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HOXD-AS1: a novel oncogenic long intergenic non-coding RNA in humans

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Abstract. – OBJECTIVE: Long non-coding RNAs are an emerging special class of regulatory RNAs with more than 200 nucleotides that play vital roles in gene regulation, metabolism, drug resistance, cell differentiation, and other processes. These RNAs were also reported to be dysregulated in human disease, especially malignant tumors. However, the underlying mechanisms remain elusive. HOXD cluster antisense RNA 1 (HOXD-AS1), a recently discovered long non-coding RNA, is overexpressed in many cancers. We now review recent advances in understanding the function, role, regulation, and oncogenic properties of HOXD-AS1.

MATERIALS AND METHODS: A systematic literature review in PubMed of HOXD-AS1 and cancer-related articles in English, published until June 2018, was conducted.

RESULTS: The literature suggests that HOXD-AS1 is an oncogene that regulates diverse physiological and cellular processes such as proliferation, apoptosis, migration, invasion, metastasis, chemoresistance, epithelial to mesenchymal transition, and stem cell formation by interacting with various regulatory proteins and sequestering several microRNAs such as miR-608, miR-130a, and miR-217.

CONCLUSIONS: HOXD-AS1 may be a prognostic biomarker and potential therapeutic target for various tumor diagnosis and treatment.

Key Words:
LncRNA, HOXD-AS1, Cancer.

Introduction

Cancer is one of the most lethal diseases worldwide, with approximately 14.1 million new cases and 8.2 million deaths in 2012[1]. The incidence and mortality rates have also significantly increased in recent years, accompanying changes in patient demographics and risk factors. In addition, the expanded population of cancer survivors has amplified the disease burden, especially in less economically developed countries[2]. Although early detection, screening, and therapy have continuously advanced in recent decades, most patients do not respond to treatment and have a dismal prognosis. Hence, there is an urgent need to improve diagnostic accuracy at early stages and to identify new therapeutic targets by searching for cancer-specific biomarkers, identifying genes that accelerate cancer initiation and progression, and elucidating underlying molecular mechanisms[3]. It is now clear that much of our genome is "non-coding", but pervasively transcribed into RNA[4]. Following extensive research into these non-coding RNAs, many, especially long non-coding RNAs, are thought to have diverse functions[5-9]. Among them, long non-coding RNAs are a special class with length more than 200 nucleotides and that are generated from antisense, intergenic, or promoter-proximal regions. Today, more than 27,692 long non-coding RNAs have been identified from 15,767 human genes, following dramatic developments in bioinformatics and experimental technologies[10], such as tiling microarrays and whole genome sequencing[11,12]. Remarkably, many of these long non-coding RNAs regulate various cellular and physiological processes, including gene regulation, via different mechanisms. However, an emerging model now holds that the regulatory activity of non-coding RNAs mostly depends on modularization, *i.e.*, recruitment of various combinations of regulatory proteins and possibly RNA and DNA[13]. Long non-coding RNAs have also attracted increasing research attention because of their role in human diseases, especially malignant tumors[14]. HOXD cluster antisense RNA 1 (HOXD-AS1), also called HAGLR (HOXD antisense growth-associated long non-coding RNA), is a novel cancer-related long non-coding RNA mapped to human chromosome 2q31.2 and transcribed from a HOXD cluster. HOXD belongs to Homeobox genes that form

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A, B, C, and D clusters of 9–11 which conserved genes in four different *loci*[15]. Homeobox genes were initially identified in studies of homeosis in *Drosophila*, and are critical regulators of embryogenesis and organogenesis[16]. Indeed, homeobox mutations are closely linked to developmental disorders and defects in tissues and organs[17,18]. Currently, 231 non-coding RNAs have been identified from the four human homeobox *loci*[19], of which HOXD-AS1 is on the antisense strand between HOXD1 and HOXD3. Strikingly, large-scale surveys of clinical samples of hepatocellular carcinoma[20,21], non-small cell lung cancer[22], gastric cancer[23], osteosarcoma[24], ovarian cancer[25,26], bladder cancer[27], castration-resistant prostate cancer[28], neuroblastoma[29], glioma[30], melanoma[31], cervical cancer[32], and colorectal cancer[33] indicate that HOXD-AS1 is expressed more abundantly in cancer tissues than in normal tissues. Potentially, HOXD-AS1 may modify various signaling pathways as an oncogene or sequesters target microRNAs (miRNAs) as a ceRNA (competing endogenous RNA)[34-36], and thereby alters physiological, pathological or oncogenic processes, including cell proliferation, differentiation, apoptosis, invasion, and metastasis (Figure 1 and Table I). Thus, HOXD-AS1 is a potential diagnostic marker and therapeutic target in various cancers.

