Cancer Letters 418 (2018) 119–124

Contents lists available at ScienceDirect

Cancer Letters

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

Mini-review

Targetable long non-coding RNAs in cancer treatments

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ARTICLE INFO

Article history:
Received 8 November 2017
Received in revised form
25 December 2017
Accepted 9 January 2018

Keywords:
lncRNA
Cancer
Oncogenesis
Therapeutics
Dysregulation

ABSTRACT

Aberrant expression of many long non-coding RNAs has been observed in various types of cancer, implicating their crucial roles in tumorigenesis and cancer progression. Emerging knowledge with regard to the critical physiological and pathological roles of long non-coding RNAs in cancers makes them potential targets in cancer treatments. In this review, we present a summary of the relatively well studied long non-coding RNAs that are involved in oncogenesis and outline their functions and functional mechanisms. Recent findings that may be utilized in therapeutic intervention are also highlighted. With the fast development in nucleic acid-based therapeutic reagents that can target disease associated RNAs, lncRNAs should be explored as potential targets in cancer treatments.

1. Introduction

Long non-coding RNAs (lncRNAs) are a heterogeneous group of transcripts with diverse functions and functional mechanisms [1–6]. A large number of lncRNAs have been shown to be involved in epigenetics, transcriptional initiation, transcriptional and post-transcriptional regulations, and are essential in physiological events such as gene imprinting, dosage compensation, and gametogenesis [7–9]. Unlike miRNAs, lncRNAs are able to fold into certain secondary and tertiary structures, by which they carry out their functions [10,11]. Generally, lncRNAs function as modulators of cellular processes in different ways: (a) signaling lncRNAs could function as molecular signals in cellular processes such as inactivation of X chromosome by XIST and cellular conditions leading to activation of gene transcription by enhancer RNAs (eRNAs) [12–17]; (b) decoying lncRNAs bind to their targets and thus inhibit their functions in the nucleus or cytoplasm [18–21]; (c) guide lncRNAs initially bind to specific proteins, then guide the ribonucleoprotein complexes to specific locations [22–24]; (d) scaffold lncRNAs have various domains, which can recruit various effectors [25–28].

Aberrant expression of lncRNAs may directly or indirectly lead to physiological or pathological disorders [29,30]. A series of studies have demonstrated that some lncRNAs are potential regulators of cellular differentiation and proliferation, as well as having oncogenic functions in many types of cancers [29]. It is strongly believed that altered expression of lncRNAs may attribute many cancers and other diseases. Elucidating the functions and mechanisms of the lncRNAs would provide an in-depth understanding of disease pathogenesis and pathophysiology. Moreover, due to the massive involvement of lncRNAs in cancer, they may also be explored as therapeutic targets [31]. Here, we summarize several critical lncRNAs that are involved in the progression of cancers and may be explored as potential targets in therapeutics.

2. Key lncRNAs in cancers

2.1. HOTAIR

HOTAIR is a 2.2 kb lncRNA transcribed from the antisense strand of HOXC gene cluster [32]. It is regarded as an oncogene and is pervasively overexpressed in most solid cancers and correlated with tumor invasion, progression, metastasis, and poor prognosis [33,34]. HOTAIR interacts with critical epigenetic regulators such as histone methylase PRC2 and histone demethylase complex LSD1, recruiting them to the target gene promoters and thus introducing histone H3K27-trimethylation and H3K4-demethylation, which can ultimately result in chromosome condensation and gene silencing of some tumor suppressor genes [35,36]. Also, HOTAIR regulates certain genes that are involved in cell proliferation, epithelial-mesenchymal transition (EMT), migration and

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https://doi.org/10.1016/j.canlet.2018.01.042
0304-3835/

metastasis [35,36]. Although there are some recent arguments about the molecular mechanism and developmental roles of HOTAIR, multiple lines of evidence have shown that lncRNA HOTAIR is misregulated in most carcinomas such as urothelial carcinoma, pancreatic tumors, hepatocellular carcinoma, colorectal carcinomas, ovarian cancer tissues, sarcomas, prostate cancer, melanomas among others [37–45]. Given these crucial criteria, HOTAIR is regarded as a potential biomarker of various human cancers; thus, detection of the expression level of HOTAIR is crucial for the early diagnosis of the progression stages and prediction of the survival of patients [33]. On the other hand, HOTAIR is involved in the resistance of cancer cells to cisplatin. Sun and colleagues recently found that HOTAIR can regulate the cisplatin-resistance ability of human endometrial cancer cells through the regulation of autophagy by influencing Beclin-1, multidrug resistance (MDR), and P-gp expression [46]. Liu et al. discovered that elevated HOTAIR expression is associated with drug resistance in non-small cell lung cancer (NSCLC) patients and is related to Klf4 upregulation [47]. Research aiming at downregulation of HOTAIR showed a significant reduction in cell mobility in hepatocellular carcinoma (HCC) where HOTAIR mediates migratory and invasive phenotypes of HCC cells via the inhibition of RBM38 [48]. Taken together, HOTAIR could be a potential target for cancer therapies.

