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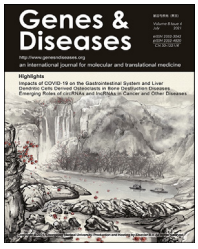

REVIEW ARTICLE

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.

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 metallopeptidase 9
ZFAS1	ZNFX1 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 complimentary 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 dysregulated 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 categories[26]: (1) antisense RNAs are located within exons and are transcribed from the opposite direction[27]; (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 mRNA[28]; (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); and[31] 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-κB1	—	Proliferation, migration, invasion	[173]
H19	Hepatic cancer	Up	p57, ANG	HIF1α	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 cytokeratin	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

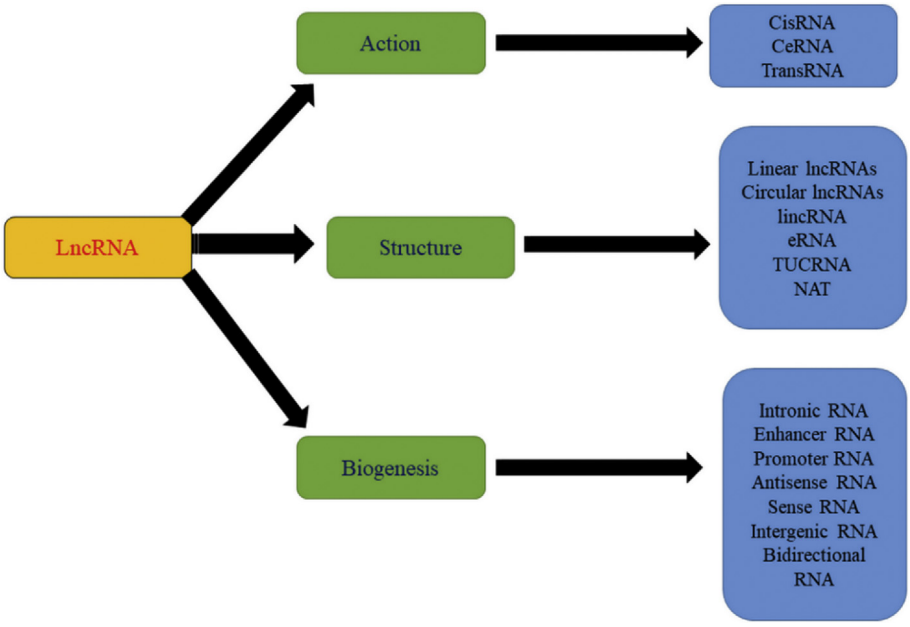

Figure 1 Classification of long non-coding RNAs. Schematic depicts the placement and classification of long non-coding RNAs into classes and sub-classes according to their action, biogenesis and structure.

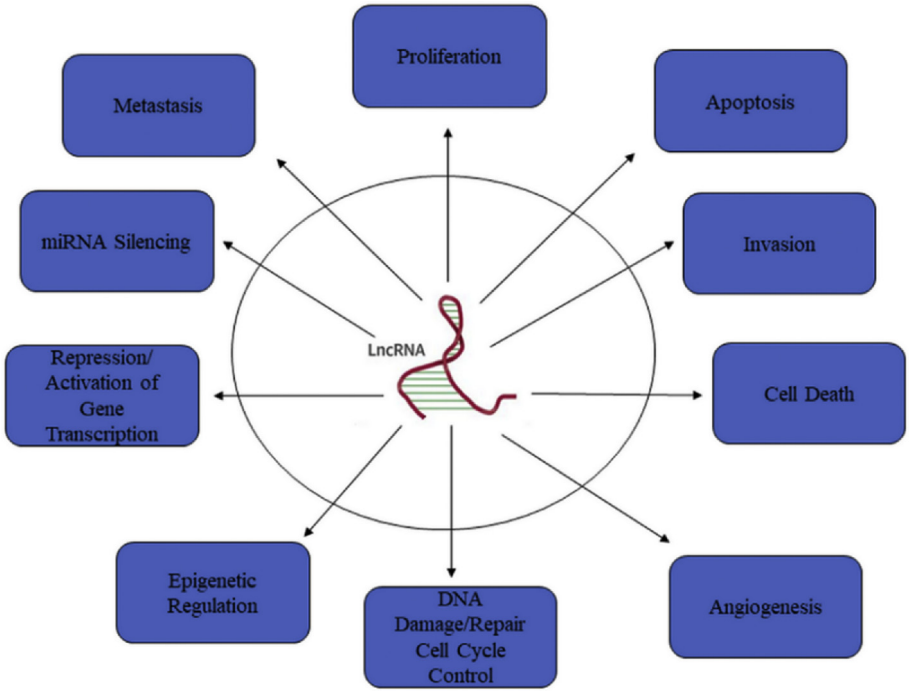

Figure 2 LncRNAs regulate various biological processes by post-transcriptional and post-translational modifications as depicted above.

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/GSK3β signaling pathway via increase expression of the AKT, phosphorylated PI3K, and GSK3β.[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 metallopeptidase 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 progression[74]; 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

ZNFX1 antisense RNA 1 (ZFAS1) a novel lncRNA transcribed in the antisense orientation of zinc finger NFX1-type containing 1(ZNFX1) 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 ones[76]; 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 patients[78]; 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 al[83] 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 ones[86]; 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 proliferation[90]; 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 α1, 3-fucosylation of CD44 promoted CRC progression.[114] Okugawa et al[39] conducted a real-time expression analysis to quantify the expression levels of HOTAIR in GC tissues. They indicated the considerably elevate 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 11q13 [122], which was characterized in a study of NSCLC was conducted by Ji et al[122] 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-catenin[131] and NF-kB[132] 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 PI3Kp85α 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.

