REVIEW ARTICLE

Clinical Analysis of Long Non-coding RNA (LncRNA): Therapeutic Targeting of Tumorigenesis and Tumor Disease

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ABSTRACT- Long non-coding RNAs (lncRNAs) are a group of longer than 200 nucleotides which are the largest and more diverse transcripts in the cells. After study from Functional Annotation of Mammalian cDNA, lncRNAs demonstrated some special characteristics such as lower quantity, higher tissue-specificity, higher stage specificity and higher cell subtype specificity. The current evidence from tumor diseases suggested that lncRNAs are an important regulatory RNA present at tumor cells, and therefore their alterations are associated with tumorigenesis and tumor diseases. Here we presented a clinical landscape of lncRNA including detection of lncRNA and their clinical application such as diagnosis biomarkers and therapeutic targets. We also discussed the challenges and resolving strategies for these clinical applications.

Key-words- Long non-coding RNA (lncRNA), sampling, Transcripts, Tumor and tumorigenesis

INTRODUCTION

Long non-coding RNAs (lncRNAs) are some longer than 200 nucleotides in which most of them have not any coding protein function [1]. After several years' study from projects called as Functional Annotation of Mammalian cDNA (FANTOMs), 35,000 non-coding transcripts identified from their projects demonstrated that lncRNAs are 10-fold lower than mRNAs with a little open reading frame (ORF) but lncRNA structures are similar to mRNAs including 5' capping, splicing, and polyadenylation [2]. Interestingly, lncRNAs have about 78% tissue-specificity, higher stage specificity and higher cell subtype specificity [3] while mRNAs are only about 19% tissue-specificity, lower stage specificity and lower cell subtype specificity.

LncRNAs sequences are located intergenic genome, and therefore they can be transcribed as complex, overlapping transcripts from protein-coding genes with sense and antisense directions. A comprehensive set of human lncRNAs are analyzed and annotated by their genomic organization, modifications, cellular locations and tissue expression profiles so that now human lncRNAs are finally discovered as a bias toward two-exon transcripts [4]. Because of lack strong conservation, lncRNA may play an adaptive selection in evolutionary pressures or environment pressures. Total RNA sequencing from cDNA libraries show that very few numbers of lncRNA have biologically translated proteins. As Fig 1, during their RNA transcriptions, lncRNAs target transcriptional activators or repressors utilized complex such as by Evf-2 functions with a co-activator for the homeobox transcription factor (D1x2), by CREB binding protein, by HDAC system, by Apolipoprotein A1 (APOA1), by Alu RNA transcripts, functional repeat sequence domains by Kcnq1ot1, by Xlsirt and Xist and heat shock RNA-1 (HSR-1) in which an RNAP III regulating its RNAP II supports lncRNA functional regulation. After transcriptional regulation, lncRNA also involve in mRNA splicing, transport, translation, and degradation. Besides those, lncRNA also play function in siRNAs, epigenetics, imprinting, active X-chromosome, telomere function. Some lncRNAs maybe have their coding proteins but its still under investigation [5]. In clinical fields, increasing evidence demonstrated that lncRNA alterations are associated with tumor diseases. Here I concluded an outline from clinical sampling, lncRNA detection and clinical application from lncRNAs aberrance in tumor diseases as Fig 2. In the end of manual, I will present some challenges, and therefore I will suggest some strategies for these future applications.

