Genome-wide analysis reveals the emerging roles of long non-coding RNAs in cancer (Review)

XIAOXIA REN

Center for Life Sciences, School of Life Sciences, Yunnan University, Kunming, Yunnan 650500, P.R. China

Received January 28, 2019; Accepted October 23, 2019

DOI: 10.3892/ol.2019.11141

Abstract. Cancer is the most intractable human disease that is primarily caused by genetic alterations. Recently, the general application of microarrays and high-throughput sequencing technology has revealed various important roles of long noncoding RNAs (lncRNAs) in cancer. This review summarizes the function, mechanism, diagnostic and treatment potential of lncRNAs identified through genome-wide analysis in cancer. Cell-, tissue- and development stage-specific expression patterns are major characteristics of cancer-associated lncRNAs, and various genetic alterations are also implicated. Microarray and sequencing analyses serve important roles in mechanistic studies of either nuclear or cytoplasmic lncRNAs. Collectively, genome-wide analysis is the inexorable trend of future studies or clinical applications of lncRNAs and offers a novel perspective regarding the prognosis and treatment of cancer.

Contents

1. Introduction

Long non-coding RNAs (lncRNAs) are transcripts longer than 200 nucleotides that lack protein-coding potential. Due to the simultaneous and synergistic availability of genome and transcriptome sequences, lncRNAs were discovered by analyzing the mouse transcriptome based on the functional annotation of 60,770 full-length cDNAs in 2002 (1). Djebali *et al* (2) have also used sequencing technology to reveal that <2% of the human genome encodes proteins, and three-quarters of the human genome is actively transcribed into non-coding RNAs. LncRNAs are highly conserved (>95%) in mammals (3), indicating their biological functionality. However, for a long time, a large number of ncRNAs have been regard as dark matter or transcriptional noise.

In recent years, the general application of genome-wide analysis, which includes microarrays and high-throughput sequencing technologies, have revealed various important biological functions of lncRNAs in cell differentiation, development and numerous diseases, especially cancer (4). In cancer, lncRNAs exhibit tissue-specific expression and are transcriptionally regulated by key tumor suppressors or oncogenes, which can influence cell cycle regulation, survival, immune response and pluripotency (5). For example, lncRNA taurine upregulated gene 1 (TUG1) is a direct transcriptional target of p53 and affects cell proliferation in human non-small cell lung and laryngeal cancer (6). Likewise, lncRNA plasmacytoma variant translocation 1 (PVT1) is adjacent to proto-oncogene Myc in the same genomic region of 8q24, and its amplification is associated with the Myc gene copy number gain, thus increasing Myc protein levels in cancer (7).

Although the above examples represent only a small proportion of lncRNA effects, they indicate the large diversity in the functions of lncRNAs in cancer. Based on these mechanisms, lncRNAs are attractive potential therapeutic targets and biomarkers of cancer, and genome-wide analysis in combination with novel computational strategies may further advance the clinical application of lncRNAs. In this review, the emerging roles of lncRNAs in cancer based on genome-wide analysis and the potential clinical applications of lncRNAs were summarized.

2. Identification of lncRNAs in cancer using genome analysis

Aberrant expression of lncRNAs in cancer. LncRNAs exhibit tissue-specific expression, and their expression level consistently changes in cancer (8). Considering their limitations in large-sample tests and tedious operation protocols, traditional molecular methods such as reverse transcription-PCR and fluorescence *in situ* hybridization do not suffice for the study

Correspondence to: Dr Xiaoxia Ren, Center for Life Sciences, School of Life Sciences, Yunnan University, East Outer Ring Road, Kunming, Yunnan 650500, P.R. China
E-mail: renxiaoxia044@163.com

Key words: long non-coding RNA, microarrays, sequencing, cancer, mechanism, genome-wide

of lncRNAs (9). The general implementation of microarrays (Table I) and high-throughput sequencing (Table II) technology overcomes these difficulties and makes great progress in cancer. To delineate genome-wide lncRNA expression patterns, polyA+ RNA sequencing (RNA-seq) data from 6,503 samples, including tumors, normal samples and cancer cell lines, were applied (10). Based on these data, a non-parametric method termed Sample Set Enrichment Analysis was developed to assess differential expression. Using this approach, known lncRNAs in breast and prostate cancer, including upregulated oncogenic lncRNA hox transcript antisense intergenic RNA (HOTAIR) and prostate cancer antigen-3 (PCA3), downregulated tumor suppressor lncRNA maternally expressed gene 3 (MEG3) were identified, and a myriad of unannotated lncRNAs exhibiting potential tissue- and cancer-specific gene signatures were also identified (Fig. 1A) (10).