References

1. Mattick J, Makunin I. Non-coding R. *Hum Mol Genet*. 2006; 15(1):R17—R29.
2. Hüttenhofer A, Schattner P, Polacek N. Non-coding RNAs: hope or hype? *Trends Genet*. 2005;21(5):289—297.
3. Phizicky EM, Hopper AK. tRNA biology charges to the front. *Genes Dev*. 2010;24(17):1832—1860.
4. Alvarez-Dominguez JR, Lodish HF. Emerging mechanisms of long noncoding RNA function during normal and malignant hematopoiesis. *Blood J Am Soc Hematol*. 2017;130(18): 1965—1975.
5. Chen LL. The biogenesis and emerging roles of circular RNAs. *Nat Rev Mol Cell Biol*. 2016;17(4):205—211.
6. Martinez J, Patkaniowska A, Urlaub H, Lührmann R, Tuschl T. Single-stranded antisense siRNAs guide target RNA cleavage in RNAi. *Cell*. 2002;110(5):563—574.
7. Teixeira FK, Okuniewska M, Malone CD, Coux RX, Rio DC, Lehmann R. piRNA-mediated regulation of transposon alternative splicing in the soma and germ line. *Nature*. 2017; 552(7684):268—272.
8. Pamudurti NR, Bartok O, Jens M, et al. Translation of circRNAs. *Mol Cell*. 2017;66(1):9—21.
9. Hansen TB, Jensen TI, Clausen BH, et al. Natural RNA circles function as efficient microRNA sponges. *Nature*. 2013; 495(7441):384—388.
10. Ambros V. The functions of animal microRNAs. *Nature*. 2004; 431(7006):350—355.
11. Dhanoa JK, Sethi RS, Verma R, Arora JS, Mukhopadhyay CS. Long non-coding RNA: its evolutionary relics and biological implications in mammals: a review. *J Anim Sci Technol*. 2018; 60(1),e25.
12. Prensner JR, Chinnaiyan AM. The emergence of lncRNAs in cancer biology. *Cancer Discov*. 2011;1(5):391—407.
13. Iyer MK, Niknafs YS, Malik R, et al. The landscape of long noncoding RNAs in the human transcriptome. *Nat Genet*. 2015;47(3):199—208.
14. Mercer TR, Dinger ME, Mattick JS. Long non-coding RNAs: insights into functions. *Nat Rev Genet*. 2009;10(3):155—159.
15. Ponting CP, Oliver PL, Reik W. Evolution and functions of long noncoding RNAs. *Cell*. 2009;136(4):629—641.
16. Quinn JJ, Chang HY. Unique features of long non-coding RNA biogenesis and function. *Nat Rev Genet*. 2016;17(1):47—62.
17. Xu Y, Zhang X, Hu X, et al. The effects of lncRNA MALAT1 on proliferation, invasion and migration in colorectal cancer through regulating SOX9. *Mol Med*. 2018;24(1),e52.
18. Chen L, Zhang Y-H, Lu G, Huang T, Cai Y-D. Analysis of cancer-related lncRNAs using gene ontology and KEGG pathways. *Artif Intell Med*. 2017;76:27—36.
19. Peng F, Wang R, Zhang Y, et al. Differential expression analysis at the individual level reveals a lncRNA prognostic signature for lung adenocarcinoma. *Mol Cancer*. 2017; 16(1),e98.
20. Liu M, Zhang H, Li Y, et al. HOTAIR, a long noncoding RNA, is a marker of abnormal cell cycle regulation in lung cancer. *Cancer Sci*. 2018;109(9):2717—2733.
21. Huarte M. The emerging role of lncRNAs in cancer. *Nat Med*. 2015;21(11):1253—1261.
22. Lin C, Yang L. Long noncoding RNA in cancer: wiring signaling circuitry. *Trends Cell Biol*. 2018;28(4):287—301.
23. Gutschner T, Diederichs S. The hallmarks of cancer: a long non-coding RNA point of view. *RNA Biol*. 2012;9(6):703—719.
24. Isin M, Dalay N. LncRNAs and neoplasia. *Clin Chim Acta*. 2015; 444:280—288.
25. Gullerova M. Long non-coding RNA. In: *Genomic Elements in Health, Disease and Evolution*. Springer; 2015:83—108.
26. Lanzafame M, Bianco G, Terracciano LM, Ng CK, Piscuoglio S. The role of long non-coding RNAs in hepatocarcinogenesis. *Int J Mol Sci*. 2018;19(3),e682.
27. Bazin J, Crespi M. Antisense movement on the clock. *New Phytol*. 2017;216(3):626—628.
28. Yu J, Wu X, Huang K, et al. Bioinformatics identification of lncRNA biomarkers associated with the progression of esophageal squamous cell carcinoma. *Mol Med Rep*. 2019; 19(6):5309—5320.
29. Wei DM, Jiang MT, Lin P, et al. Potential ceRNA networks involved in autophagy suppression of pancreatic cancer caused by chloroquine diphosphate: a study based on differentially-expressed circRNAs, lncRNAs, miRNAs and mRNAs. *Int J Oncol*. 2019;54(2):600—626.

