



REVIEW ARTICLE

Functional roles of lncRNAs in the pathogenesis and progression of cancer

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Abstract Long noncoding RNAs (lncRNAs) act as regulators of gene expression and pivotal transcriptional regulators in cancer cells via diverse mechanisms. lncRNAs involves a variety of pathological and biological activities, such as apoptosis, cell proliferation, metastasis, and invasion. By using microarray and RNA sequencing, it was identified that dysregulation of lncRNAs affects the tumorigenesis process. Taken together, these lncRNAs are putative biomarker and therapeutic target in human malignancies. In this review, I discuss the latest finding regarding the dysregulation of some important lncRNAs and their diverse mechanisms of these lncRNAs in the pathogenesis and progression of certain cancers; also, I summarize the possible roles of lncRNAs in clinical application for diagnosis and prognosis of cancer. Copyright © 2020, Chongqing Medical University. Production and hosting by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

The term non-coding RNA (ncRNA) refers to all the RNA molecules that do not encode for a protein,¹ ncRNAs are mainly transcribed by RNA polymerase II and share several characteristics with messenger RNAs (mRNAs).² ncRNAs are classified into two major categories: structural ncRNAs and

regulatory ncRNAs. Structural ncRNAs comprise of rRNAs and tRNAs. tRNAs are ncRNAs with an important role in protein synthesis since they specifically recognize mRNA codons and transfer their charged amino acid into the growing peptide during translation.³ Regulatory ncRNAs are further divided into small and long non-coding RNAs (lncRNAs).⁴ Regulatory ncRNAs are classified either as small ncRNAs if they are shorter than 200 ribonucleotides or as lncRNAs, longer than 200 ribonucleotides. Small ncRNAs include microRNAs (miRNAs), which mediate post-transcriptional RNA silencing, piwi-interacting RNAs (piRNAs), which regulate chromatin modifications and transposons repression, as well as the more recent circular RNAs (circRNAs),⁵ small interfering RNAs (siRNAs) and small

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Abbreviations

ncRNA	non-coding RNA
mRNAs	messenger RNAs
lncRNAs	long non-coding RNAs
miRNAs	microRNAs
piRNAs	piwi-interacting RNAs
circRNAs	circular RNAs
siRNAs	small interfering RNAs
snoRNAs	small nucleolar RNAs
snoRNPs	small nucleolar ribonucleoproteins
TS	tumor suppressor
lincRNAs	long intergenic RNAs
GAS5	Growth Arrest-Specific 5
BC	breast cancer
OS	overall survival
ER	estrogen receptor
TNBC	triple-negative breast cancer
LNM	lymph node metastasis
NSCLC	non-small cell lung cancer
CRC	colorectal cancer
PCa	prostate cancer
HCC	hepatocellular carcinoma
EMT	mesenchymal transition
GC	gastric cancer
HOXD-AS1	HOXD cluster antisense RNA 1
ceRNA	competing endogenous RNA
MMP9	matrix metalloproteinase 9
ZFAS1	ZNF1 antisense RNA 1
ESCC	esophageal squamous-cell carcinomas
PCAT-1	Prostate cancer-associated transcript 1
HOTAIR	HOX Transcript Antisense Intergenic RNA
LSCC	laryngeal squamous cell carcinoma
NEAT 2	nuclear enriched abundant transcript 2
CRPCa	castration-resistant PCa

nucleolar RNAs (snoRNAs). siRNAs are a kind of double-stranded ncRNA molecules with a length of about 21-25 nucleotides, can combine with the target mRNA through an entirely complementary pairing. This interferes with the expression of specific genes by degrading mRNA after transcription, preventing translation.⁶ Similarly, snoRNAs are a class of small RNA molecules nearly 60-300 nucleotides and can bind to snRNPs to form small nucleolar ribonucleoproteins (snoRNPs) complexes. The biological function of snoRNAs is to guide chemical modifications of other RNAs, including ribosomal RNAs, transfer RNAs, and small nuclear RNAs. Others like piRNAs, with a length of 30 nucleotides, are recognized as the largest class of small ncRNAs. piRNAs commonly form RNA-protein complexes through PIWI protein family to play the regulatory roles, like silencing the transcriptional gene process, maintaining germline and stem cell functions, regulating translation and mRNA stability.⁷ The increasing amount of extensive investigations indicated that circRNAs could act as gene regulators, or even can be coded into proteins.^{8,9} Nowadays, numerous researches have been conducted to determine the association between cancer and circRNAs, suggesting circRNAs can be treated as the biomarkers in

cancer. Besides, miRNAs are a family of small ncRNAs, around 22 nucleotides, which play an important role in biological pathways among multicellular organisms, including mammals. MiRNAs can exert their effects by silencing multiple mRNAs and regulating the expression of various oncogenes or tumor suppressor (TS) genes post-transcriptionally.¹⁰ lncRNAs are defined as transcripts with lengths exceeding 200 nucleotides that are not translated into protein,^{11,12} and most of them are markedly expressed in differentiated tissues or particular cancer types.¹³ lncRNAs regulate several biological processes such as differentiation, development, and biogenesis, which also involves in multiple human disorders, including certain malignancies, which are associated with the dysregulation of lncRNAs. Recent evidence demonstrated that lncRNAs play pivotal roles in cancers by regulating gene expression at the transcriptional, posttranscriptional, epigenetic, and translation levels.^{14,15} Also, although many characterized lncRNAs regulate gene expression, the underlying molecular mechanisms are diverse and poorly understood as a whole.¹⁶ However, Recent data proposed that the dysregulation of lncRNAs expression is widely involved in the pathogenesis of cancers, which includes cell proliferation, migration, invasion, and apoptosis.^{17–22} Furthermore, several studies have indicated that lncRNAs could act as oncogenes or TS genes to play pivotal regulatory roles in tumorigenesis and tumor progression.^{23,24} Thus, these findings suggest that some lncRNAs are potential targets and biomarkers for the diagnosis and prognosis of cancers.