Rinn *et al* (11) have reported that lncRNA *HOTAIR* is a spliced and polyadenylated RNA with 2,158 nucleotides and 6 exons, according to a DNA microarray. Patients with high HOTAIR expression levels exhibit an increased incidence of malignancy and lymph node metastasis (12). Another lncRNA, MEG3, which is expressed in normal tissues, has been demonstrated to be either lost or decreased in a number of human tumors and tumor-derived cell lines; MEG3 is a tumor suppressor involved in the etiology, progression and chemosensitivity of cancers (13). In addition to well-known lncRNAs, a growing number of novel lncRNAs have been identified, such as adenocarcinoma- and immune-associated lncRNAs. A lncRNA expression profile in lung adenocarcinoma and matched adjacent normal lung tissues measured by microarray demonstrated that 1,048 lncRNAs were upregulated and 1,997 lncRNAs were downregulated in lung adenocarcinoma (14). Among these lncRNAs, nine lncRNAs were validated; the expression of NONHSAT077036 was associated with N classification and clinical stage (14). Wang *et al* (15) also used the Chinese Glioma Genome Atlas microarray to identify 344 immune-associated lncRNAs. Further validation indicated that the nine immune-associated lncRNA signature, including SNHG8, ST20-AS1, PGM5-AS1, LINC00937, MIR155HG, AGAP2-AS1, MAPKAPK5-AS1, HCG18 and TUG1, exhibited prognostic value for anaplastic gliomas.

Genetic alteration of lncRNAs in cancer. Microarrays and sequencing technologies, especially whole genome sequencing, have been prominently applied to identify the genetic alterations of lncRNAs in cancer, including single nucleotide polymorphisms (SNPs), copy number alterations (CNAs) and point mutations (16). For example, a common disease genome-wide association study identified a SNP within a tumor suppressor lncRNA cancer-associated susceptibility candidate 15 (CASC15) at 6p22, which was associated with CASC15-S differential expression (17).

CBioPortal (http://www.cbioportal.org/) is an open-access resource for the interactive examination of multidimensional cancer genomics data sets that include information regarding somatic mutations, CNAs, RNA expression, DNA methylation and protein and phosphoprotein abundance (18,19). CBioPortal provides access to data from >5,000 tumor samples from 105 cancer studies in The Cancer Genome Atlas (TCGA) (20). A previous study assessed 1,000 cases of breast invasive carcinoma in this database; the results demonstrated that 577 lncRNAs exhibited alterations among the 2,730 analyzed lncRNAs (21). The deregulation of 11 lncRNAs, primarily due to CNA, was associated with poor overall survival rate; the results also suggested that greater distance from the oncogene Myc was associated with smaller alterations of CNA, which indicated that 8q24.21 was the center of CAN (21). Another team also supports this conclusion; Tseng *et al* (7) analyzed genome-wide data from two large cancer databases, including Progenetix and TCGA, and consistently observed in 98% of cases a co-gain of Myc and PVT1 across a wide variety of cancer types harboring the amplified 8q24 region, such as ovarian, oesophageal and breast cancer. According to their study, PVT1 RNA and Myc protein expression were associated in primary human tumors, and the copy number of PVT1 was co-increased in >98% of cancer cases with the increase of Myc copy numbers.

Pan *et al* (22) identified somatic mutations for papillary thyroid carcinoma (PTC) in the Chinese population using 402 pairs of tumor and normal tissues, of which 91 were characterized by exome sequencing and 311 by Sanger sequencing; the results demonstrated that the lncRNA GAS8-AS1 was the secondary most frequently altered gene and acted as a novel tumor suppressor in PTC. Liu *et al* (23) identified a single-nucleotide mutation (622U>C) in the SIRT1-AS sequence using gene-sequencing technology; bioinformatics analysis revealed that this mutation led to an alteration in the secondary structure of lncRNA SIRT1-AS and prevented it from binding to SIRT1 mRNA.

3. Mechanisms of lncRNAs identified by genome-wide analyses in cancer

The mechanisms of lncRNAs likely depend on their secondary or tertiary structures (24). Nuclear lncRNAs may act as molecular scaffolds and aid in alternative splicing or chromatin structure modification (25). Cytoplasmic lncRNAs may modulate translation and promote or inhibit mRNA degradation, acting as miRNA sponges (25,26). In addition to identifying novel lncRNAs, genome-wide analysis also serves important roles in lncRNA mechanistic studies, such as to determine its functional importance or to probe its mechanistic properties (27). Recently, these techniques were combined with approaches used to study gene-gene, gene-protein and protein-protein interactions, including chromatin immunoprecipitation (ChIP), RNA binding protein immunoprecipitation (RIP) and co-immunoprecipitation (Co-IP), to further assess the mechanistic role of lncRNAs in cancer (Fig. 1B) (4).

The mechanisms of lncRNAs in cancer identified by microarrays. Microarrays involve hybridizing a modified complementary DNA (cDNA) or a complementary RNA template of target transcripts to a set of short oligonucleotide probes immobilized on a solid surface (28). When bound to the probes, these modifications enable either direct or indirect florescence detection, and a digital signal is used to quantify the level of gene expression (28). Therefore, microarray offers a highly sensitive, highly selective and high-throughput method for the analysis of mRNAs and lncRNAs in biology and disease (29).

Table I. Typical cancer-associated lncRNAs identified by microarray.