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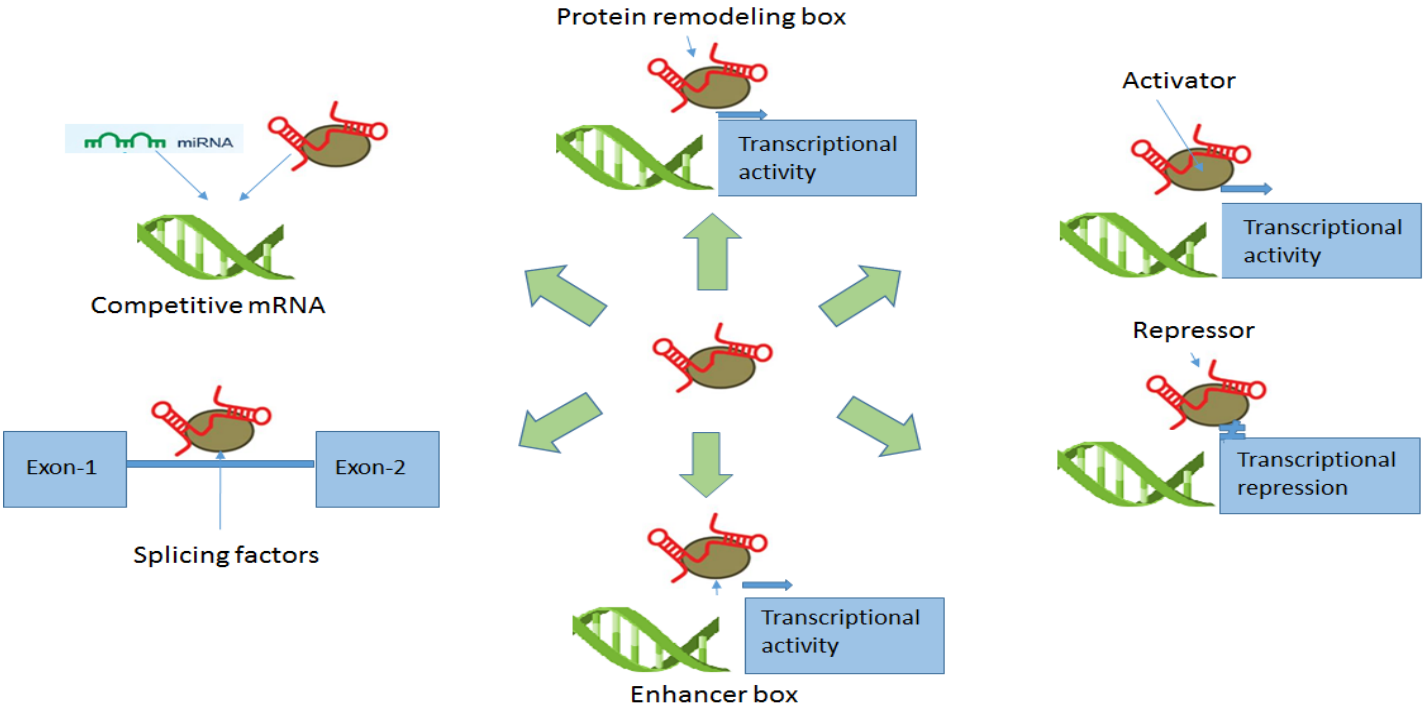