In this review, I highlight the expression, functional roles, and underlying molecular mechanisms of some important lncRNAs in cancer progression. The standard to select the candidate lncRNAs for this study were based on their altered expression in cancer cells or tumor tissue and hallmarks which includes (sustained proliferative signaling, insensitivity to growth suppressors, evasion of apoptosis, replicative immortality, induced angiogenesis, tissue invasion and metastasis, abnormal metabolic pathways, immune evasion, genomic instability, and inflammation) (Table 1). Together, I provide an overview of the emerging opportunities and challenges of targeting lncRNAs in the diagnosis and prognosis of cancer. Moreover, I summarize the expression pattern and other relevant data regarding the roles of other lncRNAs in cancer (Table 2).

Classifications, regulatory mechanisms, and biological functions of lncRNAs

With increasing studies on highly abundant and functionally important categories of lncRNAs, which include intronic, antisense, lincRNA, cisRNA, ceRNA, I provided the classification and listed out all the existing lncRNAs (Fig. 1).²⁵ lncRNAs are currently broadly classified into the following categories²⁶: (1) antisense RNAs are located within exons and are transcribed from the opposite direction²⁷; (2) bidirectional RNAs, similar to antisense RNAs, have a reverse transcription start site but are frequently located within 1 kb of the promoter region of the protein-coding mRNA²⁸; (3) long intergenic RNAs (lincRNAs) are independently transcribed ncRNAs that do not overlap with annotated protein-coding genes (lincRNAs were identified by

Table 1 Selected target lncRNAs and their expression in tumorigenesis.

lncRNA	Function	Hallmarks	References
HOTAIR	Up-regulated	3,5,6	142,143
CCAT1	Up-regulated	2	144,145
PANDA	Down-regulated	4	146
GAS5	Down-regulated	2,6,7	147,148
ANRIL	Up-regulated	6,9	149,150
H19	Up-regulated	1,5	151
MALAT1	Up-regulated	3,5,6,10	152,153
TUG1	Up-regulated	6	154
NKILA	Up-regulated	8,10	155
UCA1	Up-regulated	2	156
TERRA	Down-regulated	4	157
PVT1	Up-regulated	1,6	158
MEG3	Down-regulated	1,3	159
PCAT-1	Up-regulated	1,3,6,7	89,160
HOTTIP	Up-regulated	1,6	161
NEAT1	Down-regulated	3	162
HOXD-AS1	Up-regulated	1,2,6	163
THOR	Up-regulated	1,7	164
ZFAS1	Up-regulated	2,3,5,6	165,166

Hallmarks of cancer: (1) sustained proliferative signaling, (2) insensitivity to growth suppressors, (3) evasion of apoptosis, (4) replicative immortality, (5) induced angiogenesis, (6) tissue invasion and metastasis, (7) abnormal metabolic pathways, (8) immune evasion, (9) genomic instability, (10) inflammation.

studies using tiling arrays of genomic sequences)²⁸; and (4) sense intronic RNAs, which are defined as having transcription start sites in introns and ending before exon regions. These RNAs can act as cis-acting agents to regulate adjacent genes on the same chromosome and as trans-acting elements, causing epigenetic changes.

Regarding the targeting regulatory mechanisms, lncRNAs possess the following four functions: regulate the spatio-temporal expression of target genes (signal function)²⁹; act as adapters in functional protein complexes (scaffold function)³⁰; binds to specific proteins and direct the localization of the resultant complex (guide function); and³¹ prevent other RNAs or proteins from binding to their natural targets (bait function). For biological functions of lncRNAs, there is a considerable number of lncRNAs with the potential to participate in both normal and aggressive disease state by regulating the biological processes such as cell differentiation, cell lineage determination, organogenesis, and tissue homeostasis along with cell pluripotency induction, X-inactivation and gene imprinting.³² Knowledge of lncRNAs functions is adding another layer of complexity to our understanding of the mechanism of lncRNA. However, according to the current researches, lncRNAs are involved in both the activation and inhibition of gene expression. In previous studies, it was observed that lncRNAs crosstalk with many epigenetic factors or interface with them to regulate gene expression and modulate nuclear architecture.³³ Some lncRNAs have been found to participate in signal transduction via playing the role as of a regulator to initiate, elongate, or terminate the combinatorial actions of transcription factors.³⁴ Moreover, many

lncRNAs and their products have been linked to clinical disease phenotypes via the regulation of alternative splicing, silencing, and post-transcriptional modification of mRNA.³⁵ The functional roles of lncRNA in biological processes are summarized in Fig. 2.