Author, year	LncRNA	Cancer type	Biological function	Mechanism	(Refs.)
Rinn *et al*, 2007; Botti *et al*, 2017	HOTAIR	Breast, gastric, colorectal and cervical	Promotes metastasis	Acts as scaffold for the chromatin repressors PRC2 and LSD1. Silences HoxD and other gene loci	(11,12)
He *et al*, 2017	MEG3	Hepatocellular	Tumor suppressor; inhibits cell growth and induces apoptosis	miR-29 regulates expression of MEG3 in methylation-dependent pattern	(13)
Tee *et al*, 2016	MALAT1	Neuroblastoma, bladder, lung and gastric	Promotes cell proliferation and metastasis	Promotes tumor-driven angiogenesis by upregulating pro-angiogenic gene expression	(31)
Ji *et al*, 2015; Zhang *et al*, 2017	LINC00152	Hepatocellular and lung	Promotes proliferation, invasion, metastasis and apoptosis	Affects mechanistic targets of mTOR, Akt and EGFR pathways	(33,35)
Zhu *et al*, 2016	LOC572558	Bladder	Tumor suppressor; inhibits proliferation and induces apoptosis	Regulates the p53 signaling pathway	(37)
Prensner *et al*, 2014; Smolle *et al*, 2017	SCHLAP1	Prostate	Biomarker for metastatic progression	Unknown	(54,55)
Li *et al*, 2016	GAS5	Breast	Prognostic marker; suppresses cancer proliferation	Acts as a molecular sponge for miR-21, leading to the de-repression of phosphatase and tensin homologs	(57)

LncRNAs, long non-coding RNAs; HOTAIR, hox transcript antisense intergenic RNA; PRC2, polycomb repressive complex 2; LSD1, histone demethylase lysine-specific demethylase; MEG3, maternally expressed gene 3; miR, microRNA; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; mTOR, mechanistic target of rapamycin; EGFR, epidermal growth factor receptor; SChLAP1, second chromosome locus associated with prostate-1; GAS5, growth arrest-specific transcript 5.

The intergenic lncRNA MALAT1, was originally identified as a prognostic marker of lung cancer metastasis, and was associated with metastasis in other cancer types, such as breast, prostate, and pancreatic cancer (30). Microarray-based differential gene expression analysis has revealed that FGF2 is significantly downregulated by MALAT1, and that MALAT1-mediated FGF2 protein secretion from neuroblastoma cells induces vasculature formation to promote tumor angiogenesis (31). In addition, LINC00152 is involved in the pathogenesis of cancer; the detailed mechanism was unknown until microarray-based analysis was performed (32). LINC00152 can affect the mammalian target of rapamycin, phosphatidylinositol 3-kinase/AKT and the epidermal growth factor receptor signaling pathways as a molecular indicator that assists in the regulation of the associated target gene expression (33-36). Furthermore, using a high-throughput phospho-proteome microarray, Zhu *et al* (37) have demonstrated that Akt, mouse double minute 2 homolog and p53 phosphorylation are reduced when lncRNA LOC572558 is stably upregulated, suggesting that LOC572558 may be a tumor suppressor and regulate the p53 signaling pathway in bladder cancer.

The mechanisms of lncRNAs in cancer identified by sequencing. Sequencing involves the generation of cDNA-containing primers by PCR for library construction and analysis (38). The library is subsequently sequenced and quantified for each oligonucleotide base (38). The advantages of sequencing include a direct measure of the genome and its ability to discover novel transcripts, alternate transcript starts and stops, splicing variants and single nucleotide polymorphisms (39). Compared with microarray, sequencing offers more information when combined with functional experiments in mechanistic studies of lncRNAs (9).

A number of studies have demonstrated the association between endogenous p53 activity and the expression of lncRNAs in cancer progression (40-43). By integrating RNA-seq with p53 ChIP-seq analyses of HCT116 cells under DNA damage, two lncRNAs, PR-lncRNA-1 and PR-lncRNA-10, were identified (41). These lncRNAs are required for the efficient binding of p53 to its target genes, modulating p53 activity at the transcriptional, but not the post-transcriptional level, and contributing to apoptotic induction in response to DNA damage in cancer (41). The effect of p53 activation and genome-wide DNA binding of p53 was also determined by RNA-seq in combination with ChIP-seq analysis in SW480 cells (42). A total of 393 lncRNAs, including 270 upregulated and 123 downregulated lncRNAs, were identified as differentially regulated by p53.

Table II. Typical cancer-associated lncRNAs identified by high-throughput sequencing.

Author, year	LncRNA	Cancer type	Biological function	Mechanism	(Refs.)
Tseng *et al*, 2014	PVT1	Breast, ovarian and hepatocellular	Promotes proliferation	Controls Myc levels by regulating protein stability	(7)
Russell *et al*, 2015	CASC15	Neuroblastoma and metastatic melanoma	Tumor suppressor; inhibits proliferation and migratory	As a mediator of neural growth and differentiation to impact initiation and progression	(17)
Pan *et al*, 2016	GAS8-AS1	Papillary thyroid	Tumor suppressor; inhibits cancer growth	Unknown	(22)
Liu *et al*, 2015	SIRT1-AS	Hepatocellular	Promotes proliferation	Binds to SIRT1 mRNA at 3'UTR, masks the microRNA-29c binding site and stabilizes SIRT1 mRNA	(23)
Sánchez *et al*, 2014	PR-lncRNA-1	Colorectal	Tumor suppressor; inhibits cell survival and proliferation	Modulates gene expression response to DNA damage downstream of p53	(41)
Hünten *et al*, 2015; Kaller *et al*, 2017	LINC01021	Colorectal	Inhibits proliferation	A novel direct p53 target gene	(42,43)
Merry *et al*, 2015; Somasundaram *et al*, 2018	DACOR1	Colon	Growth suppressor	Changes DNA methylation patterns without affecting DNMT1 protein levels	(47,48)
Kondo *et al*, 2017	JHDM1D-AS1	Pancreatic	Promotes tumorigenesis	Regulates angiogenesis in response to nutrient starvation	(49)
Hu *et al*, 2019	LINK-A	Breast	Downregulates cancer antigenicity	Inactivation of protein kinase A pathways	(50)