30. Luo K, Zhang Y, Xv C, et al. Fusobacterium nucleatum, the communication with colorectal cancer. *Biomed Pharmacother*. 2019;116,e108988.
31. Jiang D, Xu L, Ni J, Zhang J, Cai M, Shen L. Functional polymorphisms in LncRNA HOTAIR contribute to susceptibility of pancreatic cancer. *Cancer Cell Int*. 2019;19(1),e47.
32. Kazemzadeh M, Safaralizadeh R, Orang AV. LncRNAs: emerging players in gene regulation and disease pathogenesis. *J Genet*. 2015;94(4):771—784.
33. Hanly DJ, Esteller M, Berdasco M. Interplay between long non-coding RNAs and epigenetic machinery: emerging targets in cancer? *Phil Trans Biol Sci*. 2018;373(1748),e20170074.
34. Long Y, Wang X, Youmans DT, Cech TR. How do lncRNAs regulate transcription? *Sci Adv*. 2017;3(9),eaao2110.
35. Li X, Wu Z, Fu X, Han W. lncRNAs: insights into their function and mechanics in underlying disorders. *Mutat Res Rev Mutat Res*. 2014;762:1—21.
36. Endo H, Shiroki T, Nakagawa T, et al. Enhanced expression of long non-coding RNA HOTAIR is associated with the development of gastric cancer. *PLoS One*. 2013;8(10),e77070.
37. Liu X-h, Sun M, Nie F-q, et al. Lnc RNA HOTAIR functions as a competing endogenous RNA to regulate HER2 expression by sponging miR-331-3p in gastric cancer. *Mol Cancer*. 2014;13(1),e92.
38. Mourtada-Maarabouni M, Pickard M, Hedge V, Farzaneh F, Williams G. GAS5, a non-protein-coding RNA, controls apoptosis and is downregulated in breast cancer. *Oncogene*. 2009;28(2):195—208.
39. Okugawa Y, Toiyama Y, Hur K, et al. Metastasis-associated long non-coding RNA drives gastric cancer development and promotes peritoneal metastasis. *Carcinogenesis*. 2014;35(12):2731—2739.
40. Gu J, Wang Y, Wang X, et al. Downregulation of lncRNA GAS5 confers tamoxifen resistance by activating miR-222 in breast cancer. *Cancer Lett*. 2018;434:1—10.
41. Li S, Zhou J, Wang Z, Wang P, Gao X, Wang Y. Long noncoding RNA GAS5 suppresses triple negative breast cancer progression through inhibition of proliferation and invasion by competitively binding miR-196a-5p. *Biomed Pharmacother*. 2018;104:451—457.
42. Han L, Ma P, Liu S-M, Zhou X. Circulating long noncoding RNA GAS5 as a potential biomarker in breast cancer for assessing the surgical effects. *Tumor Biol*. 2016;37(5):6847—6854.
43. Liang W, Lv T, Shi X, et al. Circulating long noncoding RNA GAS5 is a novel biomarker for the diagnosis of nonsmall cell lung cancer. *Medicine*. 2016;95(37),e4608.
44. Mei Y, Si J, Wang Y, et al. Long noncoding RNA GAS5 suppresses tumorigenesis by inhibiting miR-23a expression in non-small cell lung cancer. *Oncol Res*. 2017;25(6):1027—1037.
45. Shi X, Sun M, Liu H, et al. A critical role for the long non-coding RNA GAS5 in proliferation and apoptosis in non-small-cell lung cancer. *Mol Carcinog*. 2015;54(S1):E1—E12.
46. Yang Y, Shen Z, Yan Y, et al. Long non-coding RNA GAS5 inhibits cell proliferation, induces G0/G1 arrest and apoptosis, and functions as a prognostic marker in colorectal cancer. *Oncol Lett*. 2017;13(5):3151—3158.
47. Wang Q, Fan H, Yin Z, et al. Effect of curcumin on radiosensitization of CNE-2 cells and its mechanism. *Zhongguo Zhong yao za zhi*. 2014;39(3):507—510.
48. Li J, Wang Y, Zhang C-G, Xiao H-J, Hou J-M, He J-D. Effect of long non-coding RNA Gas5 on proliferation, migration, invasion and apoptosis of colorectal cancer HT-29 cell line. *Cancer Cell Int*. 2018;18(1),e4.
49. Cheng K, Zhao Z, Wang G, Wang J, Zhu W. lncRNA GAS5 inhibits colorectal cancer cell proliferation via the miR-182-5p/FOXO3a axis. *Oncol Rep*. 2018;40(4):2371—2380.
50. Yin D, He X, Zhang E, Kong R, De W, Zhang Z. Long noncoding RNA GAS5 affects cell proliferation and predicts a poor prognosis in patients with colorectal cancer. *Med Oncol*. 2014;31(11),e253.
51. Ko SY, Ko HA, Shieh TM, et al. Advanced glycation end products influence oral cancer cell survival via Bcl-xl and Nrf-2 regulation in vitro. *Oncol Lett*. 2017;13(5):3328—3334.
52. Liu L, Meng T, Yang X-H, et al. Prognostic and predictive value of long non-coding RNA GAS5 and mircoRNA-221 in colorectal cancer and their effects on colorectal cancer cell proliferation, migration and invasion. *Cancer Biomarkers*. 2018;22(2):283—299.
53. Kong H, Wu Y, Zhu M, et al. Long non-coding RNAs: novel prognostic biomarkers for liver metastases in patients with early stage colorectal cancer. *Oncotarget*. 2016;7(31):50428—50436.
54. Xue D, Zhou C, Lu H, Xu R, Xu X, He X. LncRNA GAS5 inhibits proliferation and progression of prostate cancer by targeting miR-103 through AKT/mTOR signaling pathway. *Tumor Biol*. 2016;37(12):16187—16197.
55. Yacqub-Usman K, Pickard MR, Williams GT. Reciprocal regulation of GAS5 lncRNA levels and mTOR inhibitor action in prostate cancer cells. *Prostate*. 2015;75(7):693—705.
56. Wang Y, Kong D. LncRNA GAS5 represses osteosarcoma cells growth and metastasis via sponging MiR-203a. *Cell Physiol Biochem*. 2018;45(2):844—855.
57. Dong S, Qu X, Li W, et al. The long non-coding RNA, GAS5, enhances gefitinib-induced cell death in innate EGFR tyrosine kinase inhibitor-resistant lung adenocarcinoma cells with wide-type EGFR via downregulation of the IGF-1R expression. *J Hematol Oncol*. 2015;8(1),e43.
58. Jiao G, Pan B, Zhou Z, Zhou L, Li Z, Zhang Z. MicroRNA-21 regulates cell proliferation and apoptosis in H2O2-stimulated rat spinal cord neurons. *Mol Med Rep*. 2015;12(5):7011—7016.
59. Sun M, Jin F-y, Xia R, et al. Decreased expression of long noncoding RNA GAS5 indicates a poor prognosis and promotes cell proliferation in gastric cancer. *BMC Cancer*. 2014;14(1),e319.
60. Chen X, Zeng K, Xu M, et al. SP1-induced lncRNA-ZFAS1 contributes to colorectal cancer progression via the miR-150-5p/VEGFA axis. *Cell Death Dis*. 2018;9(10),e982.
61. Guo X, Deng K, Wang H, et al. GAS5 inhibits gastric cancer cell proliferation partly by modulating CDK6. *Oncol Res Treat*. 2015;38(7—8):362—366.
62. Lu Y, Liu W-G, Lu J-H, et al. LncRNA UCA1 promotes renal cell carcinoma proliferation through epigenetically repressing p21 expression and negatively regulating miR-495. *Tumor Biol*. 2017;39(5). e1010428317701632.
63. Xia H, Jing H, Li Y, Lv X. Long noncoding RNA HOXD-AS1 promotes non-small cell lung cancer migration and invasion through regulating miR-133b/MMP9 axis. *Biomed Pharmacother*. 2018;106:156—162.
64. Wang Q, Jiang S, Song A, et al. HOXD-AS1 functions as an oncogenic ceRNA to promote NSCLC cell progression by sequestering miR-147a. *OncoTargets Ther*. 2017;10:4753—4763.
65. Zheng L, Chen J, Zhou Z, He Z. Knockdown of long non-coding RNA HOXD-AS1 inhibits gastric cancer cell growth via inactivating the JAK2/STAT3 pathway. *Tumor Biol*. 2017;39(5), e1010428317705335.
66. Qu Y, Zheng S, Kang M, et al. Knockdown of long non-coding RNA HOXD-AS1 inhibits the progression of osteosarcoma. *Biomed Pharmacother*. 2018;98:899—906.
67. Li X, Zhao X, Yang B, et al. Long non-coding RNA HOXD-AS1 promotes tumor progression and predicts poor prognosis in colorectal cancer. *Int J Oncol*. 2018;53(1):21—32.
68. Wang H, Huo X, Yang X-R, et al. STAT3-mediated upregulation of lncRNA HOXD-AS1 as a ceRNA facilitates liver cancer metastasis by regulating SOX4. *Mol Cancer*. 2017;16(1),e136.