HOXD-AS1 in Cell Proliferation and Apoptosis

Liver cancer

Regulator of G protein signaling 3 (RGS3) belongs to a superfamily that negatively regulates G protein-coupled receptor signaling via the Gαq and Gαi proteins by integrating with the corresponding Gα subunits of heterotrimeric G proteins[37]. Moreover, RGS3 blocks MEK/ERK and Akt signaling, both of which are implicated in cancer initiation and progression[38]. Notably, HOXD-AS1 is overexpressed in clinical specimens of liver cancer and significantly inhibits apoptosis by suppressing RGS3 expression[20].

Osteosarcoma and gastric cancer

In contrast to other signal transducer and activator of transcription (STAT) proteins, STAT3 has broader functions in cell differentiation, proliferation, development, apoptosis, and inflammation[39]. However, STAT3 is frequently expressed at high levels in tumor cells and tissues, such that inhibiting STAT3 also inhibits growth and apoptosis in osteosarcoma cells[40-42]. Recently, HOXD-AS1 was implicated in osteosarcoma and gastric cancer as a STAT3 regulator[23-24]. For example, HOXD-AS1 overexpression in osteosarcoma cells may boost expression of STAT3 and its target proteins (cyclin D1, Bcl-2, and MMP-2) to promote cell proliferation, accelerate colony formation, and inhibit cell cycle arrest at G1 stage and apoptosis. Conversely, knockdown of HOXD-AS1 significantly represses gastric cancer cell growth by inactivating the JAK2/STAT3 pathway.

Melanoma

Runt-related transcription factors (RUNX), including RUNX3, regulate apoptosis and are implicated in an array of human cancers[31,43-46]. For example, RUNX3 was found to suppress melanoma, lung, bladder, and gastric cancer[47]. By contrast, HOXD-AS1 stimulates melanoma cell proliferation and growth by suppressing RUNX3 expression via binding to EZH2[31].

Ovarian cancer

miR-608 regulates proliferation or apoptosis in multiple cancer cells by directly targeting NAA10[48], EGFR, Bcl-xL, MET[49], migration inhibitory factor[50], or AKT/FOXO3a signaling[51]. On the other hand, HOXD-AS1 is upregulated in both ovarian cancer tissues and cell lines, and functions as an oncogene that promotes cell proliferation and colony formation through the miR-608/FZD4 axis[25]. HOXD-AS1 also promotes cell proliferation in epithelial ovarian cancer by targeting miR-133a-3p and activating Wnt/β-catenin signaling[26], of which the latter is one of the most frequently dysregulated in cancers. Accumulating evidence also suggests that the former is a tumor suppressor against several cancers[52, 53].

Cervical cancer

The RAS–RAF–MEK–ERK pathway is a conserved cascade that regulates cell proliferation and survival[54]. However, HOXD-AS1 knockdown significantly suppresses cervical cancer cell proliferation, colony formation, and RAS/ERK signaling *in vitro*[32].

Non-small cell lung cancer

Since its discovery in the human genome at 9q33.2 in 2002[55], miR-147a, a homolog of miR-147, has been shown to potentially inhibit cell proliferation and migration by regulating cell cycle-related proteins, including pRB, CycB, CycA, and Cdk6[22,56]. Conversely, HOXD-AS1 was demonstrated to promote proliferation and inhibit

apoptosis in non-small cell lung cancer by suppressing miR-147a and upregulating pRB[22].

Bladder cancer and castration-resistant prostate cancer

HOXD-AS1 overexpression promotes cell proliferation/migration and inhibits apoptosis in bladder cancer cells *in vitro*. Accordingly, a synthetic tetracycline-controllable shRNA that artificially suppresses HOXD-AS1 also inhibits bladder cancer progression[27]. Similarly, HOXD-AS1 promotes proliferation and chemoresistance in castration-resistant prostate cancer cells via WDR5, which mediates H3K4me3 marking at promoters of target genes.