lncRNAs, long non-coding RNAs; PVT1, plasmacytoma variant translocation 1; CASC15, cancer-associated susceptibility candidate 15; GAS8-AS1, GAS8 antisense RNA 1; SIRT1-AS, sirtuin 1-antisense; SIRT1, sirtuin 1; 3'UTR, 3'-untranslated region; PR-lncRNA-1, p53-regulated lncRNA-1; DACOR1, DNMT1-associated colon cancer repressed lncRNA 1; JHDM1D-AS1, JHDM1D antisense 1; LINK-A, lncRNA long intergenic non-coding RNA for kinase activation.

In addition, 18 lncRNAs demonstrating p53 binding near the corresponding gene TSS and 17 lncRNAs displaying p53 chromatin occupancy in a 20-kbp region surrounding the corresponding gene TSS were identified (42). LINC01021 has been identified as a novel direct p53 target gene, the ectopic expression of which inhibits colorectal cancer cell proliferation and chemosensitivity (42,43).

A number of lncRNAs affect gene expression though interacting with epigenetic processes (25). Enhancer of zeste homolog 2 (EZH2), the catalytic component of polycomb repressive complex 2 (PRC2), possesses histone-lysine N-methyltransferase activity and plays an essential role in cancer (44). RIP-seq has demonstrated that the lncRNA MALAT1 binds with EZH2 to suppresses the tumor suppressor PCDH10 and promote gastric cellular migration and invasion (45). In addition to histone methylation, DNA methylation is another crucial epigenetic marker typically associated with repressed genes in human cells (46). Merry *et al* (47) identified a subset of lncRNAs that interacted with DNMT1 in HCT116 cells though RIP-seq. DNMT1-associated colon cancer-repressed lncRNA 1 (DACOR1) exhibited high tissue-specific expression in the normal colon tissue, but was repressed in a panel of colon tumors and patient-derived colon cancer cell lines (47). The genomic occupancy sites of DACOR1 significantly overlap with known differentially methylated regions, and dysregulation of DACOR1 contributes to aberrant DNA methylation patterns in colon tumors (47,48).

LncRNAs also serve pivotal roles in tumor progression and malignant transformation by regulating the nutrient-starved tumor microenvironment or immune checkpoints. Kondo *et al* (49) identified the nutrient starvation-responsive lncRNA JHDM1D antisense 1 using ChIP-seq and formaldehyde-assisted isolation of regulatory element sequencing, which was demonstrated to be upregulated and to promote tumorigenesis by regulating angiogenesis in response to nutrient starvation. In addition, Hu *et al* (50) reported that the oncogenic lncRNA long intergenic non-coding RNA for kinase activation (LINK-A) inactivated tumor suppressor