69. Lu C, Ma J, Cai D. Increased HAGLR expression promotes non—small cell lung cancer proliferation and invasion via enhanced de novo lipogenesis. *Tumor Biol*. 2017;39(4), e1010428317697574.
70. Tan Q, Zuo J, Qiu S, et al. Identification of circulating long non-coding RNA GAS5 as a potential biomarker for non-small cell lung cancer diagnosisnon-small cell lung cancer, long non-coding RNA, plasma, GAS5, biomarker. *Int J Oncol*. 2017; 50(5):1729—1738.
71. Gu P, Chen X, Xie R, et al. lncRNA HOXD-AS1 regulates proliferation and chemo-resistance of castration-resistant prostate cancer via recruiting WDR5. *Mol Ther*. 2017;25(8): 1959—1973.
72. Wang Y, Zhang W, Wang Y, Wang S. HOXD-AS1 promotes cell proliferation, migration and invasion through miR-608/FZD4 axis in ovarian cancer. *Am J Cancer Res*. 2018;8(1):170—182.
73. Zhang Y, Dun Y, Zhou S, Huang X-H. LncRNA HOXD-AS1 promotes epithelial ovarian cancer cells proliferation and invasion by targeting miR-133a-3p and activating Wnt/β-catenin signaling pathway. *Biomed Pharmacother*. 2017;96: 1216—1221.
74. Lu S, Zhou J, Sun Y, et al. The noncoding RNA HOXD-AS1 is a critical regulator of the metastasis and apoptosis phenotype in human hepatocellular carcinoma. *Mol Cancer*. 2017; 16(1),e125.
75. Liao Y, Sun Y, Chau G, et al. Identification of SOX4 target genes using phylogenetic footprinting-based prediction from expression microarrays suggests that overexpression of SOX4 potentiates metastasis in hepatocellular carcinoma. *Oncogene*. 2008;27(42):5578—5589.
76. Askarian-Amiri ME, Crawford J, French JD, et al. SNORD-host RNA Zfas1 is a regulator of mammary development and a potential marker for breast cancer. *RNA*. 2011;17(5): 878—891.
77. Fan S, Fan C, Liu N, Huang K, Fang X, Wang K. Downregulation of the long non-coding RNA ZFAS1 is associated with cell proliferation, migration and invasion in breast cancer. *Mol Med Rep*. 2018;17(5):6405—6412.
78. Zhou H, Wang F, Chen H, et al. Increased expression of long-noncoding RNA ZFAS1 is associated with epithelial-mesenchymal transition of gastric cancer. *Aging (Albany NY)*. 2016;8(9):2023—2038.
79. Pan L, Liang W, Fu M, et al. Exosomes-mediated transfer of long noncoding RNA ZFAS1 promotes gastric cancer progression. *J Canc Res Clin Oncol*. 2017;143(6):991—1004.
80. Lu X, Fang Y, Wang Z, et al. Downregulation of gas5 increases pancreatic cancer cell proliferation by regulating CDK6. *Cell Tissue Res*. 2013;354(3):891—896.
81. Pickard MR, Williams GT. Regulation of apoptosis by long non-coding RNA GAS5 in breast cancer cells: implications for chemotherapy. *Breast Cancer Res Treat*. 2014;145(2): 359—370.
82. Fang C, Zan J, Yue B, Liu C, He C, Yan D. Long non-coding ribonucleic acid zinc finger antisense 1 promotes the progression of colonic cancer by modulating ZEB1 expression. *J Gastroenterol Hepatol*. 2017;32(6):1204—1211.
83. Li T, Xie J, Shen C, et al. Amplification of long noncoding RNA ZFAS1 promotes metastasis in hepatocellular carcinoma. *Cancer Res*. 2015;75(15):3181—3191.
84. Liu G, Wang L, Han H, et al. LncRNA ZFAS1 promotes growth and metastasis by regulating BMI1 and ZEB2 in osteosarcoma. *Am J Cancer Res*. 2017;7(7):1450—1462.
85. Li N, Sun Z-H, Fang M, Xin J-Y, Wan C-Y. Long non-coding RNA ZFAS1 sponges miR-486 to promote osteosarcoma cells progression and metastasis in vitro and vivo. *Oncotarget*. 2017; 8(61):104160—104170.
86. Shi H, Liu Z, Pei D, Jiang Y, Zhu H, Chen B. Development and validation of nomogram based on lncRNA ZFAS1 for predicting survival in lymph node-negative esophageal squamous cell carcinoma patients. *Oncotarget*. 2017;8(35):59048—59057.
87. Xia B, Hou Y, Chen H, et al. Long non-coding RNA ZFAS1 interacts with miR-150-5p to regulate Sp1 expression and ovarian cancer cell malignancy. *Oncotarget*. 2017;8(12):19534—19546.
88. Nie F, Yu X, Huang M, et al. Long noncoding RNA ZFAS1 promotes gastric cancer cells proliferation by epigenetically repressing KLF2 and NKD2 expression. *Oncotarget*. 2017; 8(24):38227—38238.
89. Prensner JR, Iyer MK, Balbin OA, et al. Transcriptome sequencing across a prostate cancer cohort identifies PCAT-1, an unannotated lincRNA implicated in disease progression. *Nat Biotechnol*. 2011;29(8):742—749.
90. Prensner JR, Chen W, Han S, et al. The long non-coding RNA PCAT-1 promotes prostate cancer cell proliferation through cMyc. *Neoplasia*. 2014;16(11):900—908.
91. Xu W, Chang J, Du X, Hou J. Long non-coding RNA PCAT-1 contributes to tumorigenesis by regulating FSCN1 via miR-145-5p in prostate cancer. *Biomed Pharmacother*. 2017;95: 1112—1118.
92. Sarrafzadeh S, Geranpayeh L, Ghafouri-Fard S. Expression analysis of long non-coding PCAT-1in breast cancer. *Int J Hematol Oncol Stem Cell Res*. 2017;11(3):185—191.
93. Liu L, Liu Y, Zhuang C, et al. Inducing cell growth arrest and apoptosis by silencing long non-coding RNA PCAT-1 in human bladder cancer. *Tumor Biol*. 2015;36(10):7685—7689.
94. Yan T-H, Yang H, Jiang J-H, et al. Prognostic significance of long non-coding RNA PCAT-1 expression in human hepatocellular carcinoma. *Int J Clin Exp Pathol*. 2015;8(4):4126—4131.
95. Zhang D, Cao J, Zhong Q, et al. Long noncoding RNA PCAT-1 promotes invasion and metastasis via the miR-129-5p-HMGB1 signaling pathway in hepatocellular carcinoma. *Biomed Pharmacother*. 2017;95:1187—1193.
96. Huang J, Deng G, Liu T, Chen W, Zhou Y. Long noncoding RNA PCAT-1 acts as an oncogene in osteosarcoma by reducing p21 levels. *Biochem Biophys Res Commun*. 2018;495(4): 2622—2629.
97. Zhang X, Zhang Y, Mao Y, Ma X. The lncRNA PCAT1 is correlated with poor prognosis and promotes cell proliferation, invasion, migration and EMT in osteosarcoma. *OncoTargets Ther*. 2018;11:629—638.
98. Cui W, Wu Y, Qu H. Up-regulation of long non-coding RNA PCAT-1 correlates with tumor progression and poor prognosis in gastric cancer. *Eur Rev Med Pharmacol Sci*. 2017;21(13): 3021—3027.
99. Bi M, Yu H, Huang B, Tang C. Long non-coding RNA PCAT-1 over-expression promotes proliferation and metastasis in gastric cancer cells through regulating CDKN1A. *Gene*. 2017; 626:337—343.
100. Shi W-h, Wu Q-q, Li S-q, et al. Upregulation of the long non-coding RNA PCAT-1 correlates with advanced clinical stage and poor prognosis in esophageal squamous carcinoma. *Tumor Biol*. 2015;36(4):2501—2507.
101. Wen J, Xu J, Sun Q, Xing C, Yin W. Upregulation of long non coding RNA PCAT-1 contributes to cell proliferation, migration and apoptosis in hepatocellular carcinoma. *Mol Med Rep*. 2016;13(5):4481—4486.
102. Zhang F, Wan M, Xu Y, et al. Long noncoding RNA PCAT1 regulates extrahepatic cholangiocarcinoma progression via the Wnt/β-catenin-signaling pathway. *Biomed Pharmacother*. 2017;94:55—62.
103. Xu Z-Y, Yu Q-M, Du Y-A, et al. Knockdown of long non-coding RNA HOTAIR suppresses tumor invasion and reverses epithelial-mesenchymal transition in gastric cancer. *Int J Biol Sci*. 2013;9(6):587—597.
104. Vardhini N, Rao PJM, Murthy PB, Sudhakar G. HOXD10 expression in human breast cancer. *Tumor Biol*. 2014;35(11): 10855—10860.