HOXD-AS1 in Invasion and Metastasis

HOXD-AS1 regulates signaling pathways or miRNAs that control not only proliferation or apoptosis, but also invasion, migration, metastasis, and drug resistance. Accordingly, HOXD-AS1 is tightly linked to metastatic and invasive

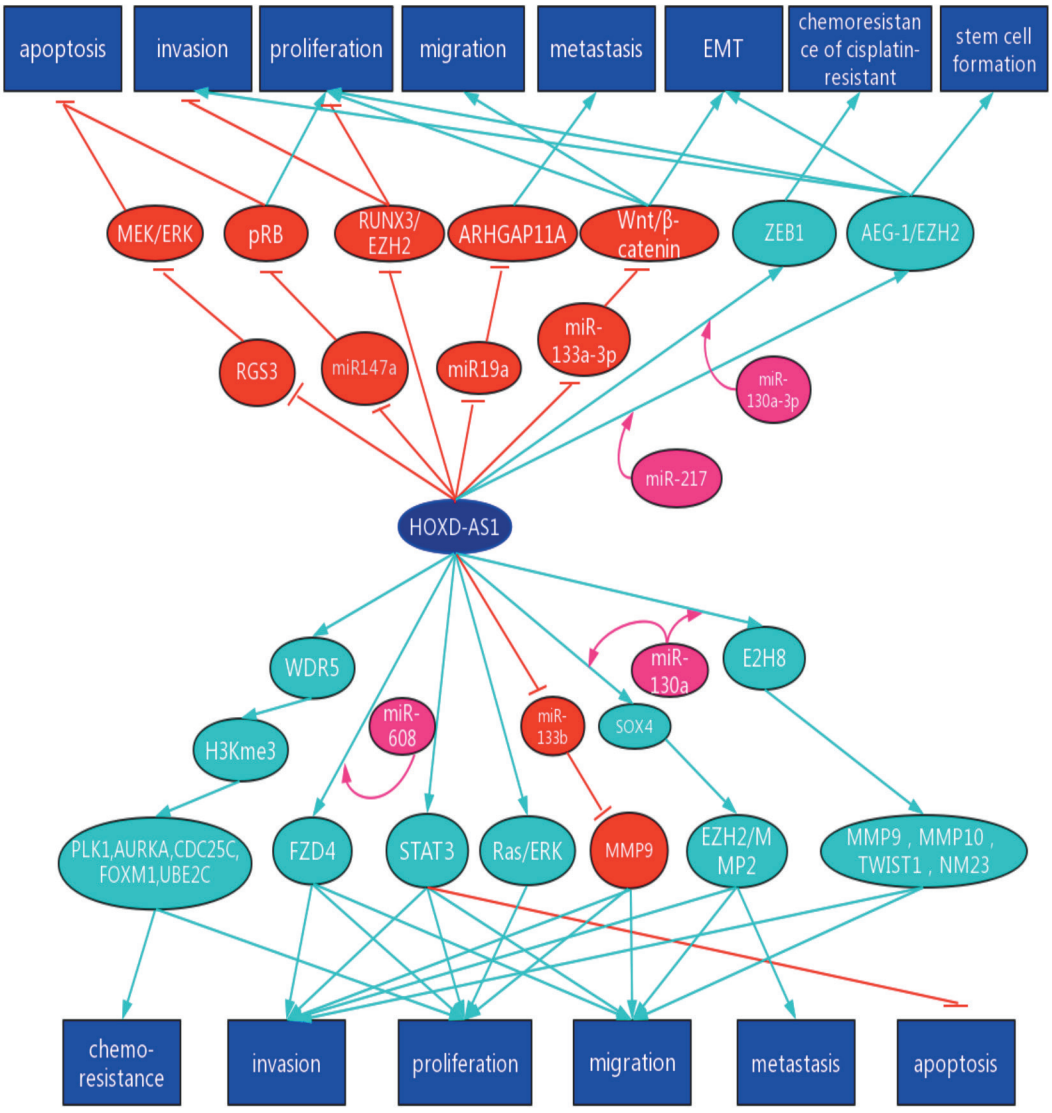

Figure 1. Regulation by HOXD-AS1. As an oncogene, HOXD-AS1 regulates processes such as proliferation, apoptosis, migration, invasion, metastasis, chemoresistance, epithelial to mesenchymal transition, and stem cell formation by assembling various combinations of regulatory proteins (WDR5, SOX4,E 2H8, RGS3, STAT3) and possibly RNA (miR-147a, miR19a, miR133a-3p, miR133b). These complexes alter signaling pathways (Ras/ERK, PI3K/ATK, Wnt/β-catenin, RUNX3) or related proteins (MMP9, pRB, ARHGAP11A). HOXD-AS1 may modulate other processes as an endogenous competing RNA that sequester miRNAs such as miR-608, miR-130a, and miR-217.

Table I. HOXD-AS1 and cancer.

Cancer type	Role	Function (Year)	Clinicopathological features	Related gene/miRNA	Signaling pathway/ Target protein	Reference
Hepatocellular carcinoma	Oncogene	Metastasis	Poor survival, higher tumor stage, PVTT tumor invasion	miR-19a	ARHGAP11A	Lu et al[20]
Hepatocellular carcinoma	Oncogene	Apoptosis (2017)	Poor survival	RGS3	MEK/ERK	Lu et al[20]
Osteosarcoma	Oncogene	Proliferation, migration, invasion, cell cycle arrest at G1, apoptosis (2018)	Poor survival, tumor- node-metastasis stage, lymph node invasion	STAT3	CyclinD1, Bcl-2, MMP2	Qu et al[24]
Melanoma	Oncogene	Proliferation, invasion (2017)	Poor survival	RUNX3	EZH2	Zhang et al[31]
Ovarian cancer	Oncogene	Proliferation, migration, invasion (2018)	Poor prognosis	miR-608	FZD4	Wang et al[25]
Ovarian cancer	Oncogene	Proliferation, invasion, epithelial-mesenchymal transition (2017)	Poor prognosis, FIGO stage, lymph node metastasis	miR-133a-3p	Wnt/β-catenin	Zhang et al[26]
