Review

Cancer Research

Long Noncoding RNA and Cancer: A New Paradigm

Arunoday Bhan, Milad Soleimani, and Subhrangsu S. Mandal

Abstract

In addition to mutations or aberrant expression in the protein-coding genes, mutations and misregulation of noncoding RNAs, in particular long noncoding RNAs (lncRNA), appear to play major roles in cancer. Genome-wide association studies of tumor samples have identified a large number of lncRNAs associated with various types of cancer. Alterations in lncRNA expression and their mutations promote tumorigenesis and metastasis. LncRNAs may exhibit tumor-suppressive and -promoting (oncogenic) functions. Because of their genome-wide expression patterns in a variety of tissues and their tissue-specific expression characteristics, lncRNAs hold strong promise as novel biomarkers and therapeutic targets for cancer. In this article, we have reviewed the emerging functions and association of lncRNAs in different types of cancer and discussed their potential implications in cancer diagnosis and therapy. *Cancer Res; 77(15); 3965–81. ©2017 AACR.*

Introduction

Cancer is a complex disease associated with a variety of genetic mutations, epigenetic alterations, chromosomal translocations, deletions, and amplification (1). Noncoding RNAs (ncRNA) are an emerging class of transcripts that are coded by the genome but are mostly not translated into proteins (2). Although not translated, ncRNAs are crucial players in a variety of cellular and physiologic functions (3). In particular, long noncoding RNAs (ncRNAs that are >200 nt long) play key roles in regulating chromatin dynamics, gene expression, growth, differentiation, and development (4). It is now well recognized that more than 75% of the human genome is functional and encodes large numbers of ncRNAs (5). On the basis of the ENCODE project, it is estimated that the human genome encodes more than 28,000 distinct long noncoding RNAs (lncRNA), many of which are still being discovered and are yet to be annotated (6). While understanding the functions of so many lncRNAs and their detailed characterization are challenging tasks, analysis of transcriptome profiles using next-generation sequencing in the last few years has revealed that thousands of lncRNAs are aberrantly expressed or mutated in various cancers (7).

Although lncRNAs are emerging as a major class of noncoding transcripts, the discovery of tremendously large numbers of lncRNAs and their diverse functions and complexity pose a major challenge to effectively classify them in different categories. At this point, lncRNAs are broadly classified on the basis of their genomic localization, modes of action, and function. Intronic lncRNAs originate from the introns of protein-coding genes; intergenic lncRNAs (lincRNA) originate from the region between two protein-coding genes; enhancer lncRNAs (elncRNA) originate from the promoter enhancer regions; bidirectional lncRNAs are localized within the vicinity of a coding transcript of the opposite strand; sense-overlapping lncRNAs overlap with one or more introns and exons of different protein-coding genes in the sense strand of the DNA; antisense transcripts originate from the antisense strands of the DNA, and they may or may not be complementary to protein coding sequences in the sense-strand (7, 8). Functionally, lncRNAs are classified as signaling, decoy, guide, and scaffold lncRNAs (9). Signaling lncRNAs are associated with specific signaling pathways and their expression indicates an active signaling event, irrespective of their roles (direct/indirect) in the signaling process (9). For example, the expression of XIST signals X-inactivation in females (10). Decoy lncRNAs act like molecular sinks for transcription factors and repressors. They interact with and titrate away transcription factors from binding to the target gene promoters facilitating gene activation or silencing (9). Examples of decoy lncRNAs include GAS5 (growth arrest specific 5), TERRA (telomeric repeat-containing RNA), and others. (9). Guide lncRNAs bind to the regulatory or enzymatically active protein complexes and direct them to specific target gene promoters or genomic loci regulating downstream signaling events and gene expressions. Examples of guide lncRNAs include AIR, CCND1 (cyclin D promoter associated lncRNA), lincRNA-p21, and others (8, 9). Scaffold lncRNAs act as a central platform to which various protein complexes tether and get directed to specific genomic location or target gene promoter–regulating gene expression and chromosomal dynamics. Examples of scaffold lncRNAs are HOTAIR, TERC, and others.

Beyond traditional ncRNAs, circular RNAs (circRNA) are also emerging as a novel class of endogenous noncoding RNAs that form covalently closed continuous loops instead of traditional linear forms. CircRNAs are conserved across species and are found to be associated with a variety of important biological processes and human diseases including cancer. CircRNAs appear to function as miRNA sponges and are involved in the regulation of mRNA splicing, transcription, and gene expression (11, 12). Generally, circRNAs are classified as exonic, intronic, and

Gene Regulation and Epigenetics Research Lab, Department of Chemistry and Biochemistry, The University of Texas at Arlington, Arlington, Texas.

A. Bhan and M. Soleimani contributed equally to this article.

Corresponding Author: Subhrangsu S. Mandal, Department of Chemistry and Biochemistry, University of Texas at Arlington, 700 Planetarium Place, Arlington, TX 76019. Phone: 817-272-3804; Fax: 817-272-3808; E-mail: smandal@uta.edu

doi: 10.1158/0008-5472.CAN-16-2634

retained-intronic circRNAs. They may be derived from exons, introns, untranslated regions, antisense transcripts, and intergenic regions. CircRNA biogenesis has been explained by various models, incorporating a range of spliceosomes and RNA-binding proteins. The most accepted model suggests that circRNA biogenesis involves joining of a 5′ splice site and a 3′ splice site as the result of back splicing (13, 14). Because of their unique structure, circRNAs are resistant to nucleases and are stable with a relatively long half-life. They may exist in tissues, serum, and urine, indicating their potential as novel biomarkers for human cancer. CircRNAs are implicated in a variety of cancers including laryngeal cancer, gastric cancer, hepatocellular cancer, bladder cancer, and esophageal cancer, among others (11, 15, 16). For example, circRNA ciRS-7, which acts as a sponge for miR-7, is involved in promoting colorectal cancer through inhibiting the repression of oncogenes such as YY1 by tumor suppressor miR-7 (15). CiRS-7 is an endogenous circRNA highly expressed in the brain and transcribed antisense to the *CDR1* (cerebellum degeneration-related antigen 1) gene (12). CircRNAs such as circ-ITCH, hsa_circ_002059, and hsa_circ_0001649 are downregulated in colorectal cancer, gastric cancer, and hepatocellular cancer, whereas circ-VCAN, circTCF25, and circ-KLDGC10 are upregulated in glioma, bladder cancer, and hepatocellular cancer (11, 12, 16–18). CircRNAs such as ci-ankrd52 and circular -ANRIL are examples of circular lncRNAs (19, 20). Similar to lncRNAs, many circRNAs display aberrant expression in various cancers and possess strong promise toward development of novel biomarkers and therapeutics.

Thus, in addition to protein-coding genes, ncRNAs, in particular lncRNAs, are rapidly emerging as a novel class of transcripts associated with a variety of cellular and biological processes including gene regulation and chromatin dynamics. They are abundantly expressed and widely associated with a variety of cancers, and the aberrant expression and mutations are closely linked to tumorigenesis, metastasis, and tumor stage (21–23). Moreover, they are specifically expressed in certain types of cancer and detected in circulating blood and/or urine (24–26). LncRNAs are a novel class of potential biomarkers and therapeutic targets for the treatment of cancer. In this article, we have reviewed the functions of various lncRNAs in different types of cancer and discussed their potential implications in diagnosis and therapy (Fig. 1).

LncRNAs in Prostate Cancer

Prostate cancer is the most common cancer and the second leading cause of cancer-related deaths in American men. The American Cancer Society estimates about 181,000 new cases of prostate cancer and 26,000 deaths from prostate cancer in the United States in 2016. There is an urgent need to develop novel diagnostic biomarkers and effective therapies for prostate cancer. Genome-wide RNA-Seq analyses identified many lncRNAs that are up- or downregulated in prostate cancer (27). Several lncRNAs, such as PCA3, PCGEM1, and PCAT-1, are highly specific to prostate cancer (Fig. 1; Table 1; ref. 28).