105. Zhao W, Geng D, Li S, Chen Z, Sun M. Lnc RNA HOTAIR influences cell growth, migration, invasion, and apoptosis via the miR-20a-5p/HMGA 2 axis in breast cancer. *Cancer Med*. 2018;7(3):842—855.
106. Avazpour N, Hajjari M, Tahmasebi Birgani M. HOTAIR: a promising long non-coding RNA with potential role in breast invasive carcinoma. *Front Genet*. 2017;8,e170.
107. Ciferri C, Lander GC, Maiolica A, Herzog F, Aebersold R, Nogales E. Molecular architecture of human polycomb repressive complex 2. *elife*. 2012;1,e00005.
108. Chang Y-T, Lin T-P, Tang J-T, et al. HOTAIR is a REST-regulated lncRNA that promotes neuroendocrine differentiation in castration resistant prostate cancer. *Cancer Lett*. 2018;433:43—52.
109. Chiyomaru T, Yamamura S, Fukuhara S, et al. Genistein inhibits prostate cancer cell growth by targeting miR-34a and oncogenic HOTAIR. *PLoS One*. 2013;8(8),e70372.
110. Xue Y, Gu D, Ma G, et al. Genetic variants in lncRNA HOTAIR are associated with risk of colorectal cancer. *Mutagenesis*. 2014;30(2):303—310.
111. Ohtsuka M, Tanemura M, Akamatsu H. Long noncoding RNAs regulate malignant phenotypes in colorectal cancer. *Biotarget*. 2018;2(2),e4.
112. Kogo R, Shimamura T, Mimori K, et al. Long noncoding RNA HOTAIR regulates polycomb-dependent chromatin modification and is associated with poor prognosis in colorectal cancers. *Cancer Res*. 2011;71(20):6320—6326.
113. Xiao Z, Qu Z, Chen Z, et al. LncRNA HOTAIR is a prognostic biomarker for the proliferation and chemoresistance of colorectal cancer via MiR-203a-3p-mediated Wnt/ss-catenin signaling pathway. *Cell Physiol Biochem*. 2018;46(3):1275—1285.
114. Nguyen H, Morokoff AP, Stylli SS, Kaye AH, Luwor RB. Peripheral biomarkers in glioblastoma patients—is it all just HOTAIR? *Non-coding RNA Invest*. 2018;2,e32.
115. Song Y, Wang R, Li L-W, et al. Long non-coding RNA HOTAIR mediates the switching of histone H3 lysine 27 acetylation to methylation to promote epithelial-to-mesenchymal transition in gastric cancer. *Int J Oncol*. 2019;54(1):77—86.
116. Jiang D, Li H, Xiang H, et al. Long chain non-coding RNA (lncRNA) HOTAIR knockdown increases miR-454-3p to suppress gastric cancer growth by targeting STAT3/cyclin D1. *Med Sci Mon Int Med J Exp Clin Res*. 2019;25:1537—1548.
117. Dong X, He X, Guan A, et al. Long non-coding RNA Hotair promotes gastric cancer progression via miR-217-GPC5 axis. *Life Sci*. 2019;217:271—282.
118. Cai H, An Y, Chen X, et al. Epigenetic inhibition of miR-663b by long non-coding RNA HOTAIR promotes pancreatic cancer cell proliferation via up-regulation of insulin-like growth factor 2. *Oncotarget*. 2016;7(52):86857—86870.
119. Gao JZ, Li J, Du JL, Li XL. Long non-coding RNA HOTAIR is a marker for hepatocellular carcinoma progression and tumor recurrence. *Oncol Lett*. 2016;11(3):1791—1798.
120. Zhai N, Xia Y, Yin R, Liu J, Gao F. A negative regulation loop of long noncoding RNA HOTAIR and p53 in non-small-cell lung cancer. *OncoTargets Ther*. 2016;9:5713—5720.
121. Wang J, Zhou Y, Lu J, et al. Combined detection of serum exosomal miR-21 and HOTAIR as diagnostic and prognostic biomarkers for laryngeal squamous cell carcinoma. *Med Oncol*. 2014;31(9),e148.
122. Ji P, Diederichs S, Wang W, et al. MALAT-1, a novel noncoding RNA, and thymosin β4 predict metastasis and survival in early-stage non-small cell lung cancer. *Oncogene*. 2003;22(39):8031—8041.
123. Tripathi V, Ellis JD, Shen Z, et al. The nuclear-retained noncoding RNA MALAT1 regulates alternative splicing by modulating SR splicing factor phosphorylation. *Mol Cell*. 2010;39(6):925—938.
124. Gutschner T, Hämmerle M, Diederichs S. MALAT1—a paradigm for long noncoding RNA function in cancer. *J Mol Med*. 2013;91(7):791—801.
125. Shen L, Chen L, Wang Y, Jiang X, Xia H, Zhuang Z. Long noncoding RNA MALAT1 promotes brain metastasis by inducing epithelial-mesenchymal transition in lung cancer. *J Neuro Oncol*. 2015;121(1):101—108.
126. Dong Y, Liang G, Yuan B, Yang C, Gao R, Zhou X. MALAT1 promotes the proliferation and metastasis of osteosarcoma cells by activating the PI3K/Akt pathway. *Tumor Biol*. 2015;36(3):1477—1486.
127. Xu S, Sui S, Zhang J, et al. Downregulation of long noncoding RNA MALAT1 induces epithelial-to-mesenchymal transition via the PI3K-AKT pathway in breast cancer. *Int J Clin Exp Pathol*. 2015;8(5):4881—4891.
128. Tian Y, Zhang X, Hao Y, Fang Z, He Y. Potential roles of abnormally expressed long noncoding RNA UCA1 and Malat-1 in metastasis of melanoma. *Melanoma Res*. 2014;24(4):335—341.
129. Liu S, Yan G, Zhang J, Yu L. Knockdown of long noncoding RNA (lncRNA) metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) inhibits proliferation, migration, and invasion and promotes apoptosis by targeting miR-124 in retinoblastoma. *Oncol Res*. 2018;26(4):581—591.
130. Chen L, Feng P, Zhu X, He S, Duan J, Zhou D. Long non-coding RNA Malat1 promotes neurite outgrowth through activation of ERK/MAPK signalling pathway in N2a cells. *J Cell Mol Med*. 2016;20(11):2102—2110.
131. Liang J, Liang L, Ouyang K, Li Z, Yi X. MALAT 1 induces tongue cancer cells' EMT and inhibits apoptosis through Wnt/β-catenin signaling pathway. *J Oral Pathol Med*. 2017;46(2):98—105.
132. Zhao G, Su Z, Song D, Mao Y, Mao X. The long noncoding RNA MALAT 1 regulates the lipopolysaccharide-induced inflammatory response through its interaction with NF-κB. *FEBS Lett*. 2016;590(17):2884—2895.
133. Lai M-c, Yang Z, Zhou L, et al. Long non-coding RNA MALAT-1 overexpression predicts tumor recurrence of hepatocellular carcinoma after liver transplantation. *Med Oncol*. 2012;29(3):1810—1816.
134. Malakar P, Shilo A, Mogilevsky A, et al. Long noncoding RNA MALAT1 promotes hepatocellular carcinoma development by SRSF1 upregulation and mTOR activation. *Cancer Res*. 2017;77(5):1155—1167.
135. Hu L, Wu Y, Tan D, et al. Up-regulation of long noncoding RNA MALAT1 contributes to proliferation and metastasis in esophageal squamous cell carcinoma. *J Exp Clin Cancer Res*. 2015;34(1),e7.
136. Sun H, Lin D-C, Cao Q, et al. Identification of a novel SYK/c-MYC/MALAT1 signaling pathway and its potential therapeutic value in Ewing sarcoma. *Clin Cancer Res*. 2017;23(15):4376—4387.
137. Han Y, Liu Y, Nie L, Gui Y, Cai Z. Inducing cell proliferation inhibition, apoptosis, and motility reduction by silencing long noncoding ribonucleic acid metastasis-associated lung adenocarcinoma transcript 1 in urothelial carcinoma of the bladder. *Urology*. 2013;81(1),e209.
138. Ying L, Chen Q, Wang Y, Zhou Z, Huang Y, Qiu F. Upregulated MALAT-1 contributes to bladder cancer cell migration by inducing epithelial-to-mesenchymal transition. *Mol Biosyst*. 2012;8(9):2289—2294.
139. Ren S, Liu Y, Xu W, et al. Long noncoding RNA MALAT-1 is a new potential therapeutic target for castration resistant prostate cancer. *J Urol*. 2013;190(6):2278—2287.
140. Vassallo I, Zinn P, Lai M, Rajakannu P, Hamou M, Hegi M. WIF1 re-expression in glioblastoma inhibits migration through attenuation of non-canonical WNT signaling by down-regulating the lncRNA MALAT1. *Oncogene*. 2016;35(1):12—21.