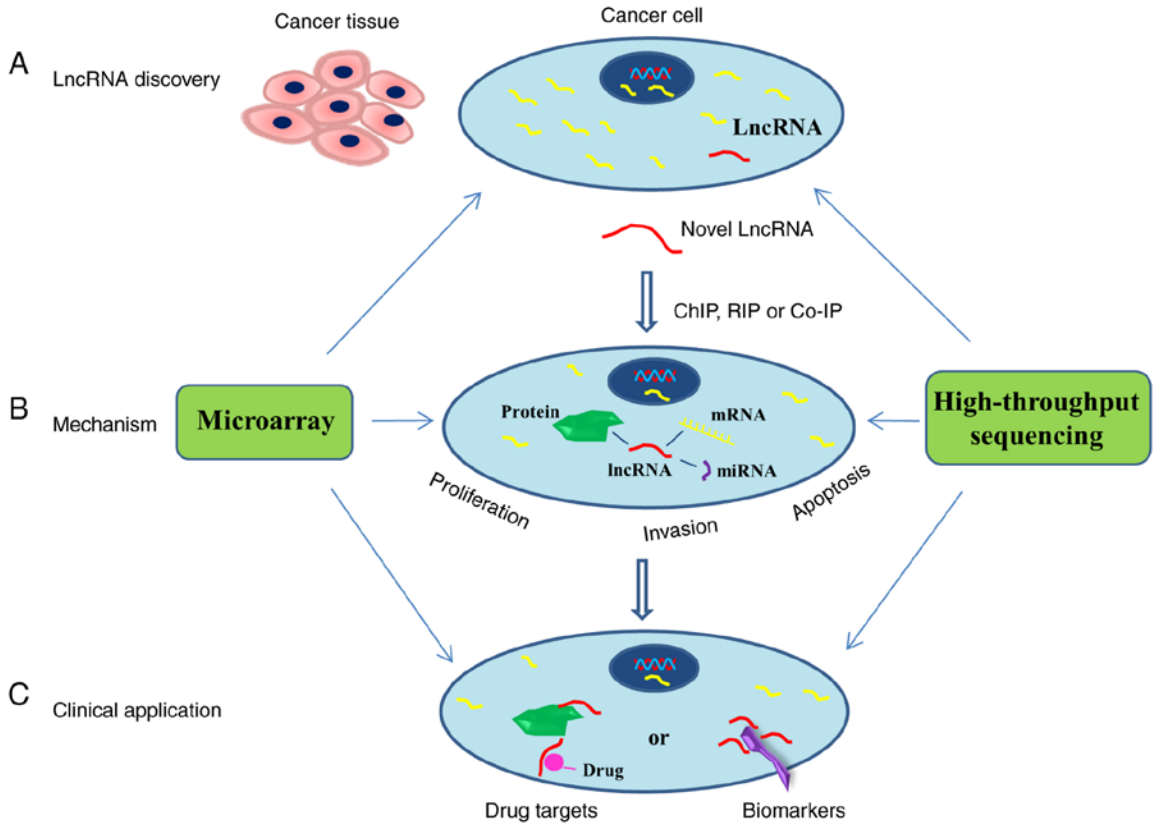

Figure 1. Schematic representation of the genome-wide analysis procedure of lncRNAs in cancer. (A) Large scale screening of novel lncRNAs in cancer by microarrays and high-throughput sequencing. (B) Microarray and high-throughput sequencing were combined with other approaches, including ChIP, RIP and Co-IP, to assess the mechanistic role of lncRNAs in cancer. (C) Based on genome-wide analysis, lncRNAs that may serve as diagnostic biomarkers or drug targets in clinical implications were identified. LncRNA, long non-coding RNA; ChIP, chromatin immunoprecipitation; RIP, RNA binding protein immunoprecipitation; Co-IP, co-immunoprecipitation.

pathways and downregulated antigen presentation through inactivation of protein kinase A pathways, thus contributing to decreased immunosurveillance and escaping from immune checkpoints by regulating immune cell gene expression programs. These results provided the basis for developing combination immunotherapy treatment regimens.

4. Cancer diagnostics and therapies based on genome-wide analysis of lncRNAs

The emerging role of lncRNAs, especially their highly tissue- and developmental stage-specific expression, provides a new range of possibilities for the diagnosis and treatment of cancer. The lncRNAs may serve as diagnostic biomarkers detected in the plasma, urine or tissue or contained in exosomes, microvesicles or apoptotic bodies and as treatment targets for drugs or radiotherapy (Fig. 1C) (51). Based on genome-wide analysis, the prognostic values of various lncRNAs for patients with cancer were evaluated, and the reported number of lncRNAs with clinical implications has increased (52).

The first lncRNA to be approved by the Food and Drug Administration was PCA3, which was used as a urine biomarker in patients with prostate cancer (53). A large-scale high-throughput study was performed using a microarray of prostate tumors from patients who experienced metastasis (n=212) and those who did not (n=333), and the lncRNA SCHLAP1 was discovered as one of the optimal predictive genes for metastasis (54). This was further validated using a clinical-grade urine test in a Clinical Laboratory Improvement Amendments-certified laboratory; SCHLAP1 has been suggested to be a promising biomarker of the aggressive clinical course of prostate cancer (55). Therapeutic resistance to trastuzumab caused by dysregulation of lncRNAs often poses a major obstacle in the clinical management of HER2-positive breast cancer (56). In addition, microarray results indicated that the expression of the lncRNA GAS5 was decreased in SKBR-3/Tr cells and breast cancer tissues from trastuzumab-treated patients, suggesting that GAS5 may serve as a novel prognostic marker and candidate drug target for HER2-positive breast cancer (57). Collectively, the prognostic values of these lncRNAs for patients with cancer were assessed by meta-analysis, which may facilitate improvements in the diagnosis and prognosis of cancer treatment (58-60). Although the majority of pioneering studies remain in the early stage, they still encourage further examination of the diagnostics and therapeutic opportunities of lncRNAs in cancer.

5. Conclusion and future perspective

The development of genome-wide analysis has resulted in a tremendous advance in the understanding of the underlying mechanisms of lncRNAs. The extensive functions and mechanisms of lncRNAs in cancers are a hot area of research. This review provides an overview of lncRNAs that were

identified by microarray and sequencing in cancer, including their functions and mechanisms, as well as their potential use in cancer diagnosis and therapies. However, this review also provides information that remains far from the realistic clinical application of lncRNAs in the treatment of cancer. The techniques that detect lncRNA interactions with key genes and proteins, the use of dependable animal models for cancer-associated lncRNAs and the implementation of reliable computational calculation methods of genome-wide analysis should be developed for future functional and mechanistic studies of lncRNAs. In addition, large clinical trials should be performed to confirm these potential lncRNA biomarkers. Furthermore, genome-wide analyses, which reduce analytic time and cost, will be indispensable in future studies and in clinical applications of lncRNAs in cancer.