Tumor suppressor lncRNA growth arrest-specific 5 (GAS5) in human cancer

GAS5 located at 1q25 with a length of 630 nt (11), and was isolated from the NIH 3T3 cell line originally.³⁶ GAS5 can produce multiple snoRNAs but does not encode protein.³⁷ In the first, GAS5 was identified as a TS in a wide variety of human cancer. However, few studies have reported up-regulation of this lncRNA in tumor tissues compared to non-tumor tissues, in breast cancer (BC), it causes apoptosis and also growth arrest of BC cell line models and is significantly down-regulated in BC cells.³⁸ Down-regulation of GAS5 in BC cells was negatively associated with later TNM stage and shorter overall survival (OS).^{39,40} Moreover, the expression levels of GAS5 were decreased in estrogen receptor-negative (ER-) in BC tissues and cells. Furthermore, a recent study showed that the low expression of GAS5 could increase the apoptosis of triple-negative breast cancer (TNBC) and ER-positive (ER+) BC cells, which was related to lymph node metastasis (LNM), clinical stage, and poor OS.⁴¹ The preoperative level of GAS5 can be used as a degree of proliferation in BC; thus, the plasma specimens of GAS5 can be used as a biomarker to evaluate the prognosis of patients after surgery.⁴² In non-small cell lung cancer (NSCLC) patients, GAS5 plasma levels were significantly lower compared to common tissues, which according to the recent studies, the diagnostic rate of GAS5 plasma levels in NSCLC was estimated to be 0.832.⁴³ Furthermore, the overexpression of GAS5 can inhibit NSCLC proliferation, invasion, and induce the apoptosis both *in vitro* and *in vivo*.^{44,45} In human colorectal cancer (CRC) tumor tissues, it was reported that the expression of GAS5 was lower than those in normal tissues, which is correlated with tumor size, TNM staging, LNM, low histological grade, less OS, distant metastasis and higher local recurrence rate. It can confirm that the expression level of GAS5 can be an independent risk factor for CRC and a predictor of prognosis.^{46–52} Moreover, the up-regulation of GAS5 can inhibit invasion, proliferation, and migration in CRC. Also, functional studies demonstrated that the overexpression of GAS5 could induce G0/G1 cell cycle arrest and apoptosis.^{46,48} A recent study has shown that overexpression of GAS5 was dramatically related to liver metastases in the early-stage of CRC patients.⁵³ Further studies discovered that the up-regulation of GAS5 could reduce the proliferation, migration, and invasion of CRC by inhibiting the expression of miR-221 and miR-182-5p.^{49,52} Also, GAS5 promoted PTEN expression by inhibiting miR-222-3p, cell metastasis, and promoting cell autophagy during the development of CRC. Recent studies have also been shown that the expression levels of GAS5 in prostate cancer (PCa) were considerably lower in PCa tissues and cell lines than in normal counterparts. Moreover, GAS5, by inactivating the AKT/mTOR signaling pathway and targeting miR-103 *in vitro* and *in vivo*, can inhibit PCa proliferation

Table 2 Summary of the dysregulated and functional role of lncRNAs in different cancers.

lncRNA	Cancer type	Expression	Target Gene/factor	Signaling pathway	Function	Ref
GAS5	Oral squamous cell carcinoma	Up	Akt, E-cadherin, PCNA, cyclinD1, N-cadherin, vimentin, snail1	PTEN	Cell proliferation, migration, invasion, and EMT	167
MEG3	Papillary carcinoma	Down	Rac1	Rac1 pathway	Suppresses migration and invasion	168
GAS5	Breast cancer	Down	Notch-1	AKT/mTOR	Cell proliferation	169
PVT1	Prostate cancer	Up	Caspase-3, caspase-9, c-Myc	EMT	Cancer growth, apoptosis	170
ZFAS1	Head and neck squamous cell carcinoma	Up	ZNFX1, miR-150-5p, EIF4E	TGF- β , VEGF, JAK/STAT, PDGF, PI3K, p53, p38, Ras, Toll receptor, Wnt	EMT, proliferation, migration, invasion, apoptosis, cell adhesion, signal transduction, differentiation, angiogenesis, oxidative stress response	171
ANRIL	Prostate cancer	Up	CBX7	—	EMT, proliferation, migration	172
BANCR	Gastric cancer	Up	NF- κ B1	—	Proliferation, migration, invasion	173
H19	Hepatic cancer	Up	p53, ANG	HIF1 α	Proliferation	174
TUG1	Non-small-cell lung cancer	Down	p53, HOXB7	AKT and MAPK	EMT, migration	175
HOTAIR	Gastric Cancer	Up	PRC2	HGF/C-Met/Snail	EMT, migration, invasion, apoptosis	176
PVT1	Non-small-cell lung cancer	Up	EZH2	Mdm2-p53	Proliferation	177
CCAT1	Gastric cancer	Up	P27, p21, p16, caspase-3, Bax, Bcl-2	ERK/MAPK	Proliferation	178
CCAT2	Colorectal cancer	Up	MYC, miR-20a	WNT	—	179
HOTAIR	Esophageal squamous cell cancer	Up	WIF-1	Wnt/ β -catenin	Migration, invasion,	180
MALAT1	Colorectal cancer	Up	β -catenin	Wnt/ β -catenin	Proliferation, migration	181
ROR	Nasopharyngeal cancer	Up	Vimentin, N-cadherin	P53	Proliferation, migration, invasion, EMT	182
PTENP1	Hepatic cancer	Down	PTEN, PHLPP (a negative AKT regulator), ULK1, ATG7, p62	PI3K/AKT	Apoptosis	183
ATB	Breast cancer	Up	ZEB1, ZNF-217	TGF- β	EMT	184
WT1-AS	Hepatic cancer	Down	WT1	JAK/STAT3	Apoptosis	185
AFAP1-AS1	Lung cancer	Up	AFAP1, RhoA, Rac2, Rab10, Rab11a, Pfn1, RhoC, Rab11 b, LIM, Lasp1	Actin cytokeleton	Migration, invasion	186
ATB	Prostate cancer	Up	E-cadherin, ZO-1, cyclin E, cyclin D1, ZEB1, ZNF217, N-cadherin, vimentin	ERK and PI3K/AKT	Proliferation, EMT	187
ANRIL	Gastric cancer	Up	PRC2, E2F1	mTOR and CDK6/E2F1	Proliferation	188
CASC11	Colorectal cancer	Up	C-Myc	WNT/ β -catenin	Proliferation, metastasis	189
LINC00963	Prostate cancer	Up	EGFR, p-AKT	EGFR	Proliferation,	190