Ovarian cancer		Proliferation, colony formation (2017)	Tumor-node-metastasis stage, lymphovascular invasion, lymph node metastasis, recurrence		Ras/ERK	Hu et al[32]
Glioma	Oncogene, ceRNA	Migration, invasion, metastasis (2018)		miR-130a	E2F8	Chen et al[30]
Thyroid cancer		2017	Clinical stage			Du et al[73]
Non-small cell lung cancer	Oncogene, ceRNA	Proliferation, apoptosis (2017)	Tumor size, tumor stage, recurrence, survival rate	miR-147a	prB	Wang et al[22]
Neuroblastoma	Potential prognostic biomarker	Angiogenesis, inflammation (2014)		Genes in retinoic acid signaling, angiogenesis, inflammation	PI3K/Akt	Yarmishyn et al[29]
Gastric cancer	Oncogene	Proliferation, colony formation (2017)	Tumor size, invasion depth, tumor-node- metastasis stage, regional, lymphatic, distant metastasis		JAK2/STAT3	Zheng et al[23]

Table continued

Table I. *Continued.* HOXD-AS1 and cancer.

Cancer type	Role	Function (Year)	Clinicopathological features	Related gene/miRNA	Signaling pathway/ Target protein	Reference
Castration- resistant prostate cancer	Oncogene	Proliferation, castration resistance, chemoresistance (2017)	Gleason score, T stage, lymph node metastasis, progression-free survival	PLK1, AURKA, CDC25C, FOXM1, UBE2C	WDR5/H3K4me3	Gu et al[28]
Bladder cancer	Oncogene	Proliferation, migration, apoptosis (2016)	Tumor size, histological grade, TNM stage			Li et al[27]
Liver cancer	Oncogene, ceRNA	Migration, invasion, metastasis (2017)	Poor prognosis, high tumor node metastasis stage, survival rate	miR-130a-3p	SOX4/EZH2, MMP2	Wang et al[21]
Colorectal cancer	Oncogene, ceRNA	Proliferation, invasion, epithelial-mesenchymal transition, stem cell formation (2018)	Poor prognosis	miR-217	AEG-1, EZH2	Li et al[33]
Non-small cell lung cancer	Oncogene	Proliferation, migration, invasion (2018)	Lymph node metastasis, high tumor node metastasis (TNM) stage, and poor overall survival rate	miR-133b	MMP9	Huan et al[74]
Cervical cancer	CeRNA	Chemoresistance of cisplatin-resistant cervical cancer cells (2018)	Poor prognosis	miR-130a-3p	ZEB1	Wen et al[75]

