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REVIEW

HOXA11-AS: a novel regulator in human cancer proliferation and metastasis

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Abstract: Multiple studies have demonstrated that lncRNAs extensively participate in human cancer proliferation and metastasis. Epigenetic modification, transcriptional and posttranscriptional regulatory mechanisms are involved in lncRNA-led tumorigenesis and transfer. Recently, a novel identified homeobox (HOX) A11 antisense lncRNA, *HOXA11-AS*, 1,628 bp in length, has been excessively highlighted to be an essential initiator and facilitator in the process of malignant tumor proliferation and metastasis. As found in many reports, *HOXA11-AS* can not only act as a molecular scaffold of PRC2, LSD1 and DNMT1 to epigenetically modify chromosomes in the nucleus but also occur as ceRNA competitively sponging miRNAs in the cytoplasm. Furthermore, *HOXA11-AS* may function as a potential biomarker for cancer diagnosis and prognosis. In this review, we summarize the evolvement and mechanisms of *HOXA11-AS* in proliferation and metastasis of various human cancers.

Keywords: *HOXA11-AS*, proliferation, metastasis, EMT, ceRNA, lncRNA, molecular scaffold

Introduction

Cell growth and aberrant proliferation is the inducer of tumor occurrence and development. Metastasis is the continuation and deterioration of cancer cell proliferation and is recognized as the most terrible feature of advanced malignant neoplasm and the major cause of death in cancer patients. Obviously, the process of tumor metastasis is extremely complicated, which contains a series of metastatic cascade.[1,2] The tumor cells initially fall off from the primary site, then experience local infiltration, vascular invasion, blood circulation, and survival, arrest in capillaries of distant organs, colonization starts and growth is renewed.[3,4] A large body of genes and their products have been reported to mediate metastatic initiation and progression, such as adhesion molecules, angiogenic factors, matrix metalloproteinases, chemokines and so on.[5–8] More recently, miRNAs and lncRNAs also emerge to be crucial regulators in cancer proliferation and metastasis.[9,10]

It is widely known that only 2% of the genome sequences is translated into proteins, while the remainder is the template for ncRNAs transcription.[11,12] Compared to miRNAs, lncRNAs exert more favorable functions in tumor malignant proliferation, invasion and migration. The novel lncRNA, *HOXA11-AS*, also known as HOXA11-AS1, is the homeobox (HOX) A11 antisense lncRNA. In the human genome, the HOX family of genes is characterized by highly conserved homeodomains. HOX genes are grouped into four clusters (A, B, C and D) located on four different chromosomes. *HOXA11-AS* gene maps to the HOXA gene cluster on chromosome 7p, which includes the protein-coding genes (*HOXA9*, *HOXA10*, *HOXA11* and *HOXA13*) and the genes for lncRNAs (*HOXA10-AS*, *HOXA11-AS* and *HOTTIP*).[13,14] As a *HOXA11*

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antisense lncRNA, *HOXA11-AS* may participate in embryo implantation, endometrial development and cervix carcinogenesis by regulating *HOXA11*.[15–17] Increasing evidences have shown that *HOXA11-AS* can be a novel regulator in the proliferation and metastasis of diverse human cancers.[18–21]

Research identifications prove that numerous lncRNAs can serve as molecular signals, decoys, guides and scaffolds, exerting their functional roles via epigenetic modification or transcriptional activation/suppression in the nucleus. For instance, lncRNA *GClnc1* promotes gastric tumorigenesis, invasiveness and metastasis by acting as a modular scaffold of WDR5 and KAT2A complexes and specifying the histone modification pattern on the target genes.[22] The lncRNA *MALAT1* can be a molecular decoy through binding to SFPQ and releasing the oncogene PTBP2 from SFPQ/PTBP2 complex, thus accelerating colorectal cancer (CRC) growth and metastasis.[23] In addition, lncRNAs also emerge as ceRNAs by sponging microRNAs, and sometimes bind with specific proteins to maintain mRNA stability or induce mRNA decay, thus participating in posttranscriptional processing in the cytoplasm.[24–26] Dramatically, *HOXA11-AS* can regulate human cancer cell growth and metastasis both transcriptionally and posttranscriptionally and turn to be cancer biomarkers and therapeutic targets.