Acknowledgments

Not applicable.

Funding

No funding was received.

Availability of data and materials

Not applicable.

Authors' contributions

XXR conceived the review, researched the literature and wrote the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The author declares that they have no competing interests.

References

1. Okazaki Y, Furuno M, Kasukawa T, Adachi J, Bono H, Kondo S, Nikaido I, Osato N, Saito R, Suzuki H, *et al*: Analysis of the mouse transcriptome based on functional annotation of 60,770 full-length cDNAs. Nature 420: 563-573, 2002.
2. Djebali S, Davis CA, Merkel A, Dobin A, Lassmann T, Mortazavi A, Tanzer A, Lagarde J, Lin W, Schlesinger F, *et al*: Landscape of transcription in human cells. Nature 489: 101-108, 2012.
3. Guttman M, Amit I, Garber M, French C, Lin MF, Feldser D, Huarte M, Zuk O, Carey BW, Cassady JP, *et al*: Chromatin signature reveals over a thousand highly conserved large non-coding RNAs in mammals. Nature 458: 223-227, 2009.
4. Jathar S, Kumar V, Srivastava J and Tripathi V: Technological developments in lncRNA biology. Adv Exp Med Biol 1008: 283-323, 2017.
5. Zheng GX, Do BT, Webster DE, Khavari PA and Chang HY: Dicer-microRNA-Myc circuit promotes transcription of hundreds of long noncoding RNAs. Nat Struct Mol Biol 21: 585-590, 2014.
6. Zhang Z, Wang X, Cao S, Han X, Wang Z, Zhao X, Liu X, Li G, Pan X and Lei D: The long noncoding RNA TUG1 promotes laryngeal cancer proliferation and migration. Cell Physiol Biochem 49: 2511-2520, 2018.
7. Tseng YY, Moriarity BS, Gong W, Akiyama R, Tiwari A, Kawakami H, Ronning P, Reuland B, Guenther K, Beadnell TC, *et al*: PVT1 dependence in cancer with MYC copy-number increase. Nature 512: 82-86, 2014.
8. Sánchez Y and Huarte M: Long non-coding RNAs: Challenges for diagnosis and therapies. Nucleic Acid Ther 23: 15-20, 2013.
9. Veneziano D, Di Bella S, Nigita G, Laganà A, Ferro A and Croce CM: Noncoding RNA: Current deep sequencing data analysis approaches and challenges. Hum Mutat 37: 1283-1298, 2016.
10. Iyer MK, Niknafs YS, Malik R, Singhal U, Sahu A, Hosono Y, Barrette TR, Prensner JR, Evans JR, Zhao S, *et al*: The landscape of long noncoding RNAs in the human transcriptome. Nat Genet 47: 199-208, 2015.
11. Rinn JL, Kertesz M, Wang JK, Squazzo SL, Xu X, Brugmann SA, Goodnough LH, Helms JA, Farnham PJ, Segal E and Chang HY: Functional demarcation of active and silent chromatin domains in human HOX loci by noncoding RNAs. Cell 129: 1311-1323, 2007.
12. Botti G, Marra L, Malzone MG, Anniciello A, Botti C, Franco R and Cantile M: LncRNA HOTAIR as prognostic circulating marker and potential therapeutic target in patients with tumor diseases. Curr Drug Targets 18: 27-34, 2017.
13. He Y, Luo Y, Liang B, Ye L, Lu G and He W: Potential applications of MEG3 in cancer diagnosis and prognosis. Oncotarget 8: 73282-73295, 2017.
14. Peng Z, Wang J, Shan B, Yuan F, Li B, Dong Y, Peng W, Shi W, Cheng Y, Gao Y, *et al*: Genome-wide analyses of long noncoding RNA expression profiles in lung adenocarcinoma. Sci Rep 7: 15331, 2017.
15. Wang W, Zhao Z, Yang F, Wang H, Wu F, Liang T, Yan X, Li J, Lan Q, Wang J and Zhao J: An immune-related lncRNA signature for patients with anaplastic gliomas. J Neurooncol 136: 263-271, 2018.
16. Evans JR, Feng FY and Chinnaiyan AM: The bright side of dark matter: lncRNAs in cancer. J Clin Invest 126: 2775-2782, 2016.
17. Russell MR, Penikis A, Oldridge DA, Alvarez-Dominguez JR, McDaniel L, Diamond M, Padovan O, Raman P, Li Y, Wei JS, *et al*: CASC15-S is a tumor suppressor lncRNA at the 6p22 neuroblastoma susceptibility locus. Cancer Res 75: 3155-3166, 2015.
18. Gao J, Aksoy BA, Dogrusoz U, Dresdner G, Gross B, Sumer SO, Sun Y, Jacobsen A, Sinha R, Larsson E, *et al*: Integrative analysis of complex cancer genomics and clinical profiles using the cBioPortal. Sci Signal 6: pl1, 2013.
19. Cerami E, Gao J, Dogrusoz U, Gross BE, Sumer SO, Aksoy BA, Jacobsen A, Byrne CJ, Heuer ML, Larsson E, *et al*: The cBio cancer genomics portal: An open platform for exploring multidimensional cancer genomics data. Cancer Discov 2: 401-404, 2012.
20. Lin C, Yuan G, Hu Z, Zeng Y, Qiu X, Yu H and He S: Bioinformatics analysis of the interactions among lncRNA, miRNA and mRNA expression, genetic mutations and epigenetic modifications in hepatocellular carcinoma. Mol Med Rep 19: 1356-1364, 2019.
21. Liu H, Li J, Koirala P, Ding X, Chen B, Wang Y, Wang Z, Wang C, Zhang X and Mo YY: Long non-coding RNAs as prognostic markers in human breast cancer. Oncotarget 7: 20584-20596, 2016.
22. Pan W, Zhou L, Ge M, Zhang B, Yang X, Xiong X, Fu G, Zhang J, Nie X, Li H, *et al*: Whole exome sequencing identifies lncRNA GAS8-AS1 and LPAR4 as novel papillary thyroid carcinoma driver alternations. Hum Mol Genet 25: 1875-1884, 2016.
23. Liu J, Wu W and Jin J: A novel mutation in SIRT1-AS leading to a decreased risk of HCC. Oncol Rep 34: 2343-2350, 2015.
24. Zampetaki A, Albrecht A and Steinhofel K: Long non-coding RNA structure and function: Is there a link? Front Physiol 9: 1201, 2018.
25. Yao RW, Wang Y and Chen LL: Cellular functions of long noncoding RNAs. Nat Cell Biol 21: 542-551, 2019.
26. Wu XS, Wang F, Li HF, Hu YP, Jiang L, Zhang F, Li ML, Wang XA, Jin YP, Zhang YJ, *et al*: LncRNA-PAGBC acts as a microRNA sponge and promotes gallbladder tumorigenesis. EMBO Rep 18: 1837-1853, 2017.