141. Pang EJ, Yang R, Fu XB, Liu YF. Overexpression of long non-coding RNA MALAT1 is correlated with clinical progression and unfavorable prognosis in pancreatic cancer. *Tumor Biol*. 2015;36(4):2403—2407.
142. Rinn JL, Kertesz M, Wang JK, et al. Functional demarcation of active and silent chromatin domains in human HOX loci by noncoding RNAs. *Cell*. 2007;129(7):1311—1323.
143. Gupta RA, Shah N, Wang KC, et al. Long non-coding RNA HOTAIR reprograms chromatin state to promote cancer metastasis. *Nature*. 2010;464(7291):1071—1076.
144. Alaiyan B, Ilyayev N, Stojadinovic A, et al. Differential expression of colon cancer associated transcript1 (CCAT1) along the colonic adenoma-carcinoma sequence. *BMC Cancer*. 2013;13(1),e196.
145. McCleland ML, Mesh K, Lorenzana E, et al. CCAT1 is an enhancer-templated RNA that predicts BET sensitivity in colorectal cancer. *J Clin Invest*. 2016;126(2):639—652.
146. Puvvula PK, Desetty RD, Pineau P, et al. Long noncoding RNA PANDA and scaffold-attachment-factor SAFA control senescence entry and exit. *Nat Commun*. 2014;5(1):1—16.
147. Schneider C, King RM, Philipson L. Genes specifically expressed at growth arrest of mammalian cells. *Cell*. 1988; 54(6):787—793.
148. Hudson WH, Pickard MR, De Vera IMS, et al. Conserved sequence-specific lincRNA—steroid receptor interactions drive transcriptional repression and direct cell fate. *Nat Commun*. 2014;5(1):1—13.
149. Nobori T, Miura K, Wu DJ, Lois A, Takabayashi K, Carson DA. Deletions of the cyclin-dependent kinase-4 inhibitor gene in multiple human cancers. *Nature*. 1994;368(6473):753—756.
150. Gil J, Peters G. Regulation of the INK4b—ARF—INK4a tumour suppressor locus: all for one or one for all. *Nat Rev Mol Cell Biol*. 2006;7(9):667—677.
151. Huarte M, Guttman M, Feldser D, et al. A large intergenic noncoding RNA induced by p53 mediates global gene repression in the p53 response. *Cell*. 2010;142(3):409—419.
152. Gutschner T, Hämmerle M, Eißmann M, et al. The noncoding RNA MALAT1 is a critical regulator of the metastasis phenotype of lung cancer cells. *Cancer Res*. 2013;73(3): 1180—1189.
153. Ji P, Diederichs S, Wang W, et al. MALAT-1, a novel noncoding RNA, and thymosin β 4 predict metastasis and survival in early-stage non-small cell lung cancer. *Oncogene*. 2003; 22(39):8031—8041.
154. Li Z, Shen J, Chan MT, Wu WKK. TUG 1: a pivotal oncogenic long non-coding RNA of human cancers. *Cell Prolif*. 2016; 49(4):471—475.
155. Zhu X, Du J, Yu J, et al. LncRNA NKILA regulates endothelium inflammation by controlling a NF-κB/KLF4 positive feedback loop. *J Mol Cell Cardiol*. 2019;126:60—69.
156. Huang J, Zhou N, Watabe K, et al. Long non-coding RNA UCA1 promotes breast tumor growth by suppression of p27 (Kip1). *Cell Death Dis*. 2014;5(1),e1008.
157. Redon S, Reichenbach P, Lingner J. The non-coding RNA TERRA is a natural ligand and direct inhibitor of human telomerase. *Nucleic Acids Res*. 2010;38(17):5797—5806.
158. Tseng Y-Y, Moriarity BS, Gong W, et al. PVT1 dependence in cancer with MYC copy-number increase. *Nature*. 2014; 512(7512):82—86.
159. Zhou Y, Zhang X, Klibanski A. MEG3 noncoding RNA: a tumor suppressor. *J Mol Endocrinol*. 2012;48(3):R45—R53.
160. Xie X, Tang B, Xiao Y-F, et al. Long non-coding RNAs in colorectal cancer. *Oncotarget*. 2016;7(5):5226—5239.
161. Lin C, Wang Y, Zhang S, Yu L, Guo C, Xu H. Transcriptional and posttranscriptional regulation of HOXA13 by lncRNA HOTTIP facilitates tumorigenesis and metastasis in esophageal squamous carcinoma cells. *Oncogene*. 2017;36(38): 5392—5406.