PCA3

PCA3 (prostate cancer antigen 3; a.k.a., DD3), a steroid receptor–regulated lncRNA transcribed from 9q21.22, is overexpressed in 95% of prostate cancer cases and is detected with high specificity in the urine of patients with malignant and benign prostate cancer (29–31; Fig. 1; Tables 1 and 2). PCA3 and Hedgehog receptor PTCH (also implicated in prostate cancer) are highly upregulated in the circulating prostate cancer cells of androgen refractory patients (32–34). Prune2 (a tumor suppressor and a target of PCA3) and PCA3 expressions are inversely correlated in prostate cancer (34). PCA3 binds to PRUNE2-pre-mRNA to form a double-stranded RNA duplex that recruits adenosine deaminase (ADA), inducing RNA editing through acting on RNA (ADAR) proteins (34).

PCGEM1

PCGEM1 (prostate cancer gene expression marker 1) is a 1.6-kb long lncRNA from the 2q32 locus. It is a highly prostate tissue-specific and androgen-regulated lncRNA that is overexpressed in prostate cancer and promotes cell proliferation and colony formation (Fig. 1; Table 1; refs. 35–37). PCGEM1 expression inhibits doxorubicin-induced apoptosis and promotes chemoresistance via inhibition of PARP cleavage and delaying the induction of tumor suppressors p53 and p21 (36). Another lncRNA PRNCR1 (prostate cancer noncoding RNA1), in conjunction with PCGEM1, regulates gene expression by promoting epigenetic modifications (36). PRNCR1 binds to acetylated androgen receptor (AR) at the enhancer, and recruits histone H3K79 methyltransferase DOT1L (disruptor of telomeric silencing 1-like), which methylates AR that aids in the recruitment of PCGEM1 to the AR N-terminal and modulates target gene expression (35). Similarly, PCGEM1 recruits the Pygopus family PHD finger 2 (PYGO2) to the enhancer-promoter regions of AR gene and regulates AR-induced gene expression (38).

PCAT-1

PCAT-1 (prostate cancer-associated ncRNA transcript 1) is a 7.8-kb long intergenic lncRNA (originating from 8q24 locus) that is overexpressed in and highly specific to high-grade localized and metastatic prostate cancer (Fig. 1; Tables 1 and 2; refs. 28, 38, 39). It is independent of chromosome 8q24 amplification that is often observed in other cancers. There is a converse correlation between the expression of PCAT-1 and EZH2 [a histone H3K27-specific methyltransferase and interacting component of polycomb repressive complex 2 (PRC2); ref. 27]. EZH2 (enhancer of zeste homolog 2) knockdown upregulates PCAT-1 (27). PRC2 binds the PCAT-1 promoter and suppresses PCAT-1 expression (27). PCAT-1 induces cell proliferation and downregulates the expression of genes including tumor suppressor gene *BRCA2*. PCAT-1 sensitizes prostate cancer cells toward PARP1 inhibitors. PCAT-1 posttranscriptionally upregulates c-Myc that promotes prostate cancer cell proliferation (28, 38).

Various other lncRNAs including MALAT1, GAS5, PCAT6, PCAT-18, lincRNA-p21, PRNCR1, TRPM2, CTBP1-AS, ANRIL, PVT1, and SCHLAP1 are also linked to prostate cancer (Fig. 1; Table 1; refs. 28, 38). PCAT-18 is a highly prostate-specific transcript upregulated in prostate cancer and regulated by AR (28). CTBP1-AS is an androgen-responsive lncRNA and an antisense transcript of the *CTBP1* gene (40). Overexpression of CTBP1-AS inhibits the expression of cell-cycle regulators such as p53 and Smad3 in prostate cancer cells, resulting in cell proliferation (41, 42).

Breast Cancer

Breast cancer is the most common and the second deadliest cancer among women. It is estimated that

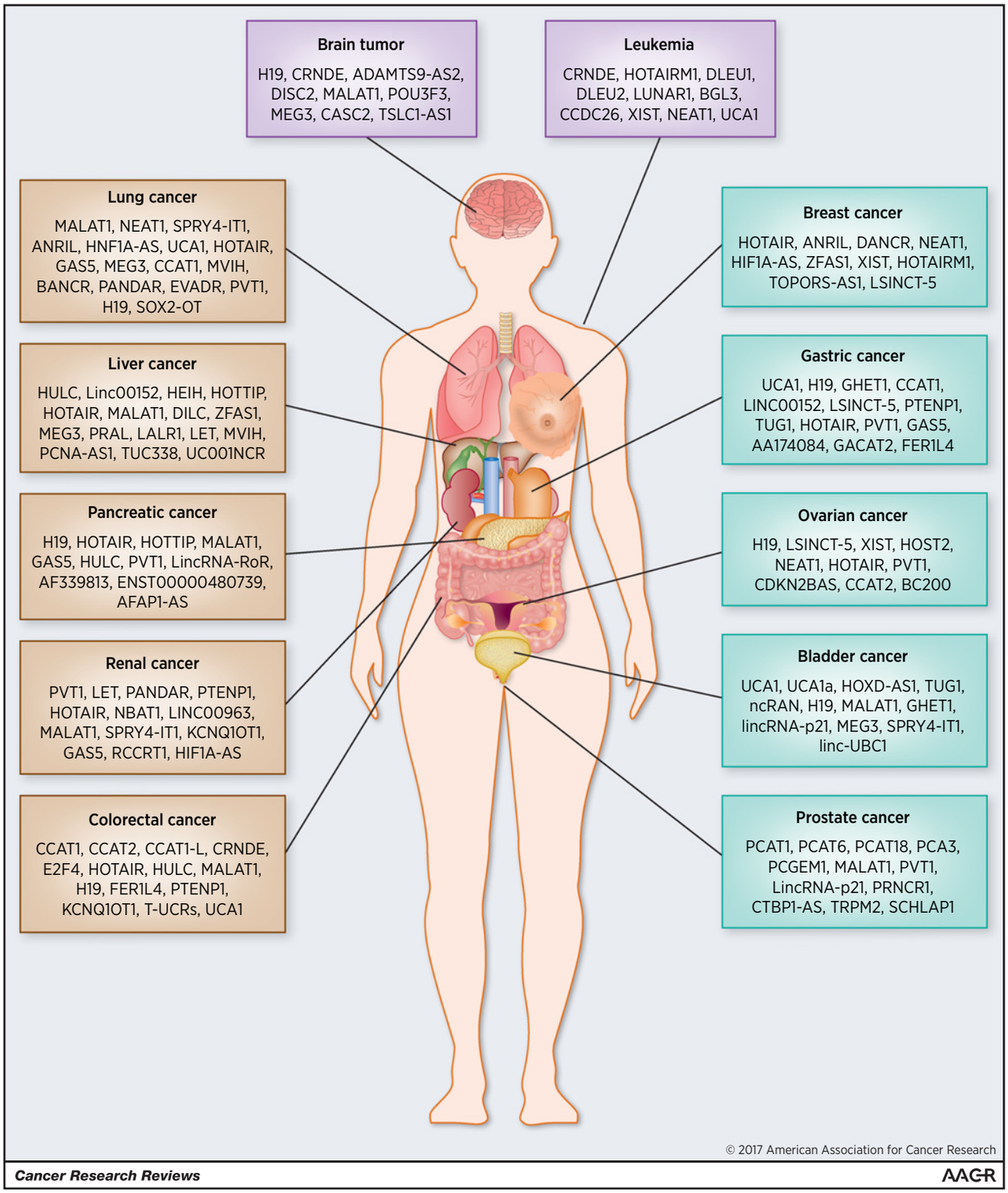

Figure 1.
LncRNAs associated with various types of cancer.