Fig. 1. lncRNA regulation mechanism

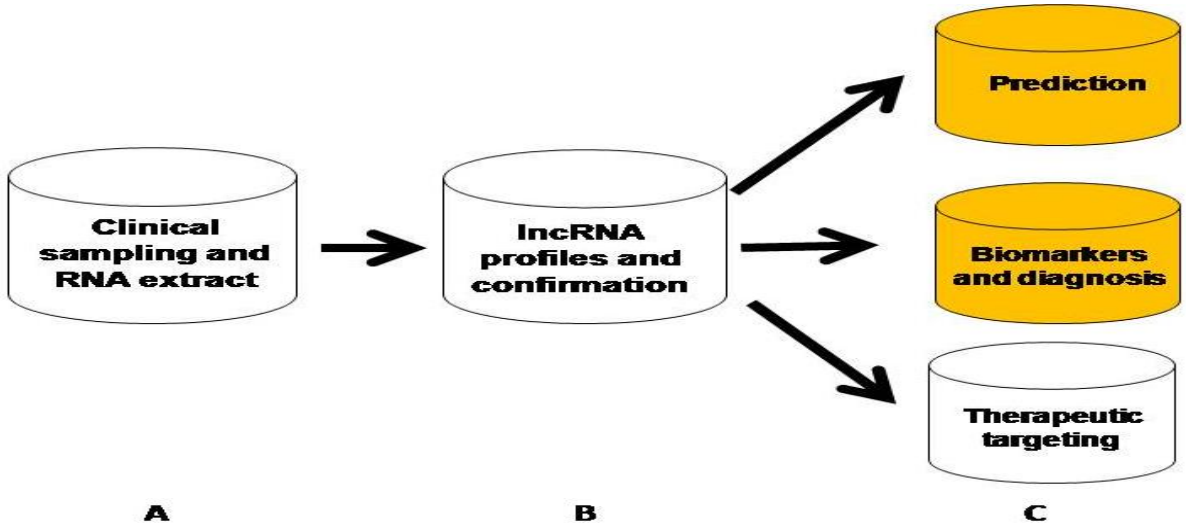

Fig. 2: Clinical lncRNA analysis. Process from sampling performance, lncRNA detection and application. Yellow color means lncRNA prediction and diagnosis which will be discussed in details in the manual

Clinical sample and detection

Samples were collected for lncRNA detection and clinical analysis for patients, either from tumor tissue or from non-tumor tissue such as body fluids. As we mentioned somewhere else, sampling methods for RNA detection including non-tumor tissue sampling and tumor tissue sampling [6]. Non-tumor tissue processes for lncRNA analysis include body liquid specimens, cell free circulating lncRNAs, circulating tumor cell (CTC) and exosome. Non-tumor tissue performances are techniques which are quickly developing in clinical application and biological companies at present. Tumor tissue sampling includes clinical sampling *in vitro*; clinical sampling *ex vivo* and tissue level sampling with down stream analyses *in silico* for lncRNA analysis concluded at Table 1. After we understand disadvantages and advantagesof RNA sampling as demnonstrated at Table 1, we need to decide a best way to harvest patient samples. If tumor samples are available such as surgically removal or biopsy, tumor cells sampling is first desirable. Because tumors are highly heterogeneous in tumor tissue, specific lncRNA are very important for downstream diagnosis and therapeutic targeting. If physician need length ways study the change or clinicians need screen lncRNA change for tumor biomarkers and study therapeutic targeting, liquid biopsy is a valuable choice because it is easily accessible and minimally invasive.

Table 1: Clinical Sampling for lncRNA Performance

	Non-tumor level				Tumor tissue level		
Methods	**Body fluid**	**CflncRNA**	**Exosome**	**CTC-lncRNA**	**Sampling in vitro**	**Sampling ex vivo**	**Tumor tissue**
Clinical application	1. Monitor lncRNA during treatment 2. prognosis 3. prediction				Precision medicine for diagnosis and treatment		
Advantages	An easily accessible, minimally invasive way				Higher Specificity and sensitivity		

There are two ways to detect lncRNA expressions: (a) specific lncRNA detection by either real time PCR or lncRNA FISH and (b) genomic detection by either microarray or next-generation RNA sequencing. Because lncRNA can be classified into antisense**,** Intergenic, intronic**,** overlapping**,** bidirectional according to the position and direction of transcription in relation to other genes, some companies set up lncRNA database with their primer designs for Q-rtPCR as Fig 3A. For example, QIAGEN set up an in house database based on human Gencode 19 with the confirmed lncRNA databases containing over 28,000 RT of lncRNA qPCR Assays, their RT2 lncRNA assays have increasingly used for experiments in tumor diseases [7]. RNA FISH is a cyto genetic technique that uses fluorescent probe to bind to lncRNA with a high degree of sequence complementarity as Fig 3B. Fluorescence microscope can find out where the fluorescent probe is bound to the lncRNA. Because lncRNA only express in transcriptional levelwithout protein expression, lncRNA FISH will be very important technique to define the lncRNA expression within cells and tissues though RNA FISH can be used to detect all three RNA (mRNA, miRNA and lncRNA) [8]. Some companies have routinely serviced a probe design with their detection system.