Besides interacting with certain proteins, HOTAIR also functions by interacting with miRNAs. Several studies have shown that the level of HOTAIR is regulated by certain miRNAs, which exhibited tumor suppression effects. This kind of function of lncRNAs in binding with microRNA is termed as competing endogenous RNA (ceRNA). Chiyomaru et al. proved that miR-141 bound to HOTAIR in a sequence-specific manner and suppressed HOTAIR expression and functions, including proliferation and invasion [49]. Moreover, the Ago2 complex cleaved HOTAIR in the presence of miR-141 [49]. In bladder cancer, HOTAIR can regulate cyclin J through inhibition of miRNA-205 expression by breaking the balance of histone modification between H3K4me3 (histone H3 at lysine 4 methylation) and H3K27me3 on miR-205 promoter [50]. Most recently, Xu and colleagues found that HOTAIR could function as a miR-148a sponge which positively regulates Snail2 expression, enhancing cell invasion and metastasis, and promoting the EMT in esophageal cancer (EC) [51].

2.2. MALAT1

The metastasis-associated lung adenocarcinoma transcript 1 (MALAT1), also known as MALAT-1 or nuclear-enriched abundant transcript 2 (NEAT2), is a highly abundant and ubiquitously expressed lncRNA with the length of ~8000 nt [52]. It localizes in the nucleus and participates in various key nuclear processes [6]. Its co-localization with SC35 splicing domains, also known as nuclear speckles or interchromatin granule clusters, in mouse and human cells, suggests a role in RNA metabolism. Meanwhile, researchers also found that MALAT1 was associated with RNA splicing and gene expression, both at the transcriptional and posttranscriptional level [53]. It is one of the first identified ncRNAs that are associated with a disease, namely lung cancer. It is now known to be associated with clinical parameters and affects tumor cell proliferation, apoptosis, migration, invasion or the metastasis of tumor cells. Also, recent studies demonstrate that the level of MALAT1 is positively associated with many types of cancers such as lung cancer, esophageal squamous cell carcinoma, glioma, breast cancer, and bladder cancer [52,54–57]. In oral squamous cell carcinoma (OSCC), Zhou et al. demonstrated that MALAT1 was overexpressed in the OSCC tissues, promoted tumor growth, and metastasis by inducing epithelial-mesenchymal transition. Knocking down of MALAT1 inhibited the growth of xenograft tumor derived from OSCC cell lines *in vivo* [58]. MALAT1 also functions via RNA-protein interaction, and some of these interactions can affect protein modifications [59,60]. For example, the METTL16 (methyltransferase-like protein 16) protein was found to interact with the triple helix 3′ end of MALAT1 [59]. By quantitative proteomic, Chen et al. revealed that MALAT1 interacted with deleted in breast cancer 1 (DBC1), leading to the release of sirtuin1 (SIRT1), which then consequently induced the deacetylation of p53 [60]. Downregulation of MALAT1 by siRNA also showed inhibition of cell proliferation and induction of apoptosis in multiple myeloma [61].

Interestingly, like HOTAIR, MALAT1 can function via interaction with miRNAs. A series of recent publications revealed that MALAT1 acted as ceRNAs. Hou et al. demonstrated that MALAT1 could promote the migration and invasion of hepatocellular carcinoma by sponging miR-204 [62]. Likewise, in ovarian carcinoma, MALAT1 is a sponge for miR-200c [63]. All these suggest that MALAT1 could be a promising prognostic biomarker and therapeutic target.