246,660 new cases and 40,450 deaths occurred from breast cancer in the United States in 2016. LncRNAs implicated in breast cancer include HOTAIR, ANRIL, ZFAS1, HOTAIRM1, NEAT1, DANCR, HIF1A-AS, XIST, TOPORS-AS1, LSINCT-5, PVT1, MALAT1, and LNP1, among others (Fig. 1; Tables 1 and 2; refs. 43, 44).

Table 1. LncRNAs: their mechanism of action and significance in cancer

LncRNA	Cancer type	Mechanism of action and function	References
PCA3 (a.k.a. DD3)	Prostate	Steroid receptor-regulated lncRNA; induces RNA editing via interaction with PRUNE2-pre-mRNA to form a double-stranded RNA duplex and ADAR proteins; knockdown results in reduced cell growth and survival and induction of apoptotic cells; (↑)	29, 31, 33, 34, 258
PCGEM1	Prostate	Promotes colony formation, cell proliferation; promotes chemoresistance via inhibition of PARP cleavage and delaying the induction of tumor suppressors p53 and p21; regulates AR target genes expression, in conjunction with lncRNA PRNCR1, AR, histone methylase DOT1L; and Pygopus family PHD finger 2 (PYGO2); knockdown results in reduced proliferation and increased apoptosis; (↑)	35–37
PCAT-1	Prostate	Promotes cell proliferation, downregulates genes and tumor suppressor genes; sensitizes prostate cancer cells towards PARP1 inhibitors; posttranscriptionally upregulates c-Myc; (↑)	27, 39
HOTAIR	Breast, hepatocellular, colorectal, pancreatic, lung, ovarian	Scaffolding lncRNA, silences genes via interaction with PRC2 and LSD1, aids in protein degradation via interaction with E3 ubiquitin ligases; knockdown reduces tumor invasiveness, disrupts of EMT; (↑)	45–53, 57, 58, 262
ANRIL	Breast, gastric, lung, liver	Controls cell proliferation and senescence via regulating tumor suppressors CDKN2A/B; represses the INK4A locus via interaction with CBX7 and PRC2; knockdown lowers multidrug resistance, reduces proliferation, and invasiveness; (↑)	66–78
MALAT1 (a.k.a. NEAT2)	Lung, prostate, breast, colorectal, liver, gastric, leukemia, brain, renal	Undergoes processing to produce a short and long RNA transcript; localized into nuclear speckles; influences SR-protein phosphorylation and modulates alternative splicing; regulates of EMT gene expression; associates with SUZ12 and regulates N-cadherin and E-cadherin expression; knockdown reduces cell growth, invasion, and migration, and differentiation into cystic tumors; (↑)	83–90
NEAT1	Leukemia, ovarian	Regulates ADARB2 expression via protein sequestration into paraspeckles; knockdown results in inhibition of cell growth; (↑)	95, 96
H19	Bladder, brain, gastric, renal, lung, ovarian, colorectal, pancreatic	Pivotal in embryonic development and tumorigenesis; maternally expressed and paternally imprinted; precursor of miRNAs (miR-675), P53 represses the H19 gene and the H19-derived miR-675 inhibits p53; interacts with EZH2, MBD1 and induces gene repression; knockdown reduces tumor size and metastasis; (↑)	1, 100–116
KCNQ1OT1	Colorectal, hepatocellular, pediatric adrenocortical; Beckwith-Wiedemann syndrome	Paternally imprinted; interacts with PRC1, PRC2, and G9a and silences KCNQ1 via induction in histone and DNA methylation; imprinting disruption of the CDKN1C/KCNQ1OT1 domain is involved in the development of both BWS and cancer; knockdown results in loss of imprinting in the 5′-domain of KCNQ1OT1; (↑)	119–123
T-UCRs	Colorectal, Barrett's adenocarcinoma, bladder, liver	CpG-island hypermethylation induced T-UCR silencing is common in many tumors; inhibits miR-596 via interaction with YY1, inhibits miR-193b; overexpression inhibits migration and invasion; (↑)	128–130
CCAT1	Colorectal, leukemia, gastric, Lung, esophageal squamous cell carcinoma	Acts as a sponge for let-7 and miR-155, regulates c-Myc, HOXB13, SPRY4; knockdown reduces cell proliferation and migration; (↑)	135, 137
HULC	Hepatocellular, pancreatic	Acts as a miRNA sponge and sequesters miR-372; potential biomarker for HCC; knockdown inhibits cell proliferation and increases chemosensitivity; (↑)	141, 142
HEIH	Hepatocellular	Linked with hepatitis-B-virus associated HCC recurrence; regulates cell-cycle–regulatory genes p15, p16, p21 via interaction with EZH2; knockdown reduces cell proliferation and suppresses tumor growth (↑)	139, 145, 146
HOTTIP	Prostate, liver, pancreatic	Controls the HOXA locus via interaction with WDR5/MLL; knockdown suppresses chemoresistance, and mesenchymal characteristics; (↑)	150–152
UCA1	Bladder, leukemia, ovarian, breast	Potential urine biomarker; promotes chemoresistance; recruits SWI/SNF to the TCF7 promoter, induces Wnt/β-catenin signaling and ER redistribution; knockdown increases chemosensitivity, reduces cell migration and tumor size; (↑)	157, 158
DLEU1, DLEU2	Leukemia	Deleted in lymphocytic leukemia; regulate NF-κB activity, acts as a precursor for miR-15a and miR-16-1 in leukemia; (↓)	164, 165

(Continued on the following page)

Table 1. LncRNAs: their mechanism of action and significance in cancer (Cont'd)

LncRNA	Cancer type	Mechanism of action and function	References
LUNAR1	Leukemia, B-cell lymphoma	Promotes T-ALL growth by inducing IGF1R expression, regulates IGF1R via interaction with mediator complex; knockdown reduces cell proliferation and viability; (↑)	166, 167
BGL3	Leukemia	Regulates Bcr-Abl through sponging miRNAs (miR-17, miR-93, miR-20a, miR-20b, miR-106a, and miR-106b) and via c-Myc-dependent DNA methylation; (↓)	168
HOTAIRM1	Breast, leukemia, colorectal	Controls myeloid autophagy and maturation via interaction with PRC2 and UTX/MLL; knockdown results in retardation of myeloid cell differentiation; (↑)	170–172
XIST	Ovarian, leukemia	Inactivates X chromosome via coating and interaction with PRC1/2, YY1, CTCF, etc.; knockdown results in enhanced sensitivity to Taxol; (↑)	174, 175
FER1L4	Gastric, endometrial	Regulates PTEN and the PI3K-AKT pathway by behaving as a ceRNA for miR-106a-5p; overexpression reduces cell growth and colony formation; (↓)	169, 195
NBAT1	Renal, neuroblastoma	Silences neuronal-specific NRSF/REST through association with PRC2; overexpression results in differentiation of neuronal precursors; (↓)	196, 197
GAS5	Breast, renal, prostate, endometrial	Acts as decoy for glucocorticoid receptor (GR), inhibits transcriptional induction by GR, causes growth arrest and apoptosis, induces PTEN via inhibiting miR-103; (↓)	198–200
TERRA	Pancreatic, cervical, gastric, breast	Facilitates heterochromatin formation via interaction with TRF1 and TRF2, aids in telomerase function by providing a RNA template; (↓)	205–207
ZFAS1	Breast, colorectal, gastric, liver	Interacts with CDK1/cyclin B, EZH2, LSD1/CoREST, acts as a sponge for miR-150, promotes cell proliferation; knockdown results in inhibition of cell proliferation, migration, and colony formation; (↑)	209–211
PVT1	Breast, pancreatic, ovarian, gastric, lung	Promote proliferation via interaction with NOP2 with the aid of TGFβ1, enhances c-Myc stability via inhibiting its phosphorylation; knockdown results in reduced cell proliferation and chemoresistance; (↑)	213–215
MEG3	Renal, gastric, ovarian, liver, lung, brain, bladder	Represses MDM2, aids in p53 accumulation, represses genomic loci of genes associated with TGFβ pathway via cooperating with PRC2; overexpression results in apoptosis and inhibition of proliferation; (↓)	218–221
TUG1	Bladder, gastric, lung	Silences cell-cycle–associated genes via interaction with PRC2; knockdown results in inhibition of cell proliferation, invasion, and colony formation; (↑)	2, 3, 275–277
Linc-RoR	Breast, pancreatic, hepatocellular, endometrial, nasopharyngeal	Induces epithelial–mesenchymal transition, drug resistance and invasiveness of cancer cells; promotes invasion, metastasis and tumor growth through activating ZEB1 pathway; (↑)	179

NOTE: ↑, upregulated in cancer (oncogenic); ↓, downregulated in cancer (tumor suppressor).

