Review Article

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Molecular mechanisms of oncogenic long non-coding RNAs

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Recent advances in RNA sequencing and bioinformatics methods have showed that long non-coding RNAs are colossally transcribed in the genomes of complex organisms. Since lncRNAs have very low sequence conservation, it was believed that these genetic materials have no function. However, increasing evidences suggest that long non-coding RNAs are engaged nearly in every step of a life cycle of genes and identified as transcriptional regulators. Accumulating reports have shown that alterations in the expression of these transcripts have been associated with various types of cancers. In this wide and diverse emerging functional landscape, the main focus of this review is to underscore the molecular mechanisms of the oncogenic lncRNAs in a parallel discussion about their characteristics and structures.

Key words: non-coding RNAs; oncogenic; molecular mechanism; structure; cancer.

Cancer is defined by malapropos prolification of cells with the loss of cell identity. Alarming statistic shows that by 2030 there will be more than 22 million incidence of all-cancer cases in human poplulation (Bray et al., 2012). A classic universal paradigm in oncogenesis is the occurance of mutations in the open reading frames (ORFs) of tumor suppressors and protein-encoding oncogenes. Therefore, all the attempts to analyze cancer in a systematical and scientific manner have focused mainly on the role and function of protein-coding genes in the pathogenesis of cancer over the last few decades.

Emerging new technologies in the field of molecular biology; and studies of the human transcriptome led to discovery of numerous non-coding RNA (ncRNA) transcripts which has dramatically altered our understanding of cell biology. Although a substantial fraction of the human genome can be transcribed, only less than two percent of the total human genome contains protein-coding genes (Birney et al., 2007). Recent data suggests that a special class of ncRNAs called long non-coding RNAs (lncRNAs) >200 bp in length plays a significant role in human disease particularly cancer. LncRNAs are introduced as a class of regulators of epigenetic processes which is one of the emerging themes in cancer biology. Nowadays, study of lncRNAs prioritized in many laboratories as one of the most promising leverage in oncology.

Although a full understanding of the molecular mechanisms of lncRNAs which govern their function is essential; achieving such target is still far beyond completion. This review provides an update and perspective on recent advances made in understanding lncRNAs mechanisms in oncogenesis. The functional comaprison of lncRNAs is highlighted; and the most recent genetic studies on lncRNAs and their linkage to cancer-associated pathways will be discussed.

Long non-coding RNAs

Initially, lncRNAs were considered as transcriptional irregularity resulting from low RNA polymerase fidelity (Nie et al., 2012). Since there is no easily documented protein product linked to RNA sequence, majority of scholars regarded lncRNAs as “transcriptional noise”; until later on when these transcripts become functionally relevant (Dinger et al., 2008; Mercer et al., 2009; van Bakel and Hughes, 2009). Recently, lncRNAs came forth as major players in regulating fundamental biological processes at almost every stage of gene expression including epigenetic modifications or modulating mRNA stability. Radical characteristics of lncRNAs make them disqualified to fit into well-established categories of structural RNAs or even small RNAs. These abundant transcripts are defined as RNA molecules that may function as spliced or primary transcripts (Spizzo et al., 2012). The total perspective of the intricacy of mammalian genomes has been changed dramatically since discovery of lncRNAs. Moreover, our understanding of other aspects of biology such as post-transcriptional process or transcriptional regulation of gene expression was tremendously altered.

LncRNAs are described as RNA genes larger than 200 bp (from 200 nt to 100 kilobases) (Costa, 2010). This description of lncRNAs separated them from small RNAs (sRNAs); however there are some well-recognized sRNAs which have more than 200 nucleotides in their structures. Therefore, only newly recognized transcripts are prospectively referred to as lncRNA. Another classification of lncRNAs is based on their location relative to nearby protein-coding genes.

According to this criterion, a lncRNA might be located in five broad categories including: sense, antisense, bidirectional, intronic and intergenic (Figure 1). Sense and antisense lncRNAs are those transciprs that their initiation points start at 3’ or inside a protein-coding gene; and overlap at least, one coding exon of another transcript on the same, or opposite strand. LncRNAs that their sequences are placed in the opposite strand from an adjacent promoter of a protein-coding gene has been called bidirectional. Although the exact designated length limit is not defined for bidirectionality lncRNAs, they are normally less than 1000 base. Intronic lncRNAs derive entirely from within an intron of a second transcript in either direction while they do not overlap any exon. Finally, lncRNA sequences that placed in the genomic interval are named intergenic. Intergenic lncRNAs are also known as large intervening non-coding RNAs or lincRNAs; and according to Mitchell Guttman et al. (2009) there must be a 5 kb between lincRNAs and protein-coding genes (Mitchell Guttman et al., 2009; Rearick et al., 2011).

A substantial number of relative published literatures have shown that dysregulation or perturbation in lncRNAs expression is directly associated to several medically relevant disorders including, but not limited to, various types of cancers (Cheetham et al., 2013; Gibb et al., 2011; Maruyama, 2012; Qiu et al., 2013; Silva et al., 2010; Zhang et al., 2013). Apart from different types of cancers, lncRNAs are directly associated with the pathogenesis of several other diseases.However, there are still many unexplored and unidentified aspects to the pathogenesis of lncRNAs.

Based on the pathogenecity of lncRNAs Hauptman et al.(2013) classified them into three different categories (Table **1**) including: oncogenic lncRNAs; tumor suppressor lncRNAs; and oncogenic and tumor suppressor lncRNAs. It is extremely challenging to compile a comprehensive list of the functionally validated lncRNAs due to the rapid progress and new developments in this field.

Therefore, in this review, among the vast and diverse emerging ncRNAs, oncogenic lncRNAs are adopted to discuss thoroughly about features like lncRNAs structure, expression, and function. Also, the role of selected lncRNAs in the regulation of epigenetic dynamics will be discussed.

Some examples of lncRNAs implicated in oncogenic functions are highlighted in this review. The Oncogenic lncRNAs which have the ability to transform normal cells into cancerous tumors are included: Steroid receptor RNA activator (SRA), HOX antisense intergenic RNA (HOTAIR); Antisense ncRNA in the INK4 locus (ANRIL) and Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1). The molecular mechanisms by which these lncRNAs exert their biological functions will be discussed.