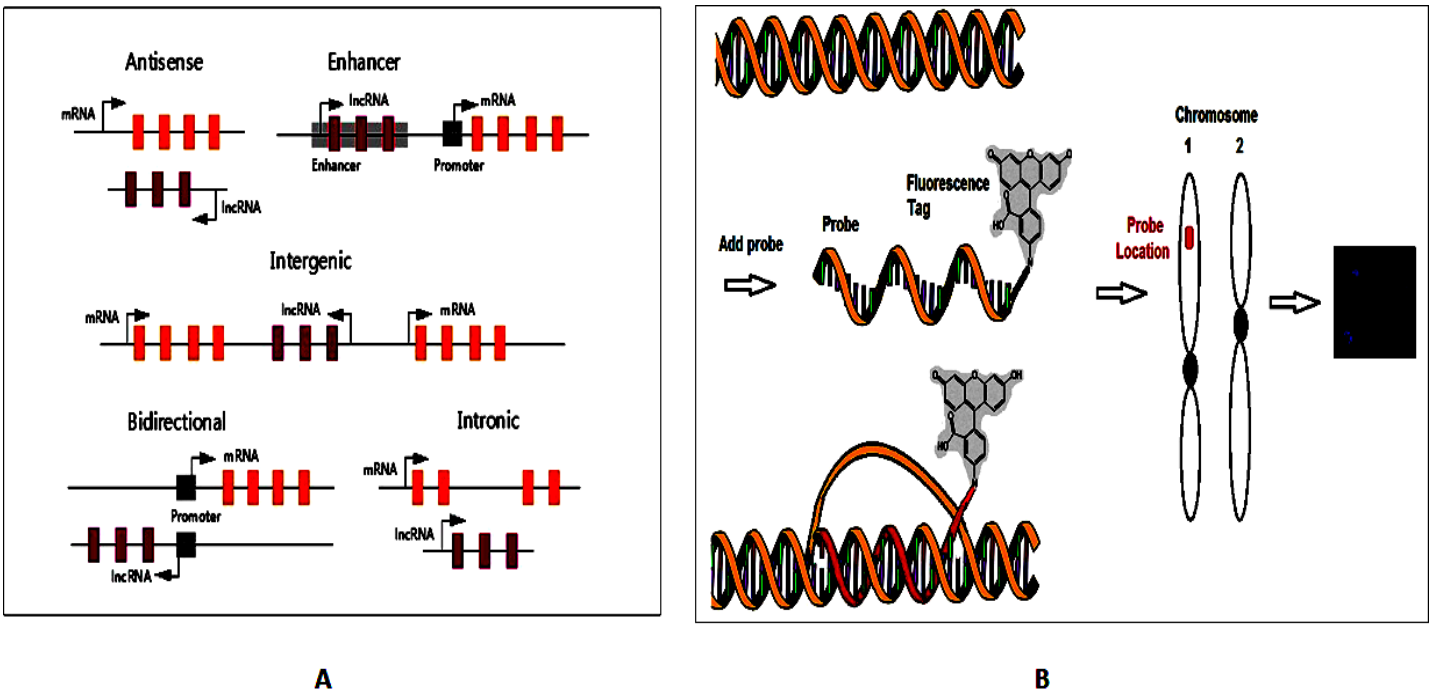

Fig. 3: Clinical specific lncRNA technique. Alltechnologies to detect lncRNA are classified.
A. Q-rtPCR which have successfully employed in clinical fields;
B. lncRNA measurement by lncRNA FISH

In microarray-based approaches as Fig 4A, two screening methods include traditional microarray and tiling array to identify lncRNAs. Because traditional microarrays can only detect the presence or absence of known lncRNAs in an RNA pool, they cannot detect novel lncRNAs. DNA tiling arrays contain oligonucleotide probes encompassing an entire length of a defined DNA regionto identify novel lncRNAs so that DNA tiling arrays are a major advantage to discover new lncRNA. Some companies developed their microarray chips to detect lncRNA such as Array star and Affymetrix with about 30,000 lncRNA expression panel assay [9].