(continued on next page)

Table 2 (continued)

lncRNA	Cancer type	Expression	Target Gene/factor	Signaling pathway	Function	Ref
LOC400891	Prostate cancer	Up	PTEN, vimentin, β -catenin, Twist, Snail	PI3K-AKT-mTOR	migration metastasis Proliferation, migration, invasion	191
PCAT5	Prostate cancer	Up	ERG	Cell proliferation pathways	Proliferation, migration, invasion	192

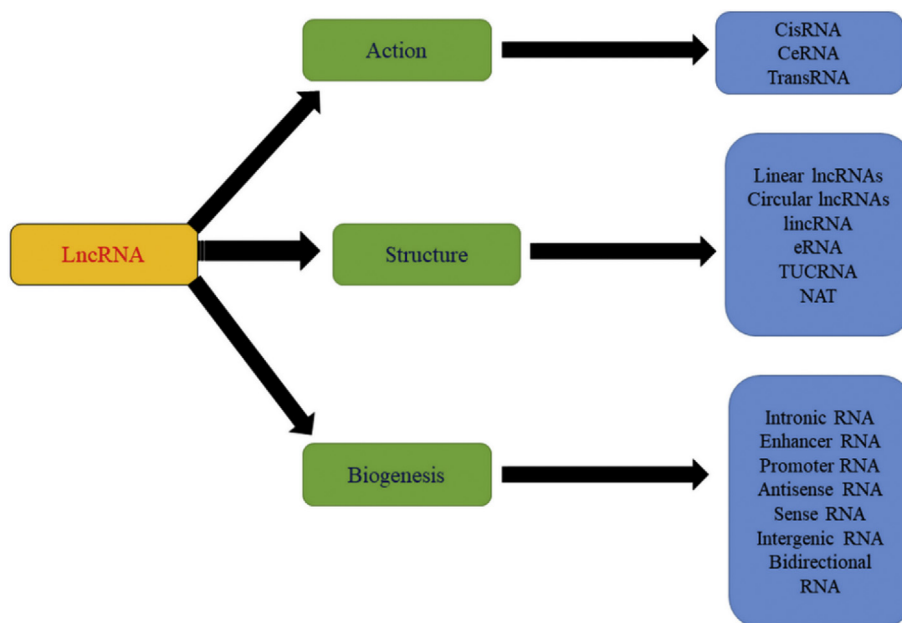


Figure 1 Classification of long non-coding RNAs. Schematic depicts the placement and classification of long non-coding RNAs into classes and sub-classes according to their action, biogenesis and structure.

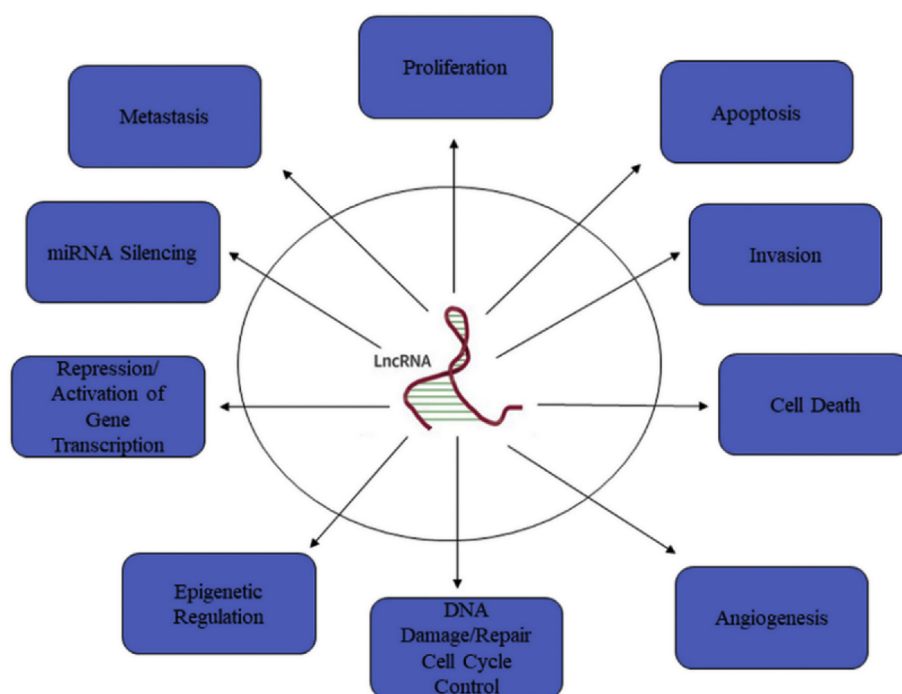


Figure 2 LncRNAs regulate various biological processes by post-transcriptional and post-translational modifications as depicted above.