HOTAIR

HOTAIR (HOX transcript antisense intergenic RNA) is one of the most well-studied lncRNAs that is overexpressed in a variety of cancers including breast, colorectal, hepatocellular, gastrointestinal, and non–small cell lung carcinomas (Table 1; refs. 4, 45–51). HOTAIR, a 2.2-kb antisense lncRNA, interacts with two major gene-silencing factors: PRC2 and LSD1 (lysine specific demethylase 1). PRC2 is a multiprotein complex comprised of EZH2 (H3K27-methylase), SUZ12, EED, and RbAp46/48 (52–54). LSD1 interacts with corepressors REST and CoREST (54, 55). H3K27-methylation by EZH2 and H3K4-demethylation by LSD1 are both critical to gene silencing (54). HOTAIR recruits PRC2 and LSD1 at the target gene, inducing gene silencing via H3K27-methylation and H3K4-demethylation (54, 56). BRCA1, a critical player in DNA damage response and breast cancer, also interacts with EZH2, which in turn interacts with HOTAIR (54, 57, 58). Thus, BRCA1 and HOTAIR are both interacting partners of EZH2 and may have competitive roles in gene expression and DNA damage response (59). HOTAIR is also implicated in assembling E3-ubiquitin ligases during protein degradation (4, 7, 53). HOTAIR, EZH2, and LSD1 are all highly expressed in breast and other cancers. HOTAIR represses tumor suppressors such as PGR (progesterone receptor), PCDH10 (Protocadherin10), PCDHB5 (Protocadherin Beta 5), and JAM2 (Junctional Adhesion Molecule 2; ref. 52). Posttranslational functions of the HOTAIR have also been identified. HOTAIR induces ubiquitin-mediated proteolysis via interaction with E3 ubiquitin ligases Dzip3 and Mex3b, along with their respective ubiquitination substrates Ataxin-1 and Snurportin-1 (60). This leads to the degradation of Ataxin-1 and Snurportin-1 (60). Being an oncogenic lncRNA, its expression is correlated to tumor invasiveness and metastasis (53). HOTAIR serves as a diagnostic and prognostic marker for multiple cancers. HOTAIR also regulates the expression of miRNAs such as miR-130a (in gallbladder cancer cells) and others (4). Studies from our laboratory show that HOTAIR is required for the viability of breast cancer cells and its expression is transcriptionally regulated by estradiol via coordination of estrogen receptors (ER) and ER coregulators, such as the MLL (mixed lineage leukemia) family of histone methyltransferases, and CBP/p300 (45, 61–65). HOTAIR is also a target of endocrine disruption by estrogenic

Table 2. LncRNAs as cancer biomarkers

Cancer	LncRNA Biomarker	Potential implications	Site of detection	References
Prostate cancer	PCA3	Detection; Prognosis	Urine; Tumor	30, 225
	LincRNA-p21	Detection; Stratification	Urine	199
	PCAT-18	Metastasis	Plasma	28
	MALAT1	Risk of tumorigenesis; Detection	Urine; Plasma	240, 241
	PVT1	Aggressiveness	Tumor	226
	TRPM2	Early identification; aggressiveness	Tumor	227
Breast cancer	ZFAS1	Detection	Tumor	212
	HOTAIR	Detection	Serum	228
	RP11-445H22.4	Detection	Serum	242
	HIF1A-AS2; AK124454	Recurrence	Tumor	229, 230
Lung cancer	MALAT1	Early detection; Risk of metastasis	Whole blood; Tumor	87, 231, 232
	SPRY4-IT1; ANRIL; NEAT1	Early detection	Plasma	92
	UCA1	Detection	Plasma; Tumor	233
Colorectal cancer	HOTAIR	Risk of tumorigenesis	Tumor	234
	HOTAIR; CCAT1; CCAT2	Detection	Serum	235
	FER1L4	Recurrence; Metastasis	Plasma	236
	XLOC_006844; LOC152578; XLOC_000303	Risk of tumorigenesis	Plasma	237
Hepatocellular cancer	HOTAIR	Recurrence after transplant	Tumor	51
	uc001ncr; AX800134	Detection (especially early-stage)	Serum	143
	HULC; Linc00152	Detection; Metastasis	Plasma	238
	RP11-160H22.5; XLOC014172; LOC149086, HEIH	Risk of tumorigenesis, prognostic factor for recurrence and survival	Plasma	239
	XLOC014172; LOC149086	Risk of metastasis		239
Bladder cancer	UCA1	Detection	Urine	243
	H19	Early recurrence	Tumor	100
	HOTAIR	Overall survival	Tumor	244
Leukemia	CRNDE	Identification of subtypes of AML (acute myeloid leukemia) (M2 or M3)	Bone marrow, Lymph nodes	245
Ovarian cancer	NEAT1	Invasiveness; Prognosis	Tumor	246
Renal cancer	LET; PVT1; PANDAR; PTENP1; LINC00963	Early detection	Serum	247
Cervical cancer	HOTAIR	Prognosis; Recurrence	Serum	248
Esophageal cancer	POU3F3; HNF1A-AS1; SPRY4-IT1	Early screening	Plasma	249
Gastric cancer	H19	Early screening	Plasma	250
	LINC00152	Detection; Invasion	Gastric juice; Tumor	251
	UCA1	Early detection; Prognosis prediction	Gastric juice; Tumor	252
	CUDR; LSINCT-5; PTENP1	Detection	Serum	253
	AA174084	Early diagnosis	Tumor; Plasma; Gastric juice	254

endocrine disruptors such as bisphenol-A (BPA) and diethylstilbestrol (DES) that may contribute to cancer (45, 61, 62).

ANRIL

ANRIL (antisense noncoding RNA in the INK4 locus; a.k.a. CDKN2B-AS) is encoded in the chromosome 9p21 region at the INK4 locus (Tables 1 and 2; refs. 66–78). Polymorphisms in the INK4 locus serve as a hotspot for a variety of diseases including cardiovascular disease, cancer, and diabetes. ANRIL is an antisense transcript of the *CDKN2B* gene (cyclin-dependent kinase inhibitor 2B) and controls cell proliferation and senescence via regulating its neighboring tumor suppressors CDKN2A/B by epigenetic mechanisms. This occurs through interacting with CBX7 (a PRC1 component) and SUZ12 (a PRC2 component) to induce gene silencing at the INK4b-ARF-INK4a locus (66). It also represses tumor suppressor p15. ANRIL is overexpressed in a variety of cancers including leukemia, breast cancer, and prostate cancer where CDKN2A/B shows opposite patterns of expression (79).

Lung Cancer

Lung cancer is the leading cause of cancer-related deaths and the second most common cancer in both men and women. Deaths caused by lung cancer exceed those of prostate, breast, and colon cancer combined. LncRNAs implicated in lung cancer include MALAT1, NEAT1, SPRY4-IT1, ANRIL, HNF1A-AS1, UCA1, HOTAIR, GAS5, MEG3, CCAT1, MVIH, H19, CCAT2, AK126698, SOX2-OT, PVT1, EVADR, PANDAR, BANCR, TUG1, and others (Fig. 1; Table 1; refs. 80–82).