RNA-seq is a very powerful technique to detect and quantify lncRNAs as Fig4B. Because disadvantage of a RNA-seq is the time and cost by the down stream analysis of the data, it is only used to discover previously unknown lncRNAs. Technically, after removal of rRNA from total RNA, which is suggestive, by some commercially available kits, both polyadenylated RNA and non-polyadenylated RNA can be used for lncRNA-seq. After sequencing, the generated reads are aligned to human hg19 reference genomes with TopHat software. The reads are used to assemble a transcriptome and discover previously un-annotated transcripts by Cufflinks. Novel lncRNAs can be identified by excluding protein-coding transcripts and annotated lncRNAs based on the databases of RefSeq, ENCODE, and FANTOM (Functional Annotation of the Mammalian Genome). Finally lncRNAs databases are generated by either lncRNAdb or NRED (Noncoding RNA Expression Database) [10].

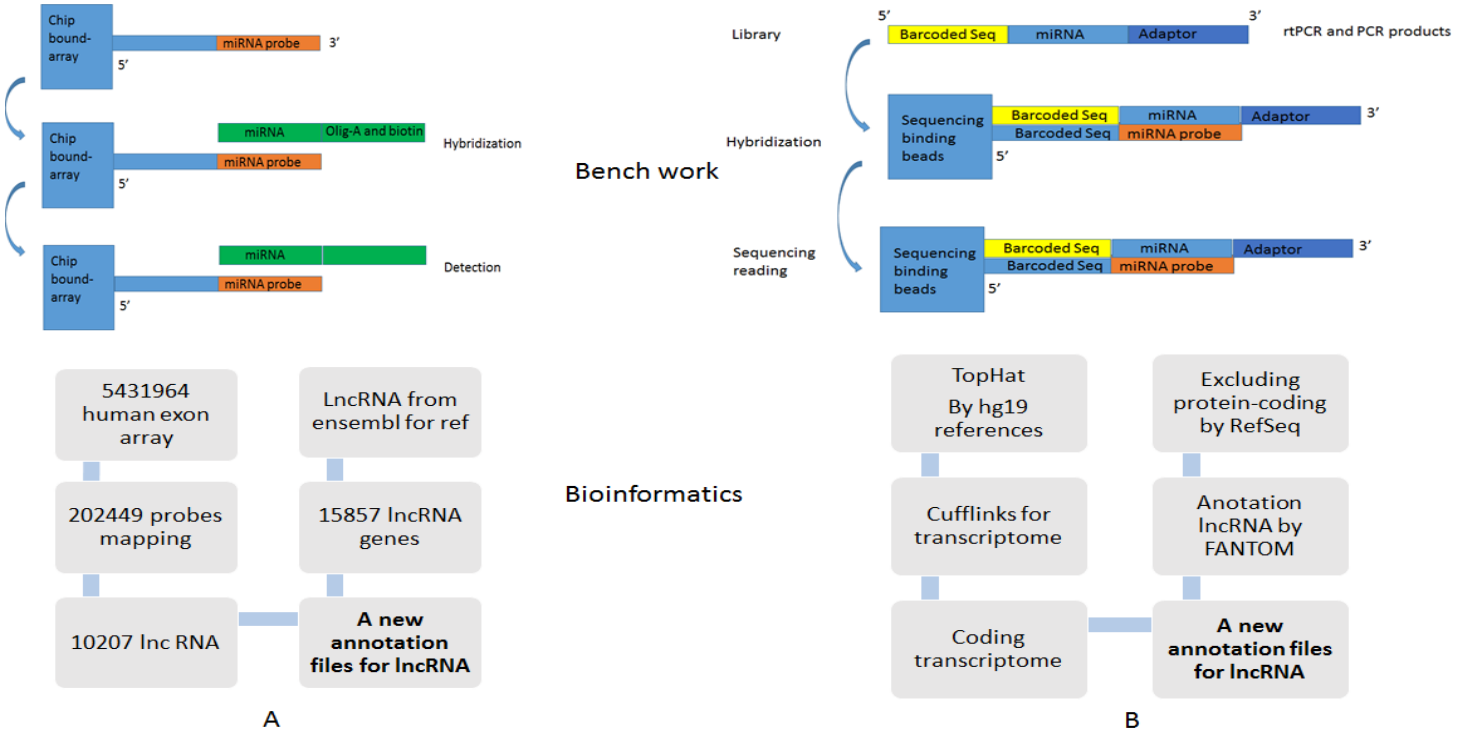

Fig. 4: Clinical genomic lncRNA technique

A. Microarray has been successfully used in both research and clinical fields for global measures;

B. RNA-seq is often applied to screen lncRNA profiles but they require an equipment and bioinformatics support

After we understand clinical lncRNA detection, clinical scientists require choosing a detection method for their application. The selection is relied on clinical purpose. For example, if lncRNA assayed as one or two lncRNAs, qPCR assay and RNA FISH are first option. The lncRNA- tiling array and RNA-seq will be very good candidates for scientists to screen new lncRNA alteration while traditional microarray can detect known lncRNA. Finally, lncRNA profiles performance also should be considered their downstream analysis such as skilled bioinformatics scientists and available tools.

Clinical Application

As I mentioned before, lncRNAs are RNAs with some special features, such as higher tissue-specificity, higher stage specificity and higher cell subtype specificity, and therefore their expression markers could be used for biomarkers of diagnostics and classification in tumor diseases and tumorigenesis.

lncRNAs Biomarkers for Tumor prediction

As Table 2 demonstrated, RNA FISH techniques are increasingly used in lncRNA aberrant detection. For example, PCA3 and PCAT1 have been routinely studied in relationship between prostate tumor and higher expression from lncRNA FISH for pathology diagnosis; GAS5 have been reported in breast tumor. UCA1 is reported to down-regulated with bladder cancer [11]. Encouragingly, exon microarrays results support lncRNA FISH after study for thirteen different cancers because some of them have been reported in prostate cancer, breast cancer andbladder cancer as lncRNA FISH results [12].

