Clinica Chimica Acta 485 (2018) 229–233

Contents lists available at ScienceDirect

Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/cca

Review

LncRNA HOXA-AS2 and its molecular mechanisms in human cancer

Jicai Wang, Zhilei Su, Shounan Lu, Wen Fu, Zhifa Liu, Xingming Jiang*, Sheng Tai*

Department of Hepatopancreatobiliary Surgery, The Second Affiliated Hospital of Harbin Medical University, No.246 XueFu Avenue, Harbin 150086, China

ARTICLE INFO

Keywords:
lncRNA
HOXA-AS2
Diagnosis
Therapeutic target
Prognosis

ABSTRACT

Long non-coding RNAs (lncRNAs), a novel class of noncoding RNAs, are commonly defined as RNA molecules more than 200 nucleotides in length. Emerging research indicated that lncRNA played a vital role in human tumorigenesis and progression by serving as tumor oncogenes or suppressors. LncRNA has been shown to get involved in participate various biological processes, such as cell growth, anti-apoptosis, migration and invasion. LncRNA HOXA cluster antisense RNA2 (HOXA-AS2) is a novel cancer-related lncRNA. It was recently found to exhibit aberrant expression in a variety of malignancies, including breast cancer, gastric cancer, gallbladder carcinoma, hepatocellular carcinoma and pancreatic cancer. The oncogenicity of lncRNA HOXA-AS2 mainly inhibits or promotes the expression of related genes through direct or indirect pathways, suggesting that HOXA-AS2 likely represents a feasible biomarker or therapeutic target in human cancers. In this review, we summarize current evidences concerning the biological functions and mechanisms of HOXA-AS2 during tumor development.

1. Introduction

As a global major public health problem, cancer has always been one of the leading causes of death worldwide and the focus of clinical studies [1]. Based on recent data about cancer statistics, approximately 1,685,210 new cancer cases were diagnosed in the America alone in 2016 and 595,690 cancer patients died [2]. In the past few years, the molecular basis of cancer has been extensively researched. Accumulating evidences indicated that long non-coding RNAs (lncRNAs) played numerous roles in the normal cellular biology, as well as in several phases of pathological processes [3,4].

Protein-coding genes account for less than 2% of the entire genome on the basis of the draft of the human genome project. More than 70% of the gene sequences are transcribed into RNAs in higher eukaryotic genomes. As we know, RNA plays a crucial part in the expression and regulation of genome through the activity of protein-coding genes and non-protein coding RNAs (ncRNAs). While these ncRNAs account for most of the RNAs [5–8]. Owing to recent advances in genome sequencing technologies, long ncRNAs (RNA transcripts longer than 200 nucleotides in length) have been implicated as critical regulators in diverse human diseases [9–14].

LncRNAs, which are usually divided into five categories including sense, antisense, bidirection, intron and intergenic region, are mainly transcribed by RNA polymerase II and lack an obvious open reading frame [15,16]. The functions of lncRNAs, which include gene imprinting, histone modification, chromatin remodeling, transcriptional activation, transcriptional interference, nuclear transport, and cell cycle regulation, depend on their subcellular localization [17–21]. LncRNAs are also reported that they may work as sponges by competitively binding to microRNAs (miRNAs) and consequently inhibiting their functions [22,23]. Multiple studies have been reported that lncRNAs are aberrantly expressed in refractory tumors in unclear pathogenesis [24–26]. LncRNAs dysregulation generally contribute to tumors development by promotion, proliferation, invasion and metastasis of tumor cells [27,28]. Besides, lncRNAs may be as potential therapeutic targets and biomarkers for diagnosis, prognostic evaluation or treatment, owing to their characteristics of high efficiency, high tissue specificity and elevated stability [29,30]. Long noncoding RNA HOXA