162. Chakravarty D, Sboner A, Nair SS, et al. The oestrogen receptor alpha-regulated lncRNA NEAT1 is a critical modulator of prostate cancer. *Nat Commun*. 2014;5(1):1—16.
163. Yang MH, Zhao L, Wang L, et al. Nuclear lncRNA HOXD-AS1 suppresses colorectal carcinoma growth and metastasis via inhibiting HOXD3-induced integrin β3 transcriptional activating and MAPK/AKT signalling. *Mol Cancer*. 2019;18(1),e31.
164. Hosono Y, Niknafs YS, Prensner JR, et al. Oncogenic role of THOR, a conserved cancer/testis long non-coding RNA. *Cell*. 2017;171(7):1559—1572.
165. Dong D, Mu Z, Zhao C, Sun M. ZFAS1: a novel tumor-related long non-coding RNA. *Cancer Cell Int*. 2018;18(1),e125.
166. He A, He S, Li X, Zhou L. ZFAS 1: a novel vital oncogenic lnc RNA in multiple human cancers. *Cell Prolif*. 2019; 52(1),e12513.
167. Zeng B, Li Y, Jiang F, et al. LncRNA GAS5 suppresses proliferation, migration, invasion, and epithelial-mesenchymal transition in oral squamous cell carcinoma by regulating the miR-21/PTEN axis. *Exp Cell Res*. 2019;374(2):365—373.
168. Wang C, Yan G, Zhang Y, Jia X, Bu P. Long non-coding RNA MEG3 suppresses migration and invasion of thyroid carcinoma by targeting of Rac1. *Neoplasma*. 2015;62(4):541—549.
169. Pei J, Wang B. Notch-1 promotes breast cancer cells proliferation by regulating LncRNA GAS5. *Int J Clin Exp Med*. 2015; 8(8):14464—14471.
170. Yang J, Li C, Mudd A, Gu X. LncRNA PVT1 predicts prognosis and regulates tumor growth in prostate cancer. *Biosci Biotechnol Biochem*. 2017;81(12):2301—2306.
171. Kolenda T, Guglas K, Kopczyńska M, et al. Oncogenic role of ZFAS1 lncRNA in head and neck squamous cell carcinomas. *Cells*. 2019;8(4),e366.
172. Yap KL, Li S, Muñoz-Cabello AM, et al. Molecular interplay of the noncoding RNA ANRIL and methylated histone H3 lysine 27 by polycomb CBX7 in transcriptional silencing of INK4a. *Mol Cell*. 2010;38(5):662—674.
173. Zhang ZX, Liu ZQ, Jiang B, et al. BRAF activated non-coding RNA (BANCR) promoting gastric cancer cells proliferation via regulation of NF-κB1. *Biochem Biophys Res Commun*. 2015; 465(2):225—231.
174. Matouk IJ, DeGroot N, Mezan S, et al. The H19 non-coding RNA is essential for human tumor growth. *PLoS One*. 2007;2(9),e845.
175. Zhang E, Yin D, Sun M, et al. P53-regulated long non-coding RNA TUG1 affects cell proliferation in human non-small cell lung cancer, partly through epigenetically regulating HOXB7 expression. *Cell Death Dis*. 2014;5(5),e1243.
176. Liu Y, Sun M, Xia R, et al. LincHOTAIR epigenetically silences miR34a by binding to PRC2 to promote the epithelial-to-mesenchymal transition in human gastric cancer. *Cell Death Dis*. 2015;6(7),e1802.
177. Wan L, Sun M, Liu GJ, et al. Long noncoding RNA PVT1 promotes non—small cell lung cancer cell proliferation through epigenetically regulating LATS2 expression. *Mol Cancer Therapeut*. 2016;15(5):1082—1094.
178. Zhang Y, Ma M, Liu W, Ding W, Yu H. Enhanced expression of long noncoding RNA CARLo-5 is associated with the development of gastric cancer. *Int J Clin Exp Pathol*. 2014;7(12): 8471—8479.
179. Ling H, Spizzo R, Atlasi Y, et al. CCAT2, a novel noncoding RNA mapping to 8q24, underlies metastatic progression and chromosomal instability in colon cancer. *Genome Res*. 2013;23(9): 1446—1461.
180. Ge XS, Ma HJ, Zheng XH, et al. HOTAIR, a prognostic factor in esophageal squamous cell carcinoma, inhibits WIF-1 expression and activates W nt pathway. *Cancer Sci*. 2013;104(12): 1675—1682.
181. Ji Q, Liu X, Fu X, et al. Resveratrol inhibits invasion and metastasis of colorectal cancer cells via MALAT1 mediated Wnt/β-catenin signal pathway. *PLoS One*. 2013;8(11),e78700.