27. Signal B, Gloss BS and Dinger ME: Computational approaches for functional prediction and characterisation of long noncoding RNAs. Trends Genet 32: 620-637, 2016.
28. Jaksik R, Iwanaszko M, Rzeszowska-Wolny J and Kimmel M: Microarray experiments and factors which affect their reliability. Biol Direct 10: 46, 2015.
29. Shi Y and Shang J: Long noncoding RNA expression profiling using arraystar LncRNA microarrays. Methods Mol Biol 1402: 43-61, 2016.
30. Sun Y and Ma L: New insights into long non-coding RNA MALAT1 in cancer and metastasis. Cancers (Basel) 11, 2019.
31. Tee AE, Bing L, Song R, Li J, Pasquier E, Cheung BB, Jiang C, Marshall GM, Haber M, Norris MD, *et al*: The long noncoding RNA MALAT1 promotes tumor-driven angiogenesis by up-regulating pro-angiogenic gene expression. Oncotarget 7: 8663-8675, 2016.
32. Xia T, Liao Q, Jiang X, Shao Y, Xiao B, Xi Y and Guo J: Long noncoding RNA associated-competing endogenous RNAs in gastric cancer. Sci Rep 4: 6088, 2014.
33. Ji J, Tang J, Deng L, Xie Y, Jiang R, Li G and Sun B: LINC00152 promotes proliferation in hepatocellular carcinoma by targeting EpCAM via the mTOR signaling pathway. Oncotarget 6: 42813-42824, 2015.
34. Wang Y, Li M, Dong C, Ma Y, Xiao L, Zuo S, Gong Y, Ren T and Sun B: Linc00152 knockdown inactivates the Akt/mTOR and Notch1 pathways to exert its anti-hemangioma effect. Life Sci 223: 22-28, 2019.
35. Zhang Y, Xiang C, Wang Y, Duan Y, Liu C, Jin Y and Zhang Y: lncRNA LINC00152 knockdown had effects to suppress biological activity of lung cancer via EGFR/PI3K/AKT pathway. Biomed Pharmacother 94: 644-651, 2017.
36. Xu J, Guo J, Jiang Y, Liu Y, Liao K, Fu Z and Xiong Z: Improved characterization of the relationship between long intergenic non-coding RNA Linc00152 and the occurrence and development of malignancies. Cancer Med 8: 4722-4731, 2019.
37. Zhu Y, Dai B, Zhang H, Shi G, Shen Y and Ye D: Long non-coding RNA LOC572558 inhibits bladder cancer cell proliferation and tumor growth by regulating the AKT-MDM2-p53 signaling axis. Cancer Lett 380: 369-374, 2016.
38. Podnar J, Deiderick H, Huerta G and Hunicke-Smith S: Next-generation sequencing RNA-Seq library construction. Curr Protoc Mol Biol 106: 4.21.1-19, 2014.
39. Metzker ML: Sequencing technologies-the next generation. Nat Rev Genet 11: 31-46, 2010.
40. Lin T, Hou PF, Meng S, Chen F, Jiang T, Li ML, Shi ML, Liu JJ, Zheng JN and Bai J: Emerging roles of p53 related lncRNAs in cancer progression: A systematic review. Int J Biol Sci 15: 1287-1298, 2019.
41. Sánchez Y, Segura V, Marín-Béjar O, Athie A, Marchese FP, González J, Bujanda L, Guo S, Matheu A and Huarte M: Genome-wide analysis of the human p53 transcriptional network unveils a lncRNA tumour suppressor signature. Nat Commun 5: 5812, 2014.
42. Hünten S, Kaller M, Drepper F, Oeljeklaus S, Bonfert T, Erhard F, Dueck A, Eichner N, Friedel CC, Meister G, *et al*: p53-regulated networks of protein, mRNA, miRNA and lncRNA expression revealed by integrated pulsed stable isotope labeling with amino acids in cell culture (pSILAC) and next generation sequencing (NGS) analyses. Mol Cell Proteomics 14: 2609-2629, 2015.
43. Kaller M, Götz U and Hermeking H: Loss of p53-inducible long non-coding RNA LINC01021 increases chemosensitivity. Oncotarget 8: 102783-102800, 2017.