MALAT1

MALAT1 [metastasis associated lung adenocarcinoma transcript; a.k.a. NEAT2 (nuclear enriched abundant transcript 2)], a 7.5-kb long lncRNA, was originally found to be overexpressed in primary non–small cell lung cancers (83–91). MALAT1 is expressed in many tissues and is evolutionarily conserved among mammals. MALAT1 undergoes posttranscriptional processing to produce a short RNA (cytoplasmic mascRNA, MALAT1-associated small cytoplasmic RNA) and a long MALAT1 transcript that are localized to nuclear speckles and influence the level of phosphorylated splicing-associated serine arginine (SR) proteins. MALAT1 is also overexpressed in other cancers including bladder carcinoma, breast cancer, prostate cancer, and ovarian cancer, and is a potential biomarker and therapeutic target (85, 91). Genome-wide analyses identified multiple mutations in the SRSF1-binding sites of MALAT1 in breast cancer, suggesting an alternation in the splicing pattern in these cancers (91).

Similar to NEAT2, NEAT1 transcripts are also associated with nuclear paraspeckles and are involved in transcriptional and posttranscriptional regulation of the expression of genes such as *ADARB2* (adenosine deaminase, RNA-specific B2; refs. 92–96). NEAT1 has two isoforms: a 3.7 kb (NEAT-1-1) and a 23 kb (NEAT-1-2) long isoform that are widely expressed in several tissues and overexpressed in breast cancer and acute myeloid leukemia. NEAT1 knockdown affects the viability and morphology of Burkitt's lymphoma cells (97).

Colorectal Cancer

Colorectal cancer is currently the third most common malignancy worldwide. LncRNAs associated with colorectal cancer include CCAT1, CCAT2, CCAT1-L, CRNDE, E2F4, HOTAIR, HULC, MALAT1, H19, FER1L4, PTENP1, KCNQ1OT1, T-UCRs, ZFAS1, OCC-1, CCAT1-L, and others (Fig. 1; Table 1; refs. 89, 98, 99).

H19

H19 (2.7 kb) is one of the first lncRNAs discovered and a pivotal player in embryonic development and tumorigenesis (1, 100–116). It is a maternally expressed and paternally imprinted gene located near the telomeric region of chromosome 11p15.5 adjacent to *IGF2* (insulin like growth factor 2) gene. H19 is conserved between rodents and humans. miR-675, a highly conserved miRNA that regulates a variety of transcripts, resides within exon-1 of the *H19* gene (103). H19 acts as a decoy for miRNAs, modulating their availability and activity. It interacts with transcription repressors, such as EZH2 and MBD1 (methyl-CpG–binding domain protein 1), and induces repression by recruiting them to target genes (including H19′s reciprocally imprinted gene *IGF2*; ref. 103). H19 is an oncogenic RNA associated with tumorigenesis starting from the early stages to metastasis (100, 101, 106, 114, 117, 118). Tumor suppressor p53 and H19 are mutually counter-regulated (59). P53 represses the *H19* gene and the H19-derived miR-675 inhibits p53 and p53-dependent protein expression (115). The p53–H19 interplay appears to play major roles in tumorigenesis and metastasis (101, 102). H19 expression is induced by hypoxic stress and linked with epithelial-to-mesenchymal transition (EMT), and its overexpression leads to the activation of genes involved in angiogenesis, cell survival, and proliferation, triggering malignancies such as liver, breast, colorectal, esophageal, lung, pancreatic, gastric, bladder, and cervical carcinomas (100, 101, 107).

KCNQ1OT1

KCNQ1OT1 (KCNQ1 overlapping transcript 1) is a 91-kb nuclear antisense lncRNA that is imprinted from the paternal allele and originates from intron 11 of the *KCNQ1* gene (potassium voltage–gated channel subfamily Q member 1; refs. 119–124). The KCNQ1OT1 domain is regulated by a functionally independent imprinting control region (ICR) located in an intron of KCNQ1 (124). The promoter of the *KCNQ1OT1* gene, located within the ICR locus, undergoes methylation on the maternally inherited chromosome and demethylation on the paternally inherited chromosome. Therefore, it preferentially allows the *KCNQ1OT1* gene expression from the paternal allele (122, 124). It interacts with chromatin-modifying enzymes like PRC1, PRC2, and G9a and regulates the silencing of KCNQ1 via induction of histone and DNA methylation (122, 124). The aberration in KCNQ1OT1 is associated with Beckwith–Wiedemann syndrome, and colorectal, hepatocellular, and pediatric adrenocortical tumors (124, 125).

T-UCRs

T-UCR lncRNAs are about 200 to 779 nt in length and are generated from ultraconserved regions (UCR) and show tissue-specific expression patterns (126, 127). T-UCR lncRNAs are altered in a variety of cancers including colorectal carcinoma, chronic lymphocytic leukemia, neuroblastomas, hepatocellular carcinoma, and prostate cancer (127). They play a key role in the suppression of miRNAs such as miR-596 and miR-193b involved in carcinogenesis and apoptosis, respectively (128–131). Modulation of T-UCR expression promotes colorectal carcinoma progression (4, 7, 132). Notably, the CpG island hypermethylation-induced epigenetic silencing of tumor suppressor miRNAs appears to be closely associated with a variety of cancers. Recent studies also demonstrate that in addition to miRNAs, various lncRNAs, such as T-UCRs, are silenced via CpG island hypermethylation, which is a common feature of many tumor types (132, 133). Furthermore, the CpG island methylation-induced silencing of protein coding and noncoding sequences in the sense strand as well as antisense-transcripts (many antisense lncRNA) is closely associated with human tumors. For example, antisense lncRNA VIM-AS1 (vimentin antisense 1), which is regulated via R-loop (three-stranded RNA-DNA hybrid) formation, is silenced in colorectal cancer through CpG island hypermethylation (134).

CCAT1

CCAT1 (colon cancer–associated transcript-1; a.k.a. CARLo-5) is an oncogenic lncRNA located at 8q24.21. CCAT1 expression is induced by c-Myc that binds to its promoter. CCAT1 epigenetically downregulates c-Myc by acting as a competing endogenous RNA (ceRNA) for miR-155 that represses c-Myc expression. It is also involved in the regulation of HOXB13 and SPRY4 (135–137). CCAT1 has been implicated in acute myeloid leukemia (AML), colorectal, esophageal, lung, and other cancers (138).

Liver Cancer

Hepatocellular carcinoma (HCC) is a leading cause of cancer-related deaths with an incidence that has tripled since 1980. Although many lncRNAs are implicated in HCC, the most studied are MALAT1, HULC, HEIH, and HOTAIR that are known to be upregulated in HCC (47, 139). Other lncRNAs implicated in liver cancer are linc00152, HEIH, HOTTIP, DILC, ZFAS1, LET, MVIH, PCNA-AS1, TUC338, lncTCF7, CCAT1, MEG3, CUDR, LALR1, and others (Fig. 1; Table 1; ref. 140).

HULC

HULC (highly upregulated in liver cancer), a 1.6-kb oncogenic lncRNA, is overexpressed in HCC (89, 141, 142). Augmented levels of the HULC transcript are observed in metastatic liver nodules from colon cancer. HULC is upregulated in both tumors and plasma of HCC patients, and is a potential biomarker for HCC. The SNP in HULC is associated with HCC susceptibility in hepatitis B virus carriers (143). HULC might function to downregulate the activity of miR-372 by acting as an endogenous sponge (144). Suppression of miR-372 by HULC represses the translational inhibition of miR-372 target genes. HULC promoter possesses a binding site for transcription factor cAMP response

element binding (CREB) and its expression is potentially regulated by CREB phosphorylation (144).