2.3. H19

H19 is the first identified imprinted lncRNA with a high expression level in embryogenesis but is barely detectable in most tissues after birth. It is a transcript from the H19/IGF2 genomic imprinted cluster, which is located on human chromosome 11p15.5. H19 is capable of folding into specific secondary structure that binds protein partners, which are found to be involved in many physiological processes like epigenetic modification, transcription, RNA metabolism, and etc. [64]. H19 was first identified as a tumor suppressor [65]. However, later studies revealed that it was significantly increased in several tumors as oncogenic [66,67]. Aberrant expression of H19 is reported in various types of tumors like breast cancer, lung cancer, cervical cancer and bladder cancer [65,68,69].

miR-675 is known to be embedded in H19's first exon, and this microRNA regulates various targets either directly or indirectly such as Igf1r, Smad1, Smad5, Cdc6, Cadherin-11, Cadherin-13, Rb, Runx1, Nodal Modulator 1, TGFBI, CALN1, c-Cbl, Cbl-b and MITF [70,71]. Recent evidence showed that overexpression of H19 and miR-675 promoted cell proliferation and inhibited cell apoptosis, whereas knockdown of H19 and miR-675 inhibited these effects through FADD/caspase 8/caspase 3 signaling pathway [72]. Furthermore, H19 can act as a ceRNA [73]. Lv et al. recently found that H19 regulated epithelial-mesenchymal transition and metastasis of bladder cancer by blocking miR-29b-3p, suggesting that H19/miR-29b-3p/DNMT3B axis might be a promising therapeutic target for bladder cancer (BC) [74]. Moreover, Zhang and colleagues found that H19 promoted TSCC progression through association with EZH2, and affected downstream β-Catenin/GSK3β/EMT signaling in tongue squamous cell carcinoma (TSCC) [75], which provided new insights for this type of cancer.

2.4. ANRIL

ANRIL (antisense non-coding RNA in the INK4A locus) is a 3.8 knt (kilo nt) lncRNA that is originally identified in familial melanoma patients with a large germline deletion in the CDKN2A/B (also known as INK4B-ARF-INK4A) gene cluster [76,77]. Recently, genome-wide association studies (GWAS) have identified ANRIL gene as a genetic susceptibility locus shared by coronary disease, intracranial aneurysm, type 2 diabetes, and also some cancers [78]. It is known to be deregulated in various carcinomas like gastric, breast, lung and bladder cancer. The most prevalent understanding of ANRIL functional mechanism is that it mediates repression of the CDKN2A/B locus, by associating with polycomb repressor complexes (PRC1 and PRC2) [79]. Zhang and colleagues found that expression of ANRIL was upregulated in gastric cancer (GC) tissues, while knockdown of ANRIL significantly repressed cell proliferation both *in vitro* and

in vivo [80]. ANRIL promoted GC cell proliferation partially by epigenetically repressing the expression of miR-99a/miR-449a [80].

Furthermore, recent studies indicated that ANRIL overexpression modulated triple-negative breast cancer (TNBC) tumorigenesis by acting as molecular sponge for miR-199a, as miR-199a could target ANRIL [81]. Conversely, miR-199a inhibitor could reverse the tumor-suppressing role of ANRIL knockdown on TNBC proliferation and apoptosis [81]. Likewise, ANRIL can also act like a miRNA sponge of miR-186 in cervical cancer development, demonstrating that ANRIL/miR-186 axis may play a vital role in cervical cancer tumorigenesis [82]. Downregulation of ANRIL could enhance radio-sensitivity in nasopharyngeal carcinoma cells, partially due to ANRIL's function as ceRNA of miR-125 [83].

2.5. PCA3

PCA3 (prostate cancer antigen 3), located on chromosome 9q21-22 in antisense orientation within intron 6 of BMCC1 (also called prune homolog 2 gene, PRUNE2) [84], is a lncRNA that has been shown to be highly expressed in the prostate and is sharply overexpressed in many prostate cancer specimens. It has long been considered to promote the proliferation and invasion of prostate cancer, and it has become one of the specific biomarkers of prostate cancer. PCA3 expression is 60–100-fold higher in more than 95% of prostate tumors compared to adjacent non-neoplastic tissues [85]. Knockdown of PCA3 leads to partial upregulation of epithelial markers such as E-cadherin, claudin-3 and cytokeratin-18, and downregulation of the mesenchymal marker vimentin [86]. It is believed that PCA3 controls PRUNE2 levels via a unique regulatory mechanism involving the formation of a PRUNE2/PCA3 double-stranded RNA that undergoes RNA editing of adenosine-to-inosine by adenosine deaminase ADAR [87]. In clinical trials, combinatory examination of urinary PCA3 and fusion gene TMPRSS2-ERG can increase specificity in prostate cancer diagnosis compared with serum PSA [88]. Actually, FDA proofed clinical assays of PCA3 have been used in prostate cancer diagnosis for more than five years now [89,90]. Interestingly, recent studies revealed that PCA3 as a ceRNA might also coordinate epithelial ovarian carcinoma (EOC) tumorigenesis through disrupting miR-106b regulated gene expression, indicating that PCA3 might be a novel and important diagnostic biomarker, and also a valuable prediction marker in the clinical care of EOC [91].