44. Yamaguchi H and Hung MC: Regulation and role of EZH2 in cancer. Cancer Res Treat 46: 209-222, 2014.
45. Qi Y, Ooi HS, Wu J, Chen J, Zhang X, Tan S, Yu Q, Li YY, Kang Y, Li H, *et al*: MALAT1 long ncRNA promotes gastric cancer metastasis by suppressing PCDH10. Oncotarget 7: 12693-12703, 2016.
46. Michalak EM, Burr ML, Bannister AJ and Dawson MA: The roles of DNA, RNA and histone methylation in ageing and cancer. Nat Rev Mol Cell Biol 20: 573-589, 2019.
47. Merry CR, Forrest ME, Sabers JN, Beard L, Gao XH, Hatzoglou M, Jackson MW, Wang Z, Markowitz SD and Khalil AM: DNMT1-associated long non-coding RNAs regulate global gene expression and DNA methylation in colon cancer. Hum Mol Genet 24: 6240-6253, 2015.
48. Somasundaram S, Forrest ME, Moinova H, Cohen A, Varadan V, LaFramboise T, Markowitz S and Khalil AM: The DNMT1-associated lincRNA DACOR1 reprograms genome-wide DNA methylation in colon cancer. Clin Epigenetics 10: 127, 2018.
49. Kondo A, Nonaka A, Shimamura T, Yamamoto S, Yoshida T, Kodama T, Aburatani H and Osawa T: Long noncoding RNA JHDM1D-AS1 promotes tumor growth by regulating angiogenesis in response to nutrient starvation. Mol Cell Biol 37, 2017.
50. Hu Q, Ye Y, Chan LC, Li Y, Liang K, Lin A, Egranov SD, Zhang Y, Xia W, Gong J, *et al*: Oncogenic lncRNA downregulates cancer cell antigen presentation and intrinsic tumor suppression. Nat Immunol 20: 835-851, 2019.
51. Schmitt AM and Chang HY: Long noncoding RNAs in cancer pathways. Cancer Cell 29: 452-463, 2016.
52. Matsui M and Corey DR: Non-coding RNAs as drug targets. Nat Rev Drug Discov 16: 167-179, 2017.
53. de Kok JB, Verhaegh GW, Roelofs RW, Hessels D, Kiemeney LA, Aalders TW, Swinkels DW and Schalken JA: DD3(PCA3), a very sensitive and specific marker to detect prostate tumors. Cancer Res 62: 2695-2698, 2002.
54. Prensner JR, Zhao S, Erho N, Schipper M, Iyer MK, Dhanasekaran SM, Magi-Galluzzi C, Mehra R, Sahu A, Siddiqui J, *et al*: RNA biomarkers associated with metastatic progression in prostate cancer: A multi-institutional high-throughput analysis of SChLAP1. Lancet Oncol 15: 1469-1480, 2014.
55. Smolle MA, Bauernhofer T, Pummer K, Calin GA and Pichler M: Current insights into long non-coding RNAs (LncRNAs) in prostate cancer. Int J Mol Sci 18, 2017.
56. Merry CR, Mcmahon S, Thompson CL, Miskimen KL, Harris LN and Khalil AM: Integrative transcriptome-wide analyses reveal critical HER2-regulated mRNAs and lincRNAs in HER2+ breast cancer. Breast Cancer Res Treat 150: 321-334, 2015.
57. Li W, Zhai L, Wang H, Liu C, Zhang J, Chen W and Wei Q: Downregulation of LncRNA GAS5 causes trastuzumab resistance in breast cancer. Oncotarget 7: 27778-27786, 2016.
58. Fradet V, Toren P, Nguile-Makao M, Lodde M, Lévesque J, Léger C, Caron A, Bergeron A, Ben-Zvi T, Lacombe L, *et al*: Prognostic value of urinary prostate cancer antigen 3 (PCA3) during active surveillance of patients with low-risk prostate cancer receiving 5α-reductase inhibitors. BJU Int 121: 399-404, 2018.
59. Ma W, Chen X, Ding L, Ma J, Jing W, Lan T, Sattar H, Wei Y, Zhou F and Yuan Y: The prognostic value of long noncoding RNAs in prostate cancer: A systematic review and meta-analysis. Oncotarget 8: 57755-57765, 2017.
60. Liu L, Meng T, Yang XH, Sayim P, Lei C, Jin B, Ge L and Wang HJ: 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 Biomark 22: 283-299, 2018.