Abbreviations: APL, Acute promyelocytic leukemia; ATRA, All trans retinoic acid; Bax, BCL2-Associated X; BC, Breast cancer; Bcl-2, B-cell lymphoma-2; c-Myc, MYC proto-oncogene; CRC, Colorectal cancer; DDIT3, DNA damage inducible transcript 3; EGFR, Epidermal growth factor receptor; EMT, Epithelial-mesenchymal transition; EZH2, Enhaner of zeste homolog 2; GBC, Gallbladder carcinoma; GC, Gastric cancer; HCC, Hepatocellular carcinoma; HOXA-AS2, HOXA cluster antisense RNA2; KLF2, Kruppel like factor 2; lncRNAs, Long non-coding RNAs; LSD1, Lysine specific demethylase 1; miRNAs, microRNAs; MMP-2/9, Matrix metalloproteinase-2/9; ncRNAs, Non-protein coding RNAs; NF-kB, Nuclear factor kappa B subunit; PC, Pancreatic cancer; P13K/AKT, Phosphoinositide 3- kinase/protein kinase B; PLK3, Polo-like kinase 3; PRC2, Polycomb repressive complex 2; RELA, NF-kB subunit; TGF-β, Transforming growth factor β; TGFBR2, Transforming growth factor beta receptor 2; TRAIL, TNF-related apoptosis-inducing ligand; TUNEL, Terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling; VE-cadherin, Vascular endothelial-cadherin; VM formation, Vasculogenic mimicry formation

* Corresponding authors.
E-mail addresses: xmjiang@hrbmu.edu.cn (X. Jiang), taisheng1973@163.com (S. Tai).

https://doi.org/10.1016/j.cca.2018.07.004
Received 26 May 2018; Received in revised form 28 June 2018; Accepted 3 July 2018
Available online 04 July 2018
0009-8981/

Table 1
Functional characterization of lncRNA HOXA-AS2 in various cancers.

Cancer types	Expression	Functions	Related genes	Role	Refs
Hepatocellular carcinoma	Upregulated	Proliferation, migration, invasion	c-Myc, Bcl-2, Bax	Oncogene	34
Gastric cancer	Upregulated	Proliferation	P21, PLK3, DDIT3, EZH2, PRC2	Oncogene	40
Colorectal cancer	Upregulated	Proliferation	P21, KLF2, EZH2, LSD1	Oncogene	44,45
Gallbladder carcinoma	Upregulated	Proliferation, migration, invasion	E-cadherin, Vimentin, N-cadherin, EMT	Oncogene	50
Breast cancer	Upregulated	Proliferation, migration, invasion	miR-520c-3p, TGFBR2, RELA	Oncogene	53
Promyelocytic leukemia	Upregulated	Anti-apoptosis	TRAIL	Oncogene	54
Pancreatic cancer	Upregulated	Proliferation	EZH2, LSD1	Oncogene	55
Malignant glioma	Upregulated	Proliferation, migration, invasion, VM formation	miR-373, EGFR, MMP-2,VE-cadherin, MMP-9, P13K/AKT	Oncogene	56

Bax: BCL2-Associated X, Bcl-2: B-cell lymphoma-2, c-Myc: MYC proto-oncogene, DDIT3: DNA damage inducible transcript 3, EGFR: epidermal growth factor receptor, EMT: epithelial-mesenchymal transition, EZH2: enhaner of zeste homolog 2, KLF2: kruppel like factor 2, LSD1: lysine specific demethylase 1, MMP-2/9: matrix metalloproteinase-2/9, P13K/AKT: phosphoinositide 3- kinase/protein kinase B, PLK3: polo-like kinase 3, PRC2: polycomb repressive complex 2, RELA: NF-kB subunit, TGFBR2: transforming growth factor beta receptor 2, TRAIL: TNF-related apoptosis-inducing ligand, VE-cadherin: vascular endothelial-cadherin, VM formation: vasculogenic mimicry formation.

Table 2
Clinical significance of lncRNA HOXA-AS2 in various cancers.