2.6. GAS5

Growth arrest specific 5 (GAS5) is a lncRNA that is associated with cell proliferation and serves crucial roles in the growth arrest of T-cells and non-transformed lymphocytes. It was initially identified from subtractive cDNA cloning for genes that are preferentially expressed during growth arrest [92]. GAS5 is a well-known lncRNA encoded at prostate cancer-associated locus 1q25 and approximately 630 nt in length. GAS5 is a tumor suppressor and is known to promote apoptosis and growth arrest. Downregulation of GAS5 could, in turn, inhibits apoptosis and keeps faster cell cycle progression [93,94]. Guo and colleagues found that the expression of GAS5 had significant association with lymph node metastasis, tumor node metastasis (TNM) staging, and the multiple cancer foci of thyroid cancer (TC), and lower expression levels of GAS5 were associated with poor prognosis of patients with TC [95]. Yang and coworkers demonstrated that overexpression of GAS5 inhibited cell proliferation and survival, and induced G0/G1 cell cycle arrest and apoptosis; on the other hand, knockdown of GAS5 expression enhanced cell proliferation and reduced G0/G1 arrest and apoptosis [96].

GAS5 can also function through the regulation of miRNAs. GAS5 suppresses cell growth and epithelial-mesenchymal transition (EMT) in osteosarcoma by regulating the miR-221/ARHI pathway as a ceRNA against miR-221 [97]. GAS5 is also believed to be a ceRNA against miR-21 [98,99]. GAS5 knockdown reduces the chemosensitivity of non-small cell lung cancer (NSCLC) cell to cisplatin (DDP) through regulation of the miR-21/PTEN axis [98]. Wen and colleagues found that GAS5 could not only regulate phosphatase and tensin homolog through miR-21 but also influence the phosphorylation of Akt, and higher GAS5 levels led to enhanced cisplatin sensitivity [99]. Bian et al. suggested that GAS5 inhibited the growth of melanoma as a ceRNA against miR-137 [100].

2.7. NEAT1

The nuclear paraspeckle assembly transcript 1 (NEAT1) gene is located on chromosome 11 (11q13.1). This lncRNA is a crucial part of paraspeckle [101,102], and plays important roles in the pathogenesis and development of several types of cancer like prostate, lung, and breast cancers [103–105]. It is found to be upregulated in most cancers, and higher expression levels are related to poor prognosis in the above tumors [106]. NEAT1 is a direct transcriptional target of HIF in many breast cancer cell lines and also in some solid tumors, accelerates cell proliferation, and reduces cell apoptosis [107].

Zhang et al. recently revealed that NEAT1 was closely associated with progression of breast cancer via promoting proliferation and EMT [108]. β-catenin and N-cad were decreased while E-cad was increased after NEAT1 was suppressed [108]. Up-regulated NEAT1 was shown to promote cell proliferation and invasion by serving as a competing endogenous RNA of miR-218 [109]. Fang and colleagues found that overexpression of NEAT1 inhibited the expression of miR-129-5p by regulating VCP/IκB, thereby promoting the proliferation of hepatocellular carcinoma (HCC) cells [110]. NEAT1 was specifically upregulated in breast cancer (BC) cell lines and promoted BC cell growth through miR-101 dependent EZH2 regulation [111]. By analyzing the ChIP-seq data, Idogawa et al. displayed that NEAT1 was a direct transcriptional target of p53. Meanwhile, the suppression of NEAT1 induction by p53 attenuated the inhibitory effect of p53 on cancer cell growth and also modulated gene transactivation [112]. Moreover, NEAT1 could function through signaling pathways. For example, NEAT1 contributed to the tumorigenesis and development of non-small cell lung cancer (NSCLC) by activating Wnt/β-catenin signaling pathway with unknown mechanisms [113].