182. Li L, Gu M, You B, et al. Long non-coding RNA ROR promotes proliferation, migration and chemoresistance of nasopharyngeal carcinoma. *Cancer Sci*. 2016;107(9):1215—1222.
183. Chen CL, Tseng YW, Wu JC, et al. Suppression of hepatocellular carcinoma by baculovirus-mediated expression of long non-coding RNA PTENP1 and MicroRNA regulation. *Biomaterials*. 2015;44:71—81.
184. Shi SJ, Wang LJ, Yu B, Li YH, Jin Y, Bai XZ. LncRNA-ATB promotes trastuzumab resistance and invasion-metastasis cascade in breast cancer. *Oncotarget*. 2015;6(13):11652—11663.
185. Lv L, Chen G, Zhou J, Li J, Gong J. WT1-AS promotes cell apoptosis in hepatocellular carcinoma through down-regulating of WT1. *J Exp Clin Cancer Res*. 2015;34(1),e119.
186. Zeng Z, Bo H, Gong Z, et al. AFAP1-AS1, a long noncoding RNA upregulated in lung cancer and promotes invasion and metastasis. *Tumor Biol*. 2016;37(1):729—737.
187. Xu S, Yi XM, Tang CP, Ge JP, Zhang ZY, Zhou WQ. Long non-coding RNA ATB promotes growth and epithelial-mesenchymal transition and predicts poor prognosis in human prostate carcinoma. *Oncol Rep*. 2016;36(1):10—22.
188. Zhang Eb, Kong R, Yin Dd, et al. Long noncoding RNA ANRIL indicates a poor prognosis of gastric cancer and promotes tumor growth by epigenetically silencing of miR-99a/miR-449a. *Oncotarget*. 2014;5(8):2276—2292.
189. Zhang Z, Zhou C, Chang Y, et al. Long non-coding RNA CASC11 interacts with hnRNP-K and activates the WNT/β-catenin pathway to promote growth and metastasis in colorectal cancer. *Cancer Lett*. 2016;376(1):62—73.
190. Wang L, Han S, Jin G, et al. Linc00963: a novel, long non-coding RNA involved in the transition of prostate cancer from androgen-dependence to androgen-independence. *Int J Oncol*. 2014;44(6):2041—2049.
191. Wang J, Cheng G, Li X, et al. Overexpression of long non-coding RNA LOC400891 promotes tumor progression and poor prognosis in prostate cancer. *Tumor Biol*. 2016;37(7):9603—9613.
192. Ylipää A, Kivinummi K, Kohvakka A, et al. Transcriptome sequencing reveals PCAT5 as a novel ERG-regulated long noncoding RNA in prostate cancer. *Cancer Res*. 2015;75(19):4026—4031.