In our review, we will summarize the biological functions, molecular mechanisms and clinical significance of *HOXA11-AS* in diverse human cancers.

HOXA11-AS in diverse human cancers

Non-small-cell lung cancer (NSCLC)

NSCLC accounts for ~80%–85% of lung cancer.[27] The survival rate of advanced NSCLC patients remains disappointing, which is attributed to the malignant invasion and migration in NSCLC.[28,29] lncRNA dysregulation in NSCLC has been demonstrated as one of the leading forces during NSCLC carcinogenesis and metastasis in several studies.[30,31] A recent study stated that no *HOXA11-AS* expression has been found in normal lung tissues.[32] Four other papers published online indicated that *HOXA11-AS* is significantly upregulated in NSCLC. Zhang et al found through a high-throughput microarray assay that the downstream gene profiles changed after *HOXA11-AS* knockdown in A549 cell line. Ectopic overexpression of *HOXA11-AS* was potentially associated with DOCK8 and TGF-beta pathway by The Cancer Genome Atlas database and bioinformatics analyses (Gene Ontology pathway, Kyoto Encyclopedia of Genes and Genomes and network analyses). In their other study, *HOXA11-AS* was proved to play a crucial role in NSCLC invasion, migration and proliferation. Collectively, both these manuscripts indicated the potential diagnostic value of *HOXA11-AS* in NSCLC.[33,34] Chen's team explored *HOXA11-AS* regulatory function in NSCLC epithelial–mesenchymal transition (EMT) process. Mechanically, *HOXA11-AS* could simultaneously interact with EZH2 and DNMT1, recruiting them to the *miR-200b* promoter regions, epigenetically repressing *miR-200b* expression.[18] Lastly, *HOXA11-AS* was also confirmed to be a ceRNA sponging for *miR-124* to regulate Sp1 expression, thus promoting NSCLC cell proliferation and invasion.[35] Collectively, these findings implicate that *HOXA11-AS* occurs as an oncogene promoting NSCLC growth and metastasis, and may be a pivotal target for NSCLC diagnosis and therapy.

Gastric cancer (GC)

In China, GC ranks second with high rates of morbidity and mortality, among all cancers.[36] The GC cells easily transfer and spread in spite of radical surgery or adjuvant chemotherapy; disappointingly, nearly 60% of postoperative patients show recurrence or metastasis.[37,38] Recently, we screened a GC-associated lncRNA *HOXA11-AS* through The Cancer Genome Atlas RNA sequencing data and other available microarray online data. *HOXA11-AS* was found to be significantly upregulated in human GC tissues, which predicts a terrible prognosis in GC patients with a high expression. Apparently, cell growth, migration and invasion were involved in *HOXA11-AS*-mediated GC cell phenotypes. Multilevel research revealed that *HOXA11-AS* was triggered by transcription factor E2F1 and emerged as a molecular scaffold of EZH2/LSD1/DNMT1 in GC cell nucleus. On the other side, *HOXA11-AS* occurred as a ceRNA sponging for *miR-1297*, antagonizing its ability to repress EZH2 protein translation.[39] On the basis of the above study, we further investigated by RNA immunoprecipitation analysis and found that *HOXA11-AS* could also bind with WDR5 and STAU1 in GC cells. Subsequently, HOXA11-AS-WDR5 was confirmed to promote *β-catenin* expression, HOXA11-AS-EZH2 could epigenetically silence *P21* expression, and HOXA11-AS-STAU1 was determined to induce *KLF2* mRNA degradation in GC cell cytoplasm.[19] In conclusion, our findings show that *HOXA11-AS* plays its carcinogenic regulatory role both transcriptionally and posttranscriptionally in GC.

