ability to bind to LSD1 and EZH2 was also reduced, leading to decreased LSD1 and EZH2 binding to the RND3 gene promoter region and decreasing the inhibitory effect on RND3, which suppresses cell growth and proliferation. Furthermore, HOXA11-AS facilitated the expression of HOXA7 in the cytoplasm via sequestration of miR-15b-5p, thus exerting an influence on trophoblast proliferation (Fig. 3J). These studies revealed that HOXA11-AS may have an oncogenic function via modulating the LSD1/EZH2-RND3 and HOXA11-AS/miR-15b-5p/HOXA7 pathways. Consequently, these results have verified that abnormal expression of HOXA11-AS is involved in the occurrence and development of PE, and that this lncRNA may function as a putative target for diagnosis and treatment in PE.

Diabetes mellitus (DM). With rapid economic development and aging of the population, the number of patients with DM is increasing annually. Persistent hyperglycemia induces hyperglycemia-associated complications that pose severe medical risks, such as diabetic arteriosclerosis (DAA), atherosclerosis (AS) and cardiomyopathy (137). Studies have revealed that the incidence of cardio-cerebrovascular diseases in DM patients is markedly higher than in non-DM patients. In view of the role of lncRNAs in a variety of different tumor types and diseases, researchers have also examined the role of lncRNA in diabetes. Jin *et al* (138) found that expression levels of HOXA11-AS and pro-inflammatory genes were substantially increased in carotid endarterectomy specimens of DM patients, and HOXA11-AS expression was also significantly increased in the carotid arteries of DM mice. Mechanistically, HOXA11-AS knockdown reduces the expression of proliferation-associated gene (*PCNA*), the cell cycle-related genes *p21* and *p53*, and platelet-derived growth factor (*PDGF*)-induced growth and migration of vascular smooth muscle cells (VSMCs) is repressed, significantly downregulating the expression of inflammation-associated genes in VSMCs induced by tumor necrosis factor- α (TNF- α). Moreover, in vascular endothelial cells (VECs), low expression levels of HOXA11-AS were shown to suppress the expression of TNF- α -induced pro-inflammatory genes and PDGF-induced vascular inflammation-related genes. Low expression levels of HOXA11-AS inhibited the PDGF-induced stimulation of the PI3K/AKT pathway by inhibiting the phosphorylation of PI3K and AKT in VSMCs and VECs (Fig. 3K). The biological functions of HOXA11-AS in DAA-induced inflammation should be further explored to identify potential new effective treatments for DAA.

3. Conclusion

In conclusion, an increasing number of studies have shown that lncRNAs are dysregulated in various types of cancer, and aberrant expression of lncRNAs is involved in the occurrence, development, and metastasis of cancer (139). lncRNAs function mainly by interacting with other DNA, RNA or protein molecules to exert their pre-transcriptional or post-transcriptional regulatory functions. At present, emerging in-depth studies are elucidating the regulatory effects of HOXA11-AS on a majority of different tumor types, including NSCLC, HCC and glioma,

although its mechanisms and targets are generally found not to be similar when comparing among the different malignancies. Table I summarizes HOXA11-AS expression patterns and its functional and clinical value in different types of human cancer. Additionally, functional characteristics and molecular mechanisms of HOXA11-AS in diverse types of cancer and other diseases are summarized in Fig. 4. Although many studies have investigated HOXA11-AS, much remains to be determined before we are in a position to fully understand the mechanism of HOXA11-AS in diseases including BC, ESCC and LSCC. However, with further research, HOXA11-AS is likely to gain in importance as a novel target and guide for the prevention, diagnosis and treatment of tumors and additional diseases.

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Availability of data and materials

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Authors' contributions

LH and YZ conceived the review. CW and LZ drafted the manuscript and revised it before submission. CW and HL collected the references. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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