Because cancer is a clinically heterogeneous disease with individual characteristics in different cancer subtypes, Their microarray data further study subtypes of four cancers, for example, GBM (proneural, neural, classical and mesenchymal), Ovarian Cancer (immunoreactive, proliferative, mesenchymal and differentiated), lung squamal cell cancer (basal, classical, primitive and secretory), six type of prostate cancers. lncRNAs with subtype-specific expression may have an important differences in individual subtypes. For example, MIAT showed specific expression in the mesenchymal subtype of ovarian cancer while RMST specially expressed in rhabdomyosarcoma. These lncRNA profiles are very suggestive although these files should be further studied in RNA FISH and Q-rtPCR to confirm these results regarding cancer subtype.

Table 2: Predicton of lncRNA Expression

Tumor Types	IncRNA	Ensembl ID	LncRNA Expression
	PCA3	ENSG00000225937	Up-regulation
Prostate Cancer	PCAT1	ENSG00000253438	Up-regulation
	PCGEM1	ENSG00000227418	Up-regulation
Breast Cancer	GAS5	ENSG00000234741	Up-regulation
Colon Cancer	KCNQ1OT1	ENSG00000258492	Up-regulation
Bladder Cancer	UCA1	ENSG00000214049	Down-regulation
	PVT1	ENSG00000249859	Up-regulation
Multiple Cancer	HULC	ENSG00000251164	Up-regulation
	MEG3	ENSG00000214548	Down-regulation

lncRNAs Biomarkers for Tumor prognosis

Now, expression level of lncRNA is still under investigation for personalized medicine, personalized medicine requires further information to support the new fields. After increasing studies of the lncRNA alterations related to tumor disease, lncRNA profiles will give physicians some support to predict prognosis of tumor disease. According to recent clinical assays, several lncRNAs increase and decrease have been demonstrated in some special tumors. As Table 3, for example, up-expressed HOTAIR, HOTTIP, DANCR and CCAT1 are related with poor survival from colon cancer patients [13]. Some lncRNAs such as RP1, RP4, RP11 and RP13 profiles are going to be used to study tumor prognosis with up-expressed and down expression in breast cancer [14]. The oncogenic lncRNA and tumor suppressive lncRNA profiles are discovered to relate with many tumor diseases, including hepatocellular carcinoma, lung cancer, colorectal cancer, breast cancer, prostate cancer, stomach cancer and glioblastoma [15].