CRC

CRC is another common gastrointestinal carcinoma and the fourth leading cause of cancer death around the world.[40,41] The key to treatment and prognosis is early detection, timely diagnosis and radical surgery. Unfortunately, it is already in an advanced stage when CRC is confirmed in a patient.[42] Recently, lncRNA *HOXA11-AS* has been reported as a tumor-suppressor gene or an oncogene in two independent CRC-relevant papers. In the first manuscript, the author found that *HOXA11-AS* was decreased in CRC tissues and cell lines. Clinicopathologic analysis further proved that *HOXA11-AS* downregulation was significantly related with CRC patients' tumor size, lymph node metastasis, TNM stage and carcinoembryonic antigen level, which indicated *HOXA11-AS* to be a tumor-suppressor gene in CRC.[43] Inversely, in Chen et al's study, *HOXA11-AS* was verified as a highly related oncogene to liver metastasis in CRC. In more detail, *HOXA11-AS* was significantly upregulated in 15 patients with liver metastasis and highly invasive cell lines; gain-/loss-of-function studies showed that *HOXA11-AS* promoted CRC cell migration and invasion; *HOXA11-AS* also functioned as an *miR-125a-5p* sponge ceRNA and indirectly influenced the expression levels of PADI2.[20] The different conclusions of these two studies may be attributed to the differences in the patients' samples collected and the selected cell types. In my opinion, *HOXA11-AS* overexpression in metastatic CRC and its downregulation in general/unassorted CRC including their separate functions should be further validated by more researchers.

Glioma

Glioma is one of the most common primary neoplasms in the central nervous system, accounting for nearly 50% of all intracranial primary tumors.[44] Recently, several studies have emphasized the important role of lncRNA *HOXA11-AS* in regulating glioma tumorigenesis and transfer. Xu et al demonstrated that *HOXA11-AS* overexpression promoted glioma cell growth and metastasis through serving as a ceRNA for *miR-214-3 p*.[45] Similarly, Cui et al's study also proved *HOXA11-AS* to be a ceRNA sponging *miR-140-5 p* in the process of glioma cell proliferation.[46] In addition, another paper published in *Cancer Lett* showed that *HOXA11-AS* acted as an oncogene in cell cycle progression in a series of bioinformatic analysis.[47] Statistically, these manuscripts together found that high expression of *HOXA11-AS* was closely correlated with shorter overall survival and poorer prognosis in patients with glioma, which suggests that *HOXA11-AS* is an effective prognostic marker in glioma patients.

Cervical cancer (CC)

CC is one of the most common gynecologic cancers, clinically due to persistent infection with human papilloma viruses.[48] In the recent 2 years, the rising star *HOXA11-AS* was demonstrated to be closely connected with CC proliferation, invasion, migration and patients' prognosis. Chen et al discovered CC-associated lncRNA *HOXA11-AS* by performing lncRNA microarray of three cervix cancer and normal cervix tissues. Furthermore, they found that *HOXA11-AS* regulated *HOXA11* expression in cervix carcinogenesis.[17] Besides, another team proved that overexpression of *HOXA11-AS* in CC was exactly relevant to EMT process by regulating EMT-related genes (*E-cadherin*, *β-catenin*, *Vimentin* and *Snail*). Noticeably, *HOXA11-AS* could promote sphere formation and maintain stemness in CC, which may contribute to CC cell proliferation, metastasis and recurrence.[49]

Breast cancer (BC)

BC has become one of the most frequent malignancies in women.[50] Obviously, distant metastasis is the leading cause of deterioration in BC patients.[51] Li et al lately found lncRNA *HOXA11-AS* to be an inducer in BC EMT process. *HOXA11-AS* was found to be highly expressed in BC tissue and cells. The functional experiments in vitro and in vivo manifested that *HOXA11-AS* knockdown could inhibit BC cell proliferation, invasion and migration. Interestingly, *HOXA11-AS* was involved in the EMT process by affecting the expression levels of *E-cadherin*, N-cadherin and *Vimentin*.[21]

Epithelial ovarian cancer (EOC)

EOC accounts for nearly 90% of all human ovarian tumors.[52] A recent study found a functional genetic variant in *HOXA11-AS* that could suppress EOC oncogenic phenotype. Firstly, the author discovered from genome-wide association study that *HOXA11-AS* SNP rs17427875 (A>T) could reduce the risk for serous EOC. Subsequently, transfection assays in vitro and in vivo suggested that *HOXA11-AS* rs17427875 minor allele inhibits EOC cell survival, migration and invasion.[53] This research provides a new insight for the regulatory effect of lncRNA genetic variant in cancer development.