and progression,⁵⁴ in contrast, inactivating the mTOR can increase GAS5 levels in androgen-responsive PCa cell lines.⁵⁵ In esophageal cancer cells, the up-regulation of GAS5 acts as a TS by increasing the expression level of PI3K and phosphorylation levels of Akt and mTOR.⁴⁰ In osteosarcoma, GAS5 has a negative effect on PI3K/AKT/GSK3 β signaling pathway via increase expression of the AKT, phosphorylated PI3K, and GSK3 β .⁵⁶ Additionally, up-regulation of GAS5 can enhance the sensitivity of lung cancer cells to EGFR-TKIs by regulating the EGFR pathway and insulin-like growth factor 1 receptor (IGF-1R).⁵⁷ Down-regulation of GAS5 was found in hepatocellular carcinoma (HCC) tissues and cells than those of adjacent normal tissues and normal liver cells. Another research discovered that increase the expression level of GAS5 inhibits the invasive of hepatocarcinoma cells by affecting the mesenchymal transition (EMT) process.⁵⁸ Moreover, the up-regulation of GAS5 significantly reduces Vim protein and consequently elevates the expression levels of E-cad; thus, it regulates the invasion and proliferation of hepatoma cells. In the clinicopathological characteristic of HCC patients, the low expression of GAS5 was correlated with tumor size, LNM, differentiation, and portal vein tumor thrombosis and advanced stage.⁵⁹ Previous studies have found that GAS5 was down-regulated in gastric cancer (GC). Furthermore, *in vivo* and *in vitro* experiments demonstrated that the GAS5 could increase proliferation and induce apoptosis in GC.⁶⁰ Also, low expression levels of GAS5 is significantly observed in GC patients with poor OS than those with higher GAS5 expression suggesting that GAS5 could be considered as an independent prognostic biomarker for GC.⁵⁹ Moreover, the down-regulation of GAS5 is related to advanced clinical stage and tumor size of GC.⁶¹

HOXD-AS1 as a novel oncogenic long non-coding RNA

HOXD cluster antisense RNA 1 (HOXD-AS1), also known as HAGLR (HOXD antisense growth-associated long noncoding RNA) is oncogenic and a novel cancer-related lncRNA localized between the *HOXD1* and *HOXD3* genes on human chromosome 2q31.2 and transcribed from a HOXD cluster.^{62–64} Recent researches indicated that HOXD-AS1 up-regulated in many cancers. Additionally, the correlation between HOXD-AS1 expression and increase proliferation, metastasis, apoptosis, and invasion is closely linked to clinical and pathological characteristics. HOXD-AS1 is considerably up-regulated in GC cells and correlated with invasion depth, TNM stages, LNM, tumor size, tumor growth, and distant metastasis.⁶⁵ The knockdown of HOXD-AS1 significantly suppressed GC cell growth by inactivating the JAK2/STAT3 pathway.^{65,66} Recent studies discovered that HOXD-AS1 is significantly increased in HCC tissues compared to adjacent normal ones. Clinical correlation analysis indicated that the up-regulation of HOXD-AS1 was significantly associated with poor prognosis and high TNM stage of HCC patients, which act as an independent risk factor for HCC survival. The expression levels of HOXD-AS1 is increased in NSCLC tissues and cells compared to normal ones, also is correlated with LNM, poor OS, TNM stage, and tumor size. In CRC tissues and cell lines, the expression

levels of HOXD-AS1 was increased, and this up-regulation is closely related to poor prognosis, furthermore by competing endogenous RNA (ceRNA) for miR-217, this lncRNA can increase the expression levels of EZH2 and AEG-1 which have been discovered to be targets of miR-217.⁶⁷ Moreover, HOXD-AS1 can regulate SOX4 expression by the transcription factor STAT3 through competitive bidding to miR-130a-3p, resulting in activation of MMP2 and EZH2 expression.⁶⁸ HOXD-AS1 also regulates the functions of NSCLC cells via various signaling pathways, which includes decreasing expression of p21,⁶⁹ up-regulation of matrix metalloproteinase 9 (MMP9) by binding with miR-133 b,⁶³ and aberrant regulation of miR-147a/pRB.⁶⁴ The clinicopathological association between high expression of HOXD-AS1 and tumor stage, Gleason score, LNM, and progression-free survival of PCa patients were discovered. Also, HOXD-AS1 can increase PCa cell proliferation via recruiting WDR5, which regulates the expression of target genes via mediating H3K4me3.⁷⁰ These data indicated that HOXD-AS1 might be used as a prognostic biomarker for PCa.⁷¹ According to the recent study, overexpression of HOXD-AS1 is considerably associated with gastric tumor size, tumor-node-metastasis stage, invasion depth, and LNM.⁶⁵ In osteosarcoma cells, STAT3 and its target proteins (Bcl-2, MMP-2, and cyclin D1) able to increase cell proliferation, inhibit cell cycle arrest at the G1 stage, apoptosis, and colony formation by up-regulation of HOXD-AS1. Up-regulation of HOXD-AS1 can be monitored in both ovarian cancer cell lines and tissues; also, the oncogenic role of this lncRNA can increase colony formation and cell proliferation.⁷² Furthermore, by targeting miR-133a-3p and activating Wnt/ β -catenin signaling, HOXD-AS1 can increase cell proliferation in epithelial ovarian cancer.⁷³ Besides, HOXD-AS1 by targeting miR19a/ARHGAP11A signaling can promote liver cancer metastasis and progression⁷⁴; 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.⁷⁵

ZFAS1 as a novel oncogenic and tumor-related long non-coding RNA in multiple human cancer