Table 3: Potential prognostic lncRNA markers

Diseases	Basic Function	LncRNA Names	Genomic location	Gene size (kb) or Probe-ID	Locus
Colon cancer	Oncogenic lncRNA	***91H***	Chr11p15	119.32	*H19/IGF2*
		CCAT1	Chr8q24.21	11.88	*c-MYC*
		CLMAT3	Chr14q32.31	1.55	*SPARC*
		DANCR	Chr4q12	7.94	–
		FEZF1-AS1	Chr7q31.32	6.42	*FEZF1*
		FTX	ChrXq13.2	329.62	*XIC*
		HOTAIR	Chr12q13.13	12.64	*HOXC*
		HOTTIP	Chr7p15.2	8.68	*HoxA*
		lncRNA-ATB	Chr14q11.2	2.73	–
		MALAT1	Chr11q13.1	8.75	*NEAT-2*
		PCAT1	Chr8q24.21	173.96	–
		PVT1	Chr8q24.21	306.72	*PVT1*
		TUG1	Chr22q12.2	9.7	*TUG1*
		UCA1	Chr19p13.12	7.37	*UCA1*
	Tumor suppressive lncRNA	***GAS5***	Chr1q25.1	4.98	*GAS5*
		LINC01296	Chr22q11.1	20.55	–
		MEG3	Chr14q32.2	81.62	*DLK1-MEG3*
		NcRAN	Chr17q25.1	7.58	*SNHG16*
		ncRuPAR	Chr5q13.3	0.48	*ncRuPAR*
		RP11-462C24.1	Chr4q25	82.27	*RPL34*
		TUSC7	Chr3q13.31	14.34	*LSAMP*
Breast cancer	lncRNA	***RP1-34M23.5***	Chr 1: 34,761,426–34,788,097 (−)	216579_at, 243747_at	*ENSG00000255811.1*
		RP11-202K23.1	Chr 1: 102,199,739–102,389,630 (−)	1566142_at, 216858_x_at, 201439_at, 224894_at, 202076_at, 1561543_at, 241072_s_at, 219086_at, 1554549_a_at, 239225_at, 227541_at.227693_at, 230223_at	*ENSG00000233359.1*
		RP11-560G2.1	Chr 12: 75,234,740–75,298,508 (+)	224370_s_at	*ENSG00000254451.2*
		RP4-591L5.2	Chr 1: 30,415,825–30,421,108 (+)	219781_s_at, 221968_s_at	*ENSG00000231949.1*
		RP13-104F24.2	Chr 17: 64,749,663–64,781,707 (−)	229747_x_at	*ENSG00000215769.8*
		RP11-506D12.5	Chr 17: 50,840,057–50,841,626 (−)	1554773_at	*ENSG00000261976.2*
		ERVH48-1	Chr 21: 42,916,803–42,925,646 (−)	232191_at	*ENSG00000233056.2*
		RP4-613B23.1	Chr 3: 42,601,963–42,654,388 (−)	231235_at, 202380_s_at, 1557736_at	*ENSG00000230084.5*
		RP11-360F5.1	Chr 4: 39,112,677–39,126,818 (−)	226001_at, 232297_at, 233866_at	*ENSG00000249207.1*
		CTD-2031P19.5	Chr 5: 55,936,143–55,941,727 (+)	204864_s_at, 212195_at	*ENSG00000262211.1*
		RP11-247A12.8	Chr 9: 129,175,807–129,177,575 (+)	226559_at	*ENSG00000268050.2*
		SNHG7	Chr9:136,721,366–136,728,184 (−)	229002_at, 1552729_at	*ENSG00000233016.6*

lncRNAs Biomarkers in circulating lncRNA and body liquid

As discussed above, non-tumor tissue processes are very "popular" techniques for downstream genomic analysis including lncRNA performance because of their non-invasive process. Non-tumor tissue processes for lncRNA analysis include body liquid specimens, cell free circulating lncRNAs, circulating tumor cell (CTC) and exosome. Clinically, at present, lncRNAbegin to be used to study special lncRNA expression in some special tumors and global profiling of the lncRNA aberrance. As shown at Table 4, MALAT-1 was discovered down-regulated in lung cancer from peripheral blood cells while HOTAIR was discovered up-regulated in colon cancer from peripheral blood cells. PCA3 is uncovered in urine of prostate cancer patients while UCA1 is found in urine of bladder cancer. Interestingly, AA174084, an lncRNA, can be discovered down-level at gastric juice in stomach cancer patients [16].