Hepatocellular carcinoma (HCC)

Previous studies proved that hepatitis C and B virus infection, excessive drinking, toxins and other auxotrophic liver diseases were involved as the leading causes of HCC.[54,55] Lately, lncRNA-cancer-associated researches have pointed out that plenty of lncRNAs also participate in HCC progression.[56] As expected, *HOXA11-AS* was proved to be highly expressed in HCC tissues and cells. Functional experiments demonstrated that *HOXA11-AS* promoted HCC proliferation through regulating cell apoptosis and cell cycle progression. Mechanistically, *HOXA11-AS* could bind with EZH2 to epigenetically inhibit *LATS1* expression.[57] Also, Liu et al proved that *HOXA11-AS* could also recruit EZH2 to *DUSP5*'s promoter region and restrain the transcription of *DUSP5*.[58]

Uveal melanoma (UM)

UM ranks first in morbidity among intraocular tumors abroad and is second only to retinoblastoma in China. This malignancy is easily transferred and 85% is transferred to the liver.[59,60] Lu et al found that *HOXA11-AS* was upregulated in UM and could be an oncogene in UM malignant phenotype. Mechanistically, *HOXA11-AS* could not only bind with EZH2 to repress *P21* transcription but also sponge for *miR-124* simultaneously.[61]

Osteosarcoma (OS)

OS is the most common malignant primary bone tumor, which is characterized by the formation of neoplastic bone-like tissue. Pulmonary metastasis occurs within just a few months, and the survival rate is only 5%–20% after amputation.[62] The lncRNA *HOXA11-AS* was confirmed to be overexpressed in OS tissues and cells. *HOXA11-AS* upregulation was closely associated with cell proliferation and invasion. Moreover, *HOXA11-AS* could function as a ceRNA regulating *ROCK1* expression via sponging *miR-124-3 p* in OS. Clinically, high expression of *HOXA11-AS* was related to OS patients' advanced stage, distant metastasis and poor prognosis.[63]

HOXA11-AS can be a potential biomarker for cancer diagnosis and prognosis

Aforementioned reports prove that *HOXA11-AS* expression levels in majority of tumors are increased. Table 1 summarizes the *HOXA11-AS*-associated clinicopathologic features, such as patients' tumor size, TNM stage and lymph node metastasis, which emphasizes the evolvement of *HOXA11-AS* in human cancer diagnosis. As shown in Table 1, aberrant expression of *HOXA11-AS* is also implicated as a prognostic biomarker in different cancer types. In particular, Li et al[64] and Mu et al[65] separately conducted a meta-analysis exploring *HOXA11-AS* to be a potential biomarker for metastasis and patients' prognosis in malignancies.

Discussion

Malignant proliferation of cancer cells and metastasis propel the progression of carcinoma deterioration. Separately, cancer metastasis is a complicated multistep process that often contributes to patients' postoperative recurrence and poor prognosis. Recent theoretical and practical research states that EMT can elucidate partial reasons for cancer invasion and dissemination. The entire EMT process includes loss of epithelial cell characteristics and acquisition of mesenchymal characteristics. During this transformation, the mesenchymal markers increase, including *Snail*, Slug, N-cadherin and *Vimentin*. On the contrary, decreased *E-cadherin* is the most common epithelial marker in EMT.[66,67] Noticeably, EMT course is exactly included in partial *HOXA11-AS*-modulated metastasis of cancers such as NSCLC, CC, and BC. The expression levels of several canonical EMT molecular markers, *E-cadherin*, N-cadherin, *Snail*, *β-catenin* and *Vimentin*, were changed after loss of or gain of *HOXA11-AS*. The functional characteristics of *HOXA11-AS* in various human cancers are all summarized in Table 2.