ZNF1 antisense RNA 1 (ZFAS1) a novel lncRNA transcribed in the antisense orientation of zinc finger NFX1-type containing 1 (ZNF1) and localized on human chromosome 20q13.13,⁷⁶ and originally identified a regulator of mammary development.⁷⁶ ZFAS1 is overexpressed and plays an oncogenic role in most types of cancers. A recent study showed that ZFAS1 was down-regulated in BC tissues and cells compared to normal ones⁷⁶; also proliferation and differentiation in BC cells can be increased by Knockdown of ZFAS1 in mammary epithelial cells, it can be indicated that ZFAS1 play as a TS gene in BC. Fan et al,⁷⁷ indicated that the up-regulation of ZFAS1 in BC cell lines considerably suppressed migration, invasion, and cell proliferation. According to a recent study, the expression levels of ZFAS1 was considerably down-regulated in HER2 BC subtypes, and more importantly, ER + BC had high expression levels of ZFAS1 compared to ER-. In GC, a recent study discovered that ZFAS1 was up-regulated in both tissues and cell lines of

GC patients⁷⁸; also, the overexpression of ZFAS1 was considerably associated with TNM stage, LNM and tumor size.⁷⁹ In CRC, ZFAS1 was up-regulated in cancer tissues compared to normal ones, and this overexpression is considerably associated with migration, invasion, and angiogenesis of CRC cells.^{80,81} Moreover, ZFAS1 act as miRNA sponge throughout miR-150-5p, and consequently targeting VEGFA in an AGO2-dependent manner, also ZFAS1 mediated activities of the downstream AKT/mTOR pathway and VEGFR2 to CRC progression.⁵⁹ Moreover, the up-regulation of ZFAS1 has considerably related to *Helicobacter pylori* (*H. pylori*) infection in CRC.⁸² Li et al⁸³ showed that ZFAS1 expression was significantly overexpressed in HCC tissues and cell lines than those normal ones. The further study discovered that high expression of ZFAS1 could enhance HCC cell invasion and tumor metastasis both *in vitro* and *in vivo*. ZFAS1, via interacting with miR-150 could suppress HCC cell invasion and metastasis by targeting ZEB1. In osteosarcoma tissues and cell lines, recent studies showed that ZFAS1 was significantly up-regulated.^{84,85} Furthermore, by Kaplan–Meier analysis in osteosarcoma patients with high expression levels of ZFAS1, it is clarified that these patients had poor OS than those with low ZFAS1. Overexpression of ZFAS1 was considerably correlated with the prognosis of osteosarcoma patients.⁸⁴ The correlation between ZFAS1 and esophageal squamous-cell carcinomas (ESCC) progression was recently discovered. ZFAS1 expression was significantly higher in ESCC tissues compared to corresponding adjacent normal ones⁸⁶; also, survival analysis showed that ESCC patients with high ZFAS1 expression had poor OS, these data indicated that ZFAS1 expression was determined to be an independent prognostic factor.⁸⁶ In ovarian cancer, recent studies validated that ZFAS1 was highly expressed in ovarian cancer tissues compared to normal ones; also, this overexpression was closely related to the poor prognosis of patients. Moreover, they found that ZFAS1 plays a critical role in increasing the proliferation, invasion, and migration of epithelial ovarian cancer cell lines.⁸⁷ ZFAS1 expression was up-regulated in GC tissues, and this expression level has been significantly correlated with LNM, TNM stage, and poor prognosis.^{79,88} ZFAS1 can increase the expression of CDK1, EMT markers including Slug, Snail, Twist, and ZEB1, effector enzyme of EGFR-RAF-ERK pathway, and dysregulate the expression of pro-apoptotic and anti-apoptotic proteins. It happens through the up-regulation of Bcl-2 (antiapoptotic) and down-regulation of Bax (pro-apoptotic proteins), which eventually leads to tumor progression.⁷⁹

PCAT-1 play an oncogenic role in many aspects of carcinogenesis

Prostate cancer-associated transcript 1 (PCAT-1) consists of 2 exons, which include exon 1 with a sequence of the retroviral long terminal repeat (LTR) and exon 2 contains an AluY repeat element from the HSMAR1 mariner family transposase sequences.⁸⁹ PCAT-1 localized on human chromosome 8q24 and 725 kb upstream of the c-Myc oncogene.⁸⁹ PCAT-1 was identified via its involvement in PCa, and up-regulation of this lncRNA was discovered to increase PCa progression and deterioration. Prensner et al