Cancer types	Overexpression of lncRNA HOXA-AS2	Refs
Hepatocellular carcinoma	Advanced TNM stages, poorer survival, larger tumor size and shorter overall survival	34
Gastric cancer	Larger tumor size higher clinical stage and poor prognosis	40
Colorectal cancer	Larger tumor size, advanced pathological stage, early lymph node metastasis and poor prognosis	44,45
Gallbladder carcinoma	Larger tumor size, advanced pathological stage and early lymph node metastasis	50
Breast cancer	Greater depth of invasion, higher TNM stages, more frequent lymphatic metastasis, positive distant metastasis and poorer postoperative survival	53
Promyelocytic leukemia	–	54
pancreatic cancer	–	55
Malignant glioma	–	56

cluster antisense RNA2 (lncRNA HOXA-AS2), which is a 1048-bp lncRNA located between the HOXA3 and HOXA4 genes in the HOXA cluster, is a promising candidate among all tumor-related lncRNAs. LncRNA HOXA-AS2 is overexpressed in numerous human cancers (Tables 1 and 2). In this review, we summarize current evidences regarding the abnormal expression, functions and regulation mechanisms of lncRNA HOXA-AS2 and discuss its potential clinical value.

2. LncRNA HOXA-AS2 deregulation in human cancers

2.1. Hepatocellular carcinoma

Hepatocellular carcinoma (HCC), which causes approximately 600,000 deaths each year, is the sixth most common cancer worldwide and the third leading cause of cancer-related death. Chronic hepatitis B/C virus infections are the significant development factors of HCC. Frequent intrahepatic and extrahepatic metastases lead to the low resectability, poor prognosis and high recurrence rate in the early stage [31–33]. Therefore, in order to identify novel biomarkers and therapeutic targets, it is vital to explore the key molecular mechanisms involved in the initiation and progression of HCC. Wang et al. [34] demonstrated that expression levels of HOXA-AS2 were markedly upregulated in 112 HCC tissues and 4 cell lines compared with those in adjacent normal hepatic tissues and hepatocyte cell line. Moreover, high HOXA-AS2 expression was significantly associated with advanced TNM stages, poorer survival, larger tumor size, and shorter overall survival. Functionally, knocking down HOXA-AS2 significantly repressed proliferation, colony formation, migration and invasion of HCC cells and obviously induced cancer cells apoptosis. Therefore, HOXA-AS2 may be a promising oncogenic lncRNA in HCC, suggesting its potential utilities as a prognostic marker or a therapeutic target. Further studies are needed to elucidate the specific regulatory mechanism of HOXA-AS2 in HCC development.

2.2. Gastric cancer

Gastric cancer (GC) is one of the most common malignancies worldwide, being the third main cause of cancer-related deaths [35–38]. With the medical technology development, early treatment of GC has achieved significant success. However, early diagnosis of GC is still difficult. Most patients of GC presented with advanced stage at the time of diagnosis, resulting in poor prognosis and low long-term survival rate [39]. Therefore, identifying novel GC biomarkers is crucial for improving diagnosis and prognostic evaluation. Xie et al. [40] demonstrated that expression of HOXA-AS2 was elevated in GC tissues compared with that in paired adjacent noncancerous tissues. Upregulated HOXA-AS2 was dramatically associated with larger tumor size, higher TNM stage and poor prognosis. HOXA-AS2 could promote GC cells proliferation in vitro and tumorigenesis in vivo. Further analysis showed that silencing HOXA-AS2 promoted G1 arrest and caused apoptosis of GC cells. These findings indicated that HOXA-AS2 exhibited a crucial role in early diagnosis and treatment of GC. HOXA-AS2 is expected to be a novel diagnostic and curative target. However, further studies are needed to elucidate biological function of HOXA-AS2 in GC cells.

2.3. Colorectal cancer

Colorectal cancer (CRC), which affects more than 1.2 million people every year, is the third most common malignant tumor and the fourth most frequent cause of cancer-related deaths in the world [41]. It is estimated that 20% of the patients exhibit metastases (survival rate of less than 5 years) when being diagnosed [42,43]. Meanwhile, one of the biggest obstacles is lack of molecular biomarkers for CRC cells progression. As such, the development of sensitive and specific biomarkers would be of great clinical relevance significance for CRC. Ding et al. [44] reported that expression of HOXA-AS2 was increased at least twofold in the CRC tissues compared with non-tumor controls. Incremental HOXA-AS2 was closely related to bigger tumor size, advanced