HEIH

HEIH (high expression in HCC), a 1.6-kb SP1-regulated long lncRNA located in the 5q34.3 locus, is differentially expressed in HCC, closely associated with HCC recurrence, and a prognostic factor for HCC (139, 145, 146). HEIH interacts with EZH2 and regulates EZH2 target genes including cell-cycle–regulatory genes p15, p16, p21, and p57 (145). Knockdown of HEIH reduces cell proliferation and suppresses tumor growth (145).

Other lncRNAs implicated in liver cancer are DILC, H19, TCF7, HOTTIP, and ZFAS1 (139, 147). DILC (downregulated in liver cancer) is a tumor suppressor whose expression is inversely related to those of EpCAM (epithelial cell adhesion molecule), CD24, and CD90 in hepatoma spheroids (148). HOTTIP (HOXA Transcript at the distal Tip) upregulation is associated with liver cancer metastasis (149, 150). HOTTIP, in conjunction with the WDR5/MLL complex, mediates the trimethylation of H3K4 and HOXA gene expression (139, 151, 152).

Bladder Cancer

Bladder cancer is the tenth most common malignancy in women and the fourth most common in men. LncRNAs implicated in bladder cancer are UCA1, UCA1a, HOXD-AS1, TUG1, ncRAN, GHET1, MALAT1, MEG3, H19, linc-UBC1, lincRNA-p21, SPRY4-IT1, and others (Fig. 1; Table 1; refs. 153–155).

UCA1

UCA1 (urothelial cancer associated-1), transcribed from 19p13.12, was originally cloned from the human bladder cell line, and is overexpressed in embryonic tissues, bladder cancers, and other cancers (156–158). It promotes chemoresistance through promoting the expression of wingless-type MMTV integration site family member 6 (Wnt6; ref. 157). It also plays a role in β-catenin translocation into the nucleus and TCF7 regulation via interaction with SWI/SNF (switch/sucrose nonfermentable) in other types of cancer (159). UCA1 is a potential urine biomarker for noninvasive diagnosis of bladder cancer. MALAT1 associates with SUZ12 and regulates N-cadherin and E-cadherin expression, promotes tumor growth and metastasis, and forms a fusion gene in renal carcinoma (153).

Leukemia

Defects in hematopoietic stem cell differentiation and proliferation cause leukemia. A variety of lncRNAs are implicated in leukemia that include CRNDE, HOTAIRM1, DLEU1, DLEU2, LUNAR1, BGL3, MALAT1, CCAT1, CCDC26, BGL3, NEAT1, NALT, UCA1, and others (Fig. 1; Table 1; refs. 160, 161). LncRNA mutations such as internal tandem duplications in the FLT3 (FMS-like tyrosine kinase 3) gene (FLT3-ITD) and mutations in the *NPM1*, *CEBPA*, *IDH2*, *ASXL1*, and *RUNX1* genes are also linked to recurrent leukemia (162, 163).

DLEU1 and DLEU2

LncRNAs DLEU1 and DLEU2 (deleted in lymphocytic leukemia 1 and 2), originating from the 13q14.3 region, are often deleted in solid tumors and hematopoietic malignancies like chronic lymphocytic leukemia (CLL) and lymphomas (164). DLEU1 and DLEU2 regulate NF-κB activity by regulating genes that affect NF-κB activity. The promoter regions of DLEU1 and DLEU2 exhibit demethylation or activation marks in CLL (164). DLEU2 acts as a precursor for various miRNAs such as miR-15a and miR-16-1 that are involved in CLL (165).

LUNAR1

LUNAR1 (leukemia-induced noncoding activator RNA-1), derived from 15q26.3, is a NOTCH-regulated oncogenic lncRNA in T-cell acute lymphoblastic leukemia (T-ALL), and it promotes T-ALL cell growth by enhancing IGF1R expression and IGF1 signaling. LUNAR1 recruits the mediator complex on the IGF1R promoter and regulates its transcription. Abnormal NOTCH1 signaling is closely associated with human T-ALL (166, 167).

BGL3

BGL3 (beta globin locus transcript 3) is a 3.6-kb lncRNA derived from chromosome 11p15.4. BGL3 expression in leukemic cells is negatively regulated by Bcr-Abl through c-Myc–mediated DNA methylation (168). Conversely, BGL3 regulates Bcr-Abl through sequestering miR-17, miR-93, miR-20a, miR-20b, miR-106a, and miR-106b (168). These miRNAs are known to repress the expression of PTEN (169).

HOTAIRM1

HOTAIRM1 (HOTAIR myeloid-specific 1), a 483-bp lncRNA transcribed from the HOXA cluster, is expressed in the myeloid lineage. Inhibition of HOTAIRM1 downregulates numerous HOXA genes critical for hematopoiesis (170–172). HOTAIRM1 has a similar expression pattern as that of HOXA1 and HOXA2 in thymus, muscle, colon, lung, kidney, spleen, etc. (173). HOTAIRM1 is induced by all-trans retinoic acid (RA) and is involved in RA-induced myeloid differentiation. HOTAIRM1 regulates myeloid differentiation genes CD11b and CD18, and also interacts with chromatin-modifying enzymes including PRC1, PRC2, and CBX1 (172).

XIST

XIST (X-inactive specific transcript) induces X-inactivation and is aberrantly expressed in leukemia (162). Homozygous and heterozygous deletion of XIST in hematopoietic stem cells leads to the development of blood cancers, suggesting that aberrant X inactivation promotes carcinogenesis (162). It regulates genes in various other cancers via interaction with PRC1, PRC2, YY1, and CTCF, among others (128, 147, 174, 175). UCA1 knockdown negatively affects the proliferation of AML cells *in vitro* (147, 176).

Other Cancers

A large number of lncRNAs are identified in various other types of cancers; however, their detailed functions and specificity remain elusive (Fig. 1; Tables 1 and 2; ref. 7). For example, pancreatic cancer, which accounts for 7% of cancer-related deaths worldwide, is associated with lncRNAs H19, HOTAIR, HOTTIP, MALAT1, GAS5, HULC, PVT1, linc-RoR, AF339813, AFAP1-AS, and others (177–181). Ovarian cancer, being the fifth deadliest cancer in women, is associated with abnormal expression of lncRNAs, such as H19, LSINCT-5, HOST2, NEAT1, HOTAIR, PVT1, CDKN2B-AS, CCAT2, UCA1, MEG3, and others (182–184). The lncRNAs implicated in renal cancer include PVT1, LET, PANDAR, PTENP1, HOTAIR, NBAT1, linc00963,

KCNQ1OT1, GAS5, CADM-AS1, RCCRT1, MEG3, SPRY4-IT1, HIF1A-AS, MALAT1, and others (185–187). The lncRNAs implicated in gastric cancer include UCA1, H19, GHET1, CCAT1, linc00152, LSINCT-5, PTENP1, TUG1, MRUL, HOTAIR, MALAT1, GACAT2, FER1L4, MEG3, HULC, PVT1, ANRIL, GAS5, and others (188–191). The expression of lncRNAs H19, MALAT1, CRNDE, ADAMTS9-AS2, DISC2, MEG3, CASC2, TSLC1-AS1, and POU3F3 is positively correlated with malignant glioma (192, 193). MEG3 is a tumor suppressor lncRNA that is highly expressed in normal brain tissue and downregulated in gliomas (194). FER1L4 (Fer-1-like protein 4) is a tumor suppressor lncRNA involved in the regulation of PTEN and inhibition of Akt phosphorylation in endometrial cancer (195). NBAT1 (neuroblastoma-associated transcript 1) represses the expression of neuronal-specific transcription factor NRSF/REST through association with PRC2 (196, 197).