identified PCAT-1 as a novel transcriptional inhibitor promotes PCa cell proliferation⁹⁰; also, in the next experiment, they discovered 121 PCa-associated ncRNA transcripts (PCATs) via RNA-Seq from a cohort of prostate tissues and cells lines. Moreover, the up-regulation of PCAT-1 increases migration, proliferation, and invasion of PCa cells.⁹¹ Furthermore, the expression level of three target genes of PCAT-1 contains BRCA2, CENPE, and CENPF was increased when PCAT-1 was knockdown in PCa cells. Xu et al reported that PCAT-1 functions as a ceRNA for miR-145-5p to modulate fascin-1 (FSCN1) expression, suggesting a role for a PCAT-1/miR-145-5p/FSCN1 regulatory axis in PCa progression.⁹¹ In BC, PCAT-1 has been discovered to be elevated in cancer specimens compared with adjacent normal samples,⁹² and also PCAT-1 promotes BC cell growth and inhibits apoptosis.⁹³ The dysregulation of PCAT-1 is closely related to clinicopathological characteristics and OS in cancer patients suggesting its potential role as a diagnosis and prognosis biomarker. Up-regulation of PCAT-1 has been shown to be considerably associated with TNM stage and metastasis in HCC and osteosarcoma,^{94–97} also tumor invasion, and LNM in GC and esophageal cancer.^{98–100} Wen et al indicated that the low expression levels of PCAT-1 significantly reduced the invasion and migration of HCC cell lines.¹⁰¹ Similarly, Zhang et al reported that PCAT-1 acted as a ceRNA against miR-122, and the silencing of PCAT-1 inhibited the progression of ESCC by reducing Wnt/ β -catenin signaling through miR-122 repression and WNT1 expression.¹⁰² In ESCC, the expression levels of PCAT-1 in tumor tissues are considerably higher than normal ones. The up-regulation of PCAT-1 was closely related to tumor invasion, TNM stage and LNM; also, the high expression of PCAT-1 indicated poor prognosis in ESCC.¹⁰⁰ According to the experiment conducted by Cui et al the expression levels of PCAT-1 was highly expressed in GC, and this expression was correlated to poor OS.⁹⁸ Also, Bi et al discovered that PCAT-1 increases cell proliferation, migration, and invasion in GC cells via regulating CDKN1A. CDKN1A was increased in PCAT-1 knockdown GC cells, and CDKN1A knockdown can rescue PCAT-1 knockdown-promoted cell proliferation and migration.⁹⁹ These results indicated that PCAT-1 plays an oncogenic role in the GC progression. Moreover, Kaplan–Meier analysis indicated that GC patients with up-regulation of PCAT-1 were considerably had low OS.⁹⁸

HOTAIR is deregulated in many human cancers

Dysregulation of HOX Transcript Antisense Intergenic RNA (HOTAIR) is frequently found in human cancer. Recent evidence suggests a role of HOTAIR in pathogenesis, disease progression, and reduced survival, but the mechanism of action remains largely unclear. Several recent studies validated the high expression of HOTAIR in multiple tumors and cell lines. However, the upstream signaling and transcriptional networks that promote the expression of HOTAIR in tumors still need to be investigated. Moreover, several studies demonstrated that the expression levels of HOTAIR are closely correlated with invasiveness, tumor stage, and poor OS in a variety of cancers. In numerous cancers, HOTAIR can acts as a pro-oncogene due to overexpression and be implicated in various hallmarks of cancer, such as

inhibition of apoptosis, cellular proliferation, genomic instability, angiogenesis, invasion, and metastasis.^{51,52} The expression of HOTAIR was discovered to be closely related to advance pathological stage, TNM stage, LNM, poor tumor differentiation, increased tumor progression, metastasis, and poor OS.^{39,103} In BC cell lines, up-regulation of HOTAIR is discovered to suppress apoptosis, promotes cell growth, migration, invasion, and maintain cell viability.^{104,105} In an analysis study by using the data from the TCGA database the correlation between the up-regulation of HOTAIR and breast carcinoma invasion was observed.¹⁰⁶ For survival and maintenance of BC cells, HOTAIR was found to be indispensable and also discovered to be transcriptionally regulated by estrogen.¹⁰⁷ Recent experiments showed that the expression levels of HOTAIR were up-regulated in PCa tissues and cells; also, overexpression of this lncRNA in PCa cells is associated with tumor growth, invasion, proliferation, migration, and anti-apoptosis in PCa.¹⁰⁸ Additionally, HOTAIR is a well-known biomarker for poor prognosis of PCa.¹⁰⁹ Also, the expression of HOTAIR by maintaining androgen receptor (AR) activity in an androgen-independent manner can increase the invasion of castration-resistant cells and proliferation. HOTAIR regulates gene expression by recruiting PRC2 complex to AR in both AR-dependent and AR-independent manner. Additionally, HOTAIR can regulate the expression of FGFR1 by sponging miR-520 b and elevate this lncRNA and target genes were discovered in PCa patients with bone metastasis. HOTAIR was up-regulated in CRC tissues and cells compared to healthy controls, and also this overexpression is related to tumor progression, metastasis, migration, cell proliferation, invasion, TNM stage, reduced survival, and worse prognosis of CRC patients.^{110–113} Pan et al proposed that the regulatory HOTAIR/miR-326/FUT6 axis by α 1, 3-fucosylation of CD44 promoted CRC progression.¹¹⁴ Okugawa et al³⁹ conducted a real-time expression analysis to quantify the expression levels of HOTAIR in GC tissues. They indicated the considerably elevated HOTAIR expression in GC tissues, and their report proposed that elevated HOTAIR expression could serve as a potential biomarker for GC prognosis. Moreover, recent studies discovered that HOTAIR recruits PRC2 to catalyze H3K27 trimethylation to repress E-cadherin and promote EMT in GC transcriptionally.¹¹⁵ HOTAIR knockdown by down-regulating of STAT3/Cyclin D1 activity increase miR454-3p expression and thereby suppress GC proliferation.¹¹⁶ HOTAIR, by triggering GCP5 expression via sponging miR-217 promotes GC carcinogenesis.¹¹⁷ In pancreatic cancer, HOTAIR by suppressing the expression of miR-663 b via remodeling the chromatin structure within the miR-663 b promoter, promotes pancreatic cancer cell proliferation.¹¹⁸ In HCC, the up-regulation of HOTAIR by regulating the Wnt/ β -catenin signal transduction pathway was found to be related to progression and tumor recurrence.¹¹⁹

Interestingly, a recent study has shown that the expression of HOTAIR was considerably higher in NSCLC tissues compared to the adjacent normal tissues, and also this lncRNA was negatively associated with p53 functionality.¹²⁰ Clinical studies have also shown an up-regulation of HOTAIR in laryngeal squamous cell carcinoma (LSCC) tissues was significantly associated with advancing pathological stage, LNM, and poor differentiation. Moreover, up-

regulation of HOTAIR and miR-21 were observed in serum exosomes of LSCC patients when compared to the polyps of vocal cords, and hence, both HOTAIR and miR-21 could serve as a potential diagnostic and prognostic biomarkers in LSCC.¹²¹ Additionally, evaluation of the tissues, cells, and plasma of lung cancer patients revealed increase HOTAIR expression levels compared to healthy individuals.