activities in several cancers, both of which are major determinants of prognosis.

Neuroblastoma and glioma

In SH-SY5Y cells stimulated with retinoic acid, a model of metastatic neuroblastoma, HOXD-AS1 controls PI3K/Akt-dependent cell differentiation. Further, knockdown experiments revealed that HOXD-AS1 regulates multiple, protein-coding, and clinically significant genes, including those involved in angiogenesis and inflammation, both hallmarks of metastatic cancer[22]. In addition, HOXD-AS1 binds miR-130a to boost expression of the transcription factor E2F8[30]. Notably, expression of E2F8 and other transcription factors are significantly correlated with expression of miRNAs[30]. E2F8 regulates metastasis-related genes such as matrix metalloproteinases (MMP9, MMP10, MMP14, and MMP15), TWIST1, and NM23, and it is aberrantly expressed in several tumors, including ovarian, hepatocellular, lung, and breast cancer[30,57]. Similarly, HOXD-AS1 overexpression promotes glioma cell migration and invasion *in vitro*[30].

Melanoma

Levels of RUNX3 are lower in primary melanomas than in normal tissues, and even lower in metastatic melanomas[46]. In contrast, HOXD-AS1 is remarkably upregulated in melanoma tissues than in skin tissues with a melanocytic nevus and promotes invasion *in vitro* via RUNX3[31].

Hepatocellular carcinoma

HOXD-AS1 promotes liver cancer metastasis and progression via miR19a/ARHGAP11A signaling[20]. Indeed, miR19a, a part of the miR-17-92 cluster, promotes the development of multiple cancers such as colon and gastric cancer[55,58], although it is anti-oncogenic in hepatocellular carcinoma and prevents metastasis or recurrence[59]. Similarly, HOXD-AS1 overexpression potentiates metastasis in liver cancer by competitively binding miR-130a-3p to protect SOX4, a critical regulator of tumor cell migration, invasion, tumorigenesis, and metastasis[60], against miRNA-mediated degradation. In turn, SOX4 upregulates the metastasis-related genes EZH2 and MMP2[21]. Moreover, STAT3 was found to activate HOXD-AS1 transcription by specifically binding to the HOXD-AS1 promoter at -938 / -928 nt.

Osteosarcoma and ovarian cancer

Inactivating STAT3 using antagonists or signaling pathway inhibitors inhibits invasion and metastasis[42,61]. Similarly, suppressing HOXD-AS1 modulates migration and invasion of osteosarcoma cells *in vitro*[24]. Conversely, HOXD-AS1 enhances migration and invasion of ovarian cancer cells[25] by upregulating frizzled family receptor 4 (FZD4) following competitive binding to miR-60, which regulates cancer invasion and migration through a variety of signaling pathways[48-50]. In contrast, HOXD-AS1 knockdown facilitates invasion and epithelial-mesenchymal transition in epithelial ovarian cancer cells by sequestering miR-133a-3p, thereby activating Wnt/β-catenin signaling[26], another critical regulator of migration and metastasis[62,63].

Castration-resistant prostate cancer

Castration-resistant prostate cancer is frequently diagnosed after the failure of androgen deprivation and is the main cause of prostate cancer death. HOXD-AS1 regulates prostate cancer cell cycle, castration resistance, and chemotherapy resistance by controlling numerous genes, including PLK1, AURKA, FOXM1, CDC25C, UBE2C, CCNA2, and CCNB1, which regulate cell cycle progression at G2 and M phase. Similarly, HOXD-AS1 may mediate castration resistance via PLK1, AURKA, CDC25C, and UBE2C, and promote chemotherapy resistance via PLK1, AURKA, CDC25C, and FOXM1[28].