The ceRNA theory serves as a posttranscriptional way, which can explain the regulatory mode of lncRNA–miRNA–mRNA. The lncRNAs function as ceRNAs sponging for miRNAs, thus affecting the expression levels of miRNAs target genes.[68,69] As expected, *HOXA11-AS* can sponge for various miRNAs in different cancers (Table 2). Certainly, apart from ceRNA-modulatory pattern, *HOXA11-AS* simultaneously interacts with EZH2/LSD1/DNMT1, epigenetically modifying the target genes in cancer.

Table 1 *HOXA11-AS* expression levels are associated with clinicopathologic features

Cancer types	Clinicopathologic features	References
Non-small-cell lung cancer	TNM stage, lymph node metastasis, poor prognosis, high diagnostic value	18, 33–35
Gastric cancer	Short survival, poor prognosis	39
Colorectal cancer	Diagnostic value, TNM stage, lymphatic metastasis, tumor size, CEA level	43
Glioma	Glioma grade, short survival, poor prognosis	45–47
Cervical cancer	TNM stage, nodal metastasis, poor prognosis	49
EOC	Reduced serous EOC risk	53
Osteosarcoma	Advanced clinical stage, distant metastasis, poor overall survival	63

Abbreviations: CEA, carcinoembryonic antigen; EOC, epithelial ovarian cancer; TNM, tumor node metastasis.

Table 2 The functional characteristics of *HOXA11-AS* in various human cancers

Cancer types	Functional effects	Related genes	Role	References
Non-small-cell lung cancer	Migration, invasion EMT process Proliferation Apoptosis Cell cycle	DOCK8, RSPO3, DMBT1, ADAMTS8, ZEB1, ZEB2, *Snail*, *E-cadherin*, N-cadherin, *miR-200b* *miR-124*, Sp1	Oncogene	18, 33–35
Gastric cancer	Migration, invasion Proliferation Cell cycle Apoptosis	PRSS8, *KLF2*, *miR-1297*, EZH2 *P21*, Cyclin D1, CDK2, *Vimentin*, *β-catenin*	Oncogene	19, 39
Colorectal cancer			Tumor suppressor gene	43
	Liver metastasis	*miR-125a-5p*, PADI2	Oncogene	20
Glioma	Migration, invasion Proliferation Apoptosis Cell cycle	*miR-214-3 p*, EZH2 *miR-140-5 p*	Oncogene	45–47
Cervical cancer	Migration, invasion EMT process Proliferation	VEGF, MMP-9, MMP-2, *E-cadherin* *β-catenin*, *Vimentin* *Snail*, *HOXA11*	Oncogene	17, 49
Breast cancer	Migration, invasion EMT process Proliferation Apoptosis Cell cycle	*E-cadherin*, *Vimentin* N-cadherin	Oncogene	21
Epithelial ovarian cancer	Migration, invasion Proliferation		Tumor suppressor gene	53
Hepatocellular carcinoma	Proliferation	*LATS1*, *DUSP5*	Oncogene	57, 58
Uveal melanoma	Invasion Cell growth Apoptosis	*P21*, *miR-124*	Oncogene	61
Osteosarcoma	Invasion Proliferation Cell cycle	*miR-124*-3 p, *ROCK1*	Oncogene	63

Abbreviation: EMT, epithelial–mesenchymal transition.

Besides relevant reports in tumor field, *HOXA11-AS* was also discussed to be a skin-related lncRNA, which was involved in Wnt pathways in keloids.[70] Additionally, *HOXA11-AS* was found to take part in the progression of fracture healing by sponging *miR-124*-3 p.[71] Moreover, *HOXA11-AS* also plays important roles in adipocyte differentiation and endometriosis in women.[72,73] To conclude, *HOXA11-AS* is a newly identified lncRNA in various human carcinomas and other diseases, but the functions and molecular mechanisms are still not fully characterized, which deserve to be further excavated in the future.

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Disclosure

The authors report no conflicts of interest in this work.

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