2.8. SPRY4-IT1

Sprouty4-Intron 1 (SPRY4-IT1) was first identified in melanoma cells, and is derived from the second intron of SPRY4 gene located at the human chromosome region 5q31.3. SPRY4-IT1 is 708 nt in length. It is believed that SPRY4-IT1 plays an important role in cell growth, apoptosis, migration and invasion [114]. Increasing lines of evidence show that SPRY4-IT1 is dysregulated in various cancers, including melanoma, breast cancer, esophageal squamous cell carcinoma, non-small cell lung cancer, and etc. Xue et al. demonstrated that SPRY4-IT1 was upregulated in esophageal squamous cell carcinoma (ESCC) tissues of advanced clinical stages [115]. Zhang and colleagues showed that overexpression of SPRY4-IT1 could increase *in vitro* motility of ESCC cells via induction of epithelial-mesenchymal transition (EMT) while silencing of SPRY4-IT1 significantly inhibited the *in vitro* motility of ESCC cells [116]. Ru et al. showed that SPRY4-IT1 promoted epithelial-mesenchymal transition through interaction with Snail1 to regulate protein stability in osteosarcoma [117]. Besides, like many other lncRNAs, SPRY4-IT1 could also behave as a miRNA sponge. Recently, SPRY4-IT1 was reported to be a ceRNA against miR-101-3p to promote proliferation and metastasis of bladder cancer cells through upregulating EZH2, a miR-101-3p target [118].

Table 1
Summary of potentially targetable lncRNAs, their functional mechanisms, and related cancer types.

LncRNA	Mechanism	Cancer type
HOTAIR	Epigenetics: interaction with PRC2, LSD1; ceRNA: miR-141, miR-148a.	urothelial carcinoma, pancreatic tumors, hepatocellular carcinoma, colorectal carcinomas, ovarian cancer tissues, sarcomas, prostate cancer, melanomas, etc.
MALAT1	Nuclear speckle; protein interaction with METTL16 and DBC1; ceRNA: miR-204, miR-200c.	lung cancer, esophageal squamous cell carcinoma, glioma, breast cancer, and bladder cancer, oral squamous cell carcinoma, etc.
H19	Epigenetics: imprinting; primary microRNA of miR-675; ceRNA: miR-296.	breast cancer, lung cancer, cervical cancer, bladder cancer, etc.
ANRIL	Epigenetics: interaction with PRC1 and PRC2; ceRNA: miR-199a, miR-186, miR-125.	gastric cancer, breast cancer, lung cancer, bladder cancer, etc.
PCA3	dsRNA formation with PRUNE2 mRNA; ceRNA: miR-106b.	epithelial ovarian carcinoma & prostate cancer
GAS5	ceRNA: miR-221, miR-21, miR-137.	thyroid cancer, non-small cell lung cancer, melanoma, colorectal cancer, osteosarcoma, etc.
NEAT1	Paraspeckle; ceRNA: miR-218, miR-129, miR-101.	prostate cancer, lung cancer, breast cancer, etc.
SPRY4-IT1	Protein interaction with Snail1; ceRNA: miR-101.	melanoma, breast cancer, esophageal squamous cell carcinoma, non-small cell lung cancer, etc.

3. Conclusion and perspectives

The main priority in clinical cancer research is identifying novel biomarkers to reliably distinguish between low-risk and high-risk patients, and to take care of patients with the most effective treatments. LncRNAs discussed above interact with factors such as proteins and miRNAs to alter cellular physiology. Multiple lines of evidence show these lncRNAs are dysregulated in numerous cancers, and their roles in cancers are verified both *in vitro* and *in vivo* (Table 1). These lncRNAs could be potential targets for future cancer treatment. There are many other lncRNAs that are already known to play critical roles in mammalian cells or in other human diseases [119–132], and it would be very important to evaluate their possible roles in cancers in future studies. On the other hand, significant advances have been achieved in developing therapeutic reagents such as EGS (external guide sequences), aptamers, siRNAs, and antisense oligos to target disease relevant RNAs [133–136]. Researches in drug delivery of RNA therapeutics are also fast moving [137,138]. Integrated and combinatory methods that incorporate lncRNAs targeted reagents may be vital in the future for the development of effective therapies for cancers.

Conflicts of interest

We declare no competing financial interests.

Acknowledgement

This work was supported by the National Basic Research Program of China (2015CB943000 to G.S.), the National Natural Science Foundation of China (31725016 and 31471225 to G.S.; 31600657 to L.C.), the Major/Innovative Program of Development Foundation of Hefei Center for Physical Science and Technology (2016FXCX006 to G.S.), and the Open Project of the CAS Key Laboratory of Innate Immunity and Chronic Disease (KLIICD-201603 to G.S.). Anhui Natural Science Foundation for Young Scholars (1608085QC64 to L.C.).

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