MALAT1: a potential biomarker in cancer

MALAT1 also termed nuclear enriched abundant transcript 2 (NEAT 2), an 8500 nts lncRNA, located on human chromosome 11q13¹²², which was characterized in a study of NSCLC was conducted by Ji et al¹²² At the molecular level, MALAT1 lncRNA is recruited to nuclear speckles and has been reported to regulate pre-mRNA splicing.¹²³ Up-regulation of MALAT1 was found in numerous types of cancer; also, the association between the overexpression of MALAT1 and tumor cell proliferation, migration, invasion, and apoptosis have been discovered.¹²⁴ MALAT1 was first identified to be considerably associated with the metastasis of NSCLC, and therefore MALAT1 was proposed to be a prognostic marker.¹²² Furthermore, increase the expression levels of MALAT1 contributed to brain metastasis by promoting EMT in NSCLC.¹²⁵ In the previous study reported that MALAT1 via PI3K/Akt pathway promotes tumor proliferation and metastasis in osteosarcoma.¹²⁶ Furthermore, another study indicated that the expression levels of MALAT1 could regulate EMT via the PI3K-AKT pathway,¹²⁷ which was involved in the progression of osteosarcoma.¹²⁸ Moreover, MALAT1 is involved in the regulation of other signaling pathways such as MAPK/ERK^{129,130} WNT/ β -catenin¹³¹ and NF- κ B¹³² which, leads to a modification of proliferation, cell death, cell cycle, migration, invasion, immunity, angiogenesis, and tumorigenicity. MALAT1 was overexpressed in HCC, and this up-regulation may be associated with a high recurrence risk of tumor following by liver transplantation.¹³³ MALAT1 was also found to regulate HCC progression through the mTOR pathway.¹³⁴ Additionally, the up-regulation of MALAT1 was shown to promote tumor proliferation and metastasis by dephosphorylating of ATM-CHK2 pathway in ESCC.¹³⁵ In retinoblastoma (RB), MALAT1 promotes tumor growth via suppressing miR-124, then overexpression of Slug as a member of the MAPK/ERK pathway leads to an induction of MAPK/ERK pathway.¹²⁹ Furthermore, the down-regulation of MALAT1 in osteosarcoma leads to cell proliferation and phosphorylation of main molecules PI3Kp85 α and Akt in PI3K/AKT signaling pathway.^{126,131} Also, MALAT1 may serve as a target of c-MYC that promote MALAT1 expression and cell proliferation in Ewing's sarcoma (EWS).¹³⁶ The up-regulation of MALAT1 was related to the ability of proliferation and apoptosis in urothelial carcinoma of bladder cancer cells.¹³⁷ Moreover, a previous study revealed that MALAT1 increase EMT-associated cell migration and may be activated via Wnt signaling in bladder cancer.¹³⁸ Another study indicated that MALAT1 is closely related to the maintenance of tumorigenicity and the progression of castration-resistant PCa (CRPCa).¹³⁹ Another study revealed that MALAT1 was the top down-regulated gene in the WNT inhibitory factor 1-expressing cells, and identified that knockdown of

MALAT1 could reduce the migration of glioblastoma cells.¹⁴⁰ In GC, the up-regulation of MALAT1 was reported to increase the development and metastasis of cancer.³⁹ In a clinical study on pancreatic cancer, the overexpression of MALAT1 was identified as an unfavorable predictor for its clinical progression and prognosis.¹⁴¹

Conclusion

In this review, the role and importance of lncRNAs in the pathogenesis, metastasis, and progression of various malignant tumors were discussed. Taken together, I extended the role of lncRNAs in the regulation of several target genes and signaling pathways, which involves in cancer progression. The use of lncRNAs as biomarkers have many advantages, which include, they are much stable in body fluids and can be non-invasively monitored via molecular techniques (PCR, sequencing) compared to classical biopsies. Moreover, they are differentially expressed in body fluids, and their expression is tissue-specific. Recent experimental evidence indicated that lncRNAs could be used as valid diagnostic and prognostic biomarkers for human tumors. Dysregulation of lncRNAs can occur in response to the presence of a tumor or a change in status, enabling them to be used for a variety of applications, which includes screening, diagnosis, staging, prognosis, and monitoring of recurrence after treatment. The aims of recent researches have been analyzed the expression of the lncRNAs in cancer patients, in order to investigate novel prognostic and diagnostic biomarkers in patients. In this review, although a significant number of lncRNAs dysregulation was observed in cancer and emerge as potential biomarkers for diagnosis and prognosis, besides, validations are nonetheless in need. Moreover, future well-designed, large-size patient cohort studies are required to investigate not only functional characterization, but also optimize isolation procedures and tissue-specific delivery methods to confirm the clinical value for the use of lncRNAs as a diagnostic and prognostic biomarker, and a therapeutic target in cancers. Further insight into the biological significance and functioning of lncRNAs will require additional studies to be conducted, which may lead to the discovery of yet more mechanisms of action.

Conflict of Interests

The authors declare no conflict of interest.

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