HOXD-AS1 as Competing Endogenous RNA

MiRNAs are a class of non-coding RNAs 19-25 nucleotides in length that destabilize target mRNAs or inhibit translation[64]. Since miRNAs contain specific miRNA response elements and an mRNA contains multiple such elements, a single miRNA may repress various transcripts while each mRNA can be sensitive to multiple miRNAs[65]. Competing endogenous RNAs, also known as RNA sponges, cross-regulate miRNAs by "target mimicry"[65], in which transcripts containing miRNA response elements relieve suppression of target genes with the same miRNA response elements[66]. This cross-regulation is widespread, and defects may trigger disease, including cancer[67]. Several studies have now confirmed that HOXD-AS1 is also a competing endogenous RNA[21,22,30]. For example, HOXD-AS1 may favor cell proliferation, cell invasion, epithelial-mesenchymal transition, stem cell formation, and metastasis in colorectal cancer by sequestering miR-217[33], which inhibits proliferation and induces apoptosis in these cells via multiple target genes[68,69]. MiR-217 may also repress epithelial-mesenchymal

transition in other cancers[70-72]. In glioma cells, miR-130a simultaneously binds HOXD-AS1 and E2F8, and it is in a mutually inhibitory relationship with the former, suggesting that HOXD-AS1 acts as a competing endogenous RNA in this case[30]. Consequently, HOXD-AS1 controls cell migration and invasion via E2F8 and miR-130a. In non-small cell lung cancer cells and tissues, HOXD-AS1 expression is negatively correlated with that of miR-147, which binds HULC, as assessed by dual-luciferase reporter assay. The effects of silencing HOXD-AS1 on cell cycle progression and apoptosis are abrogated by inhibiting miR-147a, confirming that HOXD-AS1 also acts as a competing endogenous RNA in non-small cell lung cancer[22]. Following computational analysis by miRanda and validation by luciferase assay, HOXD-AS1 and SOX4 were found to share the same binding site for miR-130a-3p. Accordingly, overexpression of HOXD-AS1 sharply diminishes SOX4 transcripts by sequestering miR-130a-3p. Conversely, HOXD-AS1 knockdown promotes SOX4 recruitment, implying that HOXD-AS1 partly regulates SOX4 via miR-130a-3p. Ultimately, HOXD-AS1 regulates metastasis in hepatocellular cancer cells by competitive binding to miR-130a-3p, thereby preventing SOX4 from miRNA-mediated degradation and activating the metastasis-related genes EZH2 and MMP2.

Conclusions

The literature clearly indicates that HOXD-AS1 is oncogenic, overexpressed in many cancers, and that is a possible therapeutic target that has attracted increasing research attention. Abundant HOXD-AS1 expression not only promotes proliferation, apoptosis, invasion, and metastasis, but it is also closely linked to clinical and pathological characteristics. For example, HOXD-AS1 overexpression correlates with tumor size, histological grade, and tumor-node-metastasis stage in bladder cancer[27]. HOXD-AS1 upregulation is also linked to Gleason score, T stage, and lymph node metastasis in castration-resistant prostate cancer[28]. Similarly, HOXD-AS1 is more likely to be upregulated in metastatic hepatocellular carcinoma than in non-metastatic forms[20], and HOXD-AS1 overexpression is significantly associated with gastric tumor size, invasion depth, tumor-node-metastasis stage, and regional and lymphatic metastasis[23]. Furthermore, HOXD-AS1 acts as a competing endogenous RNA that mediates liver cancer metastasis, promotes proliferation of non-small cell lung cancer cells, and accelerates glioma migration and invasion. Finally, prognosis is poor in almost all patients abundantly expressing HOXD-AS1. Today, we are only beginning to understand the mechanisms by which HOXD-AS1 regulates physiological and pathological processes in some cancers. Thus, further studies are required not only to fully elucidate such mechanisms, but also to investigate its significance in other forms of cancer. In any case, HOXD-AS1 may be regarded as an oncogene, a competing endogenous RNA, or, more importantly, a prognostic biomarker and potential therapeutic target.

Conflict of Interest

The Authors declare that they have no conflict of interest.

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