GAS5 (growth arrest specific 5) and SRA (steroid receptor RNA activator) are two lncRNAs implicated in hormone signaling (198–201). GAS5 produces two splice variant lncRNAs, and its introns also give rise to several snoRNAs (small nucleolar RNA) involved in the biosynthesis of ribosomal RNA from its introns. GAS5 interacts with glucocorticoid receptor (GR) and suppresses the expression of GR-regulated genes (202). It causes growth arrest and apoptosis and induces PTEN via inhibiting miR-103 (198). GAS5 acts as a tumor suppressor and its misregulation and genetic aberrations are associated with breast cancer, prostate cancer, leukemia, gastric cancer, and others (203). The lncRNA SRA interacts with various steroid hormone receptors and stimulates transcriptional activation, and is associated with breast, uterine, ovarian, and prostate cancers (204).

TERRA

TERRA (telomeric repeat-containing RNA) is a set of lncRNAs (ranging in size from 100 bp to 9 kb) transcribed from telomeres. LncRNAs containing UUAGGG repeats are generally called TERRA (205–208). TERRA interacts with telomere-associated TRF1 and TRF2 (telomere repeat factors 1 and 2), subunits of the origin recognition complex (ORC), heterochromatin protein 1 (HP1), H3K9-methylated histone, and facilitates heterochromatin formation at telomeres. TERRA is known to negatively regulate telomerase and act as a tumor suppressor (207, 208).

ZFAS1

ZFAS1 (ZNFX1 antisense RNA 1) is a spliced and polyadenylated lncRNA transcribed from the 5′ end of *ZNFX1*. It is derived from chromosome 20q13.13, and is implicated in different types of cancer including gastric cancer, colorectal cancer, and hepatocellular cancer, among others. It interacts with CDK1 and cyclin B to control p53-dependent cell-cycle regulation (209). In addition, it promotes cell proliferation by recruiting EZH2 and LSD1/CoREST to the promoters of genes including KLF2 (Kruppel like factor 2) and NKD2 (naked cuticle 2) to regulate their expression (210). It also acts as a sponge for tumor suppressor miR-150 (211). Knockdown of ZFAS1 results in the repression of cell proliferation, migration, and colony formation (210, 212).

PVT1

PVT1 (plasmacytoma variant translocation 1) is an oncogenic, intergenic lncRNA derived from 8q24.21 with multiple splice isoforms (213–215). It is upregulated in different types of cancer such as ovarian cancer, cervical cancer, and pancreatic cancer, among others. It suppresses the phosphorylation of Myc, thereby enhancing its stability (216). Furthermore, it promotes proliferation via interaction with NOP2 (nucleolar protein 2 homolog) with the help of TGFβ (213). PVT1 promotes cell proliferation and invasion in gastric cancer by recruiting EZH2 to repress the expression of tumor suppressor genes p15 and p16 (214). It associates with a multifunctional DNA- and RNA-binding protein called nucleolin involved in oncogene expression and ribosomal biogenesis, among other activities (217).

MEG3

MEG3 (maternally expressed 3) is an imprinted, tumor-suppressive lncRNA transcribed from chromosome 14q32.2 (218–221). It is a polyadenylated lncRNA overexpressed in human pituitary, but downregulated in cancer cells (219). Overexpression of MEG3 in bladder cancer cells has been shown to induce autophagy and increase cell proliferation (222). MEG3 is involved in the accumulation of tumor suppressor p53 and regulation of TGF-β pathway genes involved in cell invasion, immune regulation, etc. It also interacts with PRC2 to repress MDM2 (murine double minute 2), which contributes to p53 accumulation (221, 223).

LncRNAs as Biomarkers and in Gene Therapy

Numerous lncRNAs are aberrantly expressed in various tumors and some appear to be cancer-specific. Many lncRNAs (or their processed fragments) are stable in body fluids and detectable in the plasma and urine of cancer patients (24, 224). Their levels are indicative of the severity of the disease. All these factors render lncRNAs an attractive choice for their applications as noninvasive biomarkers and therapeutic targets for the treatment of cancer (Table 2; refs. 28, 30, 92, 143, 212, 225–254). LncRNAs differ from protein-coding genes in many respects. First, due to their greater abundance than protein-coding genes, a modulation in larger number of lncRNA expression may be observed in a given subtype of cancer, which provides a larger window for the detection of subtype-specific lncRNA-based biomarker. Subtype/tissue–specific lncRNA expressions are crucial for developing novel diagnostic biomarker and personalized therapy (43, 245). LncRNAs, being large in size, may fold into complex secondary/tertiary structures and scaffolds through which they may interact with various proteins, transcriptional regulators, mRNA (complementary), and DNA sequences, which may aid in cancer initiation and progression. The presence of a large number of regulatory interaction sites in lncRNAs provides a wider platform for developing novel structure-based cancer drugs. Furthermore, given their participation in diverse cell signaling pathways and tissue-specific expression, lncRNAs can be utilized to formulate novel strategies for specific cancer subtype diagnosis and targeting (255, 256).

Few lncRNAs are already implicated as biomarkers and some of them are in clinical trials (Table 2; refs. 230, 257). For example, lncRNA PCA3, which is highly upregulated and specific to prostate cancer, is detectable in urine with levels that correspond to the severity of prostate cancer (30, 31, 225). As it can be detected in urine, PCA3 has advantages over the widely used serum-based prostate cancer biomarker PSA (prostate-specific antigen) for noninvasive diagnosis of prostate cancer (258). In addition, PCAT-1, PRNCR1, PCGEM, PlncRNA1, and PCAT-18 are highly

expressed in prostate tumors and are potential diagnostic markers (Table 2; refs. 44, 259). Circulating HOTAIR may also be used to diagnose breast cancer (228). ZFAS1, HIF1a-AS2, and others are also implicated as biomarkers for breast cancer (Table 2). Similarly, MALAT1, UCA1, ANRIL, and NEAT1 can be used to predict early stage as well as metastatic lung cancers (Table 2; ref. 85). The expression of HOTAIR, CCAT1, FER1L4, and others is linked to colorectal cancer (Table 2). CpG-island methylation of T-UCR promoter is also linked to colorectal cancer diagnosis. LncRNAs H19, HULC, HEIH, linc00152, and MVIH are highly upregulated in hepatocellular cancer (HCC) and are valuable HCC biomarkers (Table 2; ref. 260). HULC expression correlates with histologic grade and oncoprotein hepatitis B virus X (HBx; ref. 261). Hepatitis B virus (HBV)-positive hepatocellular cancer can be detected using lncRNAs uc001ncr and AX800134. Uc001ncr and AX800134 have a 100% detection rate in HCC patients (143). HOTAIR overexpression may be used to predict the recurrence of HCC and is highly expressed in 65.7% of recurrence HCC patients (47, 262). UCA1, H19, and HOTAIR expression may be used as a biomarker to detect bladder cancer (Table 2; ref. 176). CRNDE is expressed in the APL (acute promyelocytic leukemia) subtype of AML ten times more than the other subtypes. This makes CRNDE a suitable biomarker to detect the APL subtype of AML (245). LET, PVT1, PANDAR, and PTENP1 expression is linked to renal cancer (Table 2). Thus, lncRNAs appear to be promising novel diagnostic and prognostic markers for a variety of cancers (Table 2); however, there are still many challenges and validations required for their clinical applications.

