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Review

Long non-coding RNA HOXD-AS1 in cancer

Lianlian Li[a,*], Yong Wang[b], Xiaoyu Zhang[a], Qiwei Huang[c], Yutao Diao[a], Haipeng Yin[a], Hongyan Liu[a,*]

[a] Institute of Basic Medicine, Shandong Academy of Medical Sciences, Jinan 250062, China
[b] Shandong Xinchuang Biotechnology Co., LTD, Jinan 250102, China
[c] Shandong Laboratory Animal Center, Jinan 250002, China

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ABSTRACT

Cancer is one of the leading causes of death worldwide with a high risk of incidence and mortality. Long non-coding RNAs (lncRNAs) have been shown to participate in various biological processes, including tumorigenesis and progression. The HOXD-AS1 (also known as HAGLR and Mdgt) gene is located between the HOXD1 and HOXD3 genes in the HOXD cluster and has been reported to play a critical role in the development and progression of cancers. This review summarizes the current knowledge on the biological functions and mechanisms of HOXD-AS1 in different human cancers, including bladder, cervical, colorectal, gastric, ovarian, and prostate cancers, glioma, hepatocellular carcinoma, melanoma, osteosarcoma, and non-small cell lung cancer. The aberrant expression of HOXD-AS1 in these cancers was related with clinical features of patients with cancers. HOXD-AS1 regulates the growth, invasion, and migration of tumor cells through different underlying mechanisms. In conclusion, HOXD-AS1 may be considered as a promising diagnostic/prognostic biomarker or a novel therapeutic target for cancers.

1. Introduction

Cancer is one of the leading causes of death, with global death due to cancers in 2015 reaching 8.8 million, which was an increase of 17.0% over 2005 [1]. According to recent cancer statistics, approximately 14.1 million new cancer cases and 8.2 million deaths occurred worldwide in 2012 [2], an estimated 4.3 million new cancer cases and 2.8 million cancer deaths occurred in China in 2015 [3], and 1.7 million new cancer cases and 0.6 million cancer deaths are projected to occur in the United States in 2018 [4]. With increasing morbidity and mortality, cancer has become a major public health problem worldwide. In the past few years, many molecules have been studied as biomarkers for diagnosis/prognosis and molecular targets for cancer therapy, including long non-coding RNAs (lncRNAs).

LncRNAs are poorly conserved and operationally defined as non-protein-coding RNA genes that are more than 200 nucleotides in length [5]. According to the relationship with their adjacent protein-coding genes, lncRNAs can be roughly classified as sense, antisense, intronic, bidirectional and intergenic lncRNAs [6]. They regulate fundamental biochemical and cellular processes by diverse mechanisms at transcriptional, post-transcriptional or epigenetic levels [7]. Their primary methodology is as follows [7–12]: i) as decoys, lncRNAs can interact with transcription factors to interfere with transcription; ii) as sponges, lncRNAs can adsorb microRNA and subsequently prevent mRNA from the microRNA-mediated degradation; iii) as scaffolds or bridges, lncRNAs can directly interact with proteins to modulate protein activity, alter protein localization, or affect the structural or organizational role of proteins; iv) lncRNAs can recruit chromatin modifiers to alter the level of chromatin modification and then affect the expression of genes; and v) lncRNAs can directly interact with mRNA to suppress translation, modulate alternative splicing patterns or affect the stability of mRNA.

In recent years, an increasing number of studies have shown the important role of lncRNAs in cancer [13–15]. Generally, lncRNA dysregulation contributes to initiation and progression of tumors by regulating proliferation, invasion, metastasis, and survival of tumor cells [16]. Moreover, lncRNAs may be used as potential diagnostic or prognostic biomarkers and therapeutic targets [17]. HOXD-AS1, also known as HAGLR (HOXD antisense growth-associated long noncoding RNA) and Mdgt, is transcribed from the HOXD cluster and its gene is located between the HOXD1 and HOXD3 genes on human chromosome 2q31.1. It has been reported to play important roles in gut development [18] and processes associated with various cancers. In the present review, we searched for a term (“HOXD-AS1” or “HAGLR” or “Mdgt”) from the

* Corresponding authors.
E-mail addresses: lotuslee1985@126.com (L. Li), hyliudycui@aliyun.com (H. Liu).

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Table 1
The role of HOXD-AS1 in human cancers/tumors.

Cancers/Tumors	Aberrant expression	Associated clinical features	Biological functions	Related molecules	REF
Bladder cancer	Upregulated	Tumor size, histological grade, and TNM stage	Increase cell proliferation and migration, suppress cell apoptosis		[19]
Cervical cancer	Upregulated	TNM stages, lymphovascular invasion, lymph node metastasis, and recurrence	Promote cell proliferation, colony formation capacity, and chemo-resistance to cisplatin	Ras/ERK pathway	[20]
				miR-130a-3p/ZEB1	[21]
Colorectal cancer	Upregulated	Poor prognosis	Promote cell proliferation, invasion, metastasis, and stem cell formation	miR-217/AEG1/EZH2	[22]
Gastric cancer	Upregulated	Tumor size, invasion depth, TNM stages, regional lymph nodes, lymphatic metastasis, and distant metastasis	Promote cell proliferation and colony formation capacity	JAK2/STAT3 pathway	[23]
Glioma	Upregulated	Glioma grade	Promote cell migration and invasion	miR-130a/E2F8	[24]
Hepatocellular carcinoma	Upregulated	Poor prognosis and high TNM stage	Promote cancer cell growth, migration, invasion and metastasis and inhibit apoptosis	STAT3/HOXD-AS1/miR-130a-3p/SOX4/MMP2/EZH2	[25]
				miR-19a/ARHGAP11A, and RGS3/MEK/ERK	[26]
Melanoma	Upregulated	Poor survival	Promote cell proliferation and invasion	EZH2/RUNX3	[27]
NSCLC	Upregulated	Tumor size, stage, recurrence, and TNM status, stage, lymph node metastasis, and poor overall survival	Promote cell proliferation, migration, invasion and cell cycle progression, and suppress cell apoptosis	p21 and MMP9	[28]
				miR-133b/MMP9	[29]
				miR-147a/pRB	[30]
Osteosarcoma	Upregulated	Tumor stage, lymph node metastasis and overall survival rate	Promote cell proliferation, colony formation, migration and invasion, and suppress cell cycle arrest at G1 stage and apoptosis	STAT3 and its target protein (CyclinD1, Bcl2, and MMP2)	[31]
Ovarian cancer	Upregulated	Advanced FIGO stage, lymph node metastasis, and poor overall survival	Promote cell proliferation and colony formation, migration, invasion	miR-608/FZD4	[32]
				miR-133a-3p and Wnt/β-catenin pathway	[33]
Prostate cancer	Upregulated	Gleason score, tumor stage, lymph nodes metastasis, and PFS	Promote proliferation, castration resistance and chemo-resistance	Recruit WDR5	[34]

FIGO, Federation of Gynecology and Obstetrics; NSCLC, non-small cell lung cancer; PFS, progression-free survival; RA, retinoic acid; REF, reference; TNM, tumor lymph node metastasis.