Table 4: Circulating lncRNA prognostic lncRNA markers for tumor diseases

Cancer Type	lncRNA	Samples	Change
Lung cancer	*MALAT1*	Peripheral blood cells	Down regulation
Colon cancer	*HOTAIR*	Peripheral blood cells	Up regulation
Prostate cancer	*PCA3*	Urine	Up regulation
Liver cancer	*PRP11-160H22.5, LOC149086, XLOC014172*	plasma	Up regulation
Bladder cancer	*UCA1*	Urine	Up regulation
Stomach cancer	*AA174084*	Gastric juice	Down regulation

lncRNAs predicting tumorigenesis

According to a genome- wide survey on somatic copy-number alterations (SCNAs) of long noncoding RNA (lncRNA), about 21.8% of lncRNA genes were located in regions with focal SCNAs [17]. For example, by integrating bioinformatics analyses of lncRNA SCNAs and LncRNA expression, focally amplified lncRNA on chromosome 1(FAL1) partially repress p21 which is tumor suppressive mechanism [18]. The important somatic genetic alteration in SCNAs is either amplified or deleted, and thus some of the genes show increased or decreased expression levels finally leading to aberrance from normal cell into cancer cells. The data have suggested that the lncRNAs located in the SCNAs are related with tumorigenesis so that they called a relationship as driver of tumorigenesis, or lncRNAs with SCNAs should result in corresponding gene expression changes [19]. These lncRNA between SCAN and expression profiles are very suggestive although these profiles should be further confirmed for cancer driver.

Clinical challenge for application

When the aberrant lncRNAs are discovered in tumor diseases, the aberrant detection will unfold a great chance for tumor diagnosis and therapeutic targets. LncRNAs can be readily detected in biological fluids and their highly specific expression pattern can be assayed, and therefore lncRNAs could successfully be used for accurate diagnostics and classification. Although this application are going to apply for circulating blood from clinical patients, the emerging techniques of circulating lncRNAs is restrained by the known information for tumor diagnosis, for example, it is cause of tumor diseases of lncRNA or an lncRNA consequence of the disease itself.

In the therapeutic purpose, although some companies and organizations such as the Allen Institution for Brain Science, CuRNA, Regulus Therapeutics, Miragen Therapeutics, and Santaris Pharmaare developing lncRNA- based strategies against cancer [20], there are several challenges for lncRNAs treatment. For example, (A) LncRNAs can be blocked by functional molecules such as small molecule inhibitors, however, our current limited knowledge influences using small molecular inhibitors in the complicated complexes [21]; (B) Silencing of lncRNAs through RNAi technology for LncRNA expression levels may be uncertain because of their secondary structure or intracellular localization. Its potential application on patients is more limited as it involves targeted genetic manipulation [22]; (C) Structure disruption could be designed to bind to lncRNAs and change or mimic their secondary structure. The targeting of harmful lncRNAs can be applied for gene therapy to specific cellsbut some lncRNA has toxicity for normal cells [23]. Although the potential application of lncRNAs is huge for therapeutic purpose, their complicated structures and functions should be further studied.

It is indisputable that the clearer after we study lncRNA function and structure, the more chances for clinical scientists to apply for lncRNA into clinical diagnosis and treatment. Expectantly, lncRNA can approach our desire

which will fit lncRNA detection from laboratories into bedside patients for treatment of tumor disease.

ACKNOWLEDGMENT

Under the support of Dr. H. D. Preisler, we had set up the method to analyze clinical genomic analysis including single-cell genomic profiles of tumor cell from solid tumors and leukemia. Now we are going to use new genomic platform to continue working in lncRNA aberrance. Mention of trade names or commercial products in this article is solely for the purpose of providing specific information and does not imply recommendation.

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