As lncRNA expressions are differentially modulated in different types of cancer and their expression levels correlate with tumorigenesis, tumor aggressiveness, and stages, they are potential targets for cancer therapy. There are several ways by which lncRNAs may be targeted to modulate their expression: (i) lncRNA transcript degradation/destabilization by using lncRNA-specific siRNAs, antisense oligonucleotide (ASO), gapmers, and ribozymes; (ii) modulating lncRNA transcription by altering the lncRNA-coded promoter activity (e.g., via inhibition of transcription factors binding to respective promoters); (iii) blocking interactions between lncRNAs and regulatory factors—small synthetic molecules/peptides can be developed that are designed to block the binding of lncRNAs with protein, DNA, RNA, or other interacting complexes by associating with specific binding pockets; and (iv) functional disruption of lncRNAs using aptamers that can be selected to bind at specific structural regions to target lncRNAs and antagonize their association with their binding partners (263, 264). For example, siRNA-mediated downregulation of HOTAIR expression leads to reduced tumor cell viability and invasiveness and induction of apoptosis in breast tumors (228). CCAT2 is upregulated in colorectal cancer and has been targeted by specific miRNAs to suppress colorectal cancer growth (265–267). Antisense-mediated silencing of MALAT1 prevents *in vivo* lung cancer metastasis (85). Breast cancer progression can be hindered through systemic knockdown of MALAT1 using antisense oligonucleotide (85, 91, 201). Antisense-mediated lncRNA targeting has shown to be promising in the treatment of other disorders like Angelman's syndrome through silencing lncRNA UBE3A-AS (268, 269). Oncogenic lncRNA H19 is overexpressed in a variety of cancers such as pancreatic tumors. The H19 promoter has been used to express diphtheria toxin (DTA) in pancreatic cancer cells (117, 118, 270). Administration of pancreatic tumors with a H19-DTA plasmid construct resulted in a significant decrease in tumor size and metastasis. The H19 (and IGF2) regulatory sequences can be used to inhibit the growth and metastasis of colorectal cancer. Overall, lncRNA-based targeted cancer therapies are promising; however, at present, they are at their infancy and require further development of experimental strategies, siRNA/antisense delivery strategies, screening novel small-molecule libraries, and many clinical trials prior to their success in targeted, lncRNA-based gene therapy.

Apart from evaluating the direct significance of lncRNAs in cancer diagnosis and therapy, they can also be considered for improving therapeutic efficacy and development of combination therapy. Therapeutic resistance (such as chemo- or radioresistance) is a major challenge in cancer treatment; however, this could be improved by increasing the therapeutic sensitivity of tumors by modulating a critical cell signaling pathway that confers resistance. As lncRNAs are closely associated with many cell signaling processes, the modulation of their expression could be done to improve the therapeutic sensitivity of tumors. One approach is to resensitize chemoresistant cells by modulating factors associated with DNA damage response pathways. For example, knockdown of HOTAIR enhances the sensitivity of cancer cells to chemotherapeutic agents like cisplatin and doxorubicin (271–273). Cisplatin-mediated upregulation of HOTAIR in human lung adenocarcinoma cells suppressed p21 (WAF1/CIP1) signaling pathway and caused a G_0–G_1 arrest by modulating the p53 expression and HOXA1 methylation (157, 274). LncRNA TUG1 (taurine upregulated gene 1; refs. 2, 3, 275–277) overexpression is responsible for the chemoresistance of lung cancer cells. TUG1 regulates the expression of LIM-kinase 2b and other cell-cycle–associated genes through recruiting EZH2 to its promoter. TUG1 knockdown has been shown to enhance chemosensitivity in lung cancer (278). Silencing CRNDE results in the suppression of cell proliferation and chemoresistance in colorectal cancer. CRNDE inhibits the expression of miR-181a-5p, which in turn silences Wnt/β-catenin signaling (279). Similarly, HOTTIP promotes chemoresistance via activation of Wnt/β-catenin signaling (280). GAS5 modulates chemoresistance in gastric cancer by acting as a sponge for miR-23a that inhibits the expression of metallothionein 2A (MT2A; ref. 281). In a similar role, CCAT1 sponges let-7c–mediated release of Bcl-xL. This involves EMT and resistance to docetaxel (136). MALAT1 knockdown causes resensitization of glioblastoma multiforme cells to temozolomide. The MALAT1-mediated chemoresistance in glioblastoma multiforme cells is made possible via inhibition of miR-203, thereby activating the expression of thymidylate synthase (282). Other lncRNAs that may be targeted to increase the chemosensitivity of tumors include HULC (gastric cancer), H19 (breast cancer), ODRUL (osteosarcoma), OMRUL (lung cancer), and PVT1 (pancreatic cancer; refs. 216, 283–285). Thus, it is evident that the modulation of lncRNA expression can be exploited to improve the therapeutic sensitivity of tumors and may also be used for combination therapy.

Conclusions

LncRNAs are emerging stars in cancer, diagnosis, and therapy (286). The discovery of huge numbers of lncRNA, their wide range of expression patterns in various types of cancer, their tumor specificity, and their stability in circulating body fluids (plasma and urine) provide a new foundation for developing diagnosis and therapies for cancer. LncRNA expression may also be used to

predict the cancer prognosis and patients outcome. LncRNAs are major regulators of chromatin dynamics and gene regulation, associated with a variety of cell signaling pathways, and their expressions are influenced by a variety of factors including hormones, nutrients, age, and sex (162, 287–290). Aberrant expression, mutations and SNPs of lncRNAs are associated with tumorigenesis and metastasis. Some lncRNAs act as oncogenes, whereas others act as tumor suppressors (291). Oncogenic lncRNAs include PCA3, PCGEM1, PCAT1, PCAT18, CTBP-AS, SCHLAP1, HOTAIR, ANRIL, MALAT1, NEAT1, H19, KCNQ1OT1, lncTCF-7, HOTTIP, HULC, HEIH, TUG1, UCA1, PVT1, and LSINCT5 (286). Tumor suppressor lncRNAs include GAS5, MEG3, DILC, NBAT-1, DLEU1, DLEU2, TERRA, BGL3, and others. Novel lncRNAs are still being discovered (292). Thus, lncRNAs holds strong promise towards the discovery of novel diagnostics and therapeutics for cancer. However, there are still many challenges. First, given the large number of lncRNAs and their up- or downregulation in various cancers, it is crucial to identify the most important lncRNAs associated with a specific types/subtype of cancer. Second, the field of lncRNAs is at its infancy at this point; the structural and functional information on most lncRNAs remain uncharacterized. Without detailed understanding on the structure and functions of lncRNAs, developing lncRNA-based therapies is like "shooting in the dark". In addition, unlike protein-coding genes, lncRNAs are poorly conserved across different species; therefore, the structural and functional information as well as the promising therapeutic strategies developed using *in vitro* and animal models may not be easily extended to immediate human application and may need detailed clinical studies. To fully explore the potential of lncRNAs in cancer diagnosis and targeted therapy, it is important to characterize each lncRNA in detail, identify their cellular functions, roles in diseases, and SNPs. The cause–effect relationships of each lncRNA need to be established for determining their tissue specificity and linking them to tumor stage. The future studies on the use of lncRNAs as biomarkers and therapeutics should focus not only on their identification and functional characterization, but also on optimizing isolation procedures, characterizing variations by internal and external factors using large numbers of statistically significant patient cohorts, and development of proper animal models for testing and validations, prior to clinical trials. Development of technologies for efficient detection of lncRNAs and their tissue-specific delivery methods are critical to the success of the diagnostics and therapeutics. Recent advancements in CRISPR/Cas9 technologies for gene knockout, knock-in, and point mutations may facilitate understanding the biological roles of lncRNAs and aid in the development of lncRNA-based targeted cancer therapy. Nevertheless, discovering novel lncRNAs, identifying their function and association with various cancer subtypes, developing novel lncRNA-based strategies for diagnosis and targeted therapies appear very promising, bring a new paradigm in cancer research, and may emerge as a major therapeutic strategy for the treatment of cancer in the near future.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

We thank Mandal lab members for helpful discussions. We sincerely apologize to all the colleagues whose contributions are not cited here due to the limitation in the scope and length of the article.

Grant Support

This work was supported by NIH grant 1R15 ES019129-01.

Received September 26, 2016; revised April 5, 2017; accepted May 4, 2017; published OnlineFirst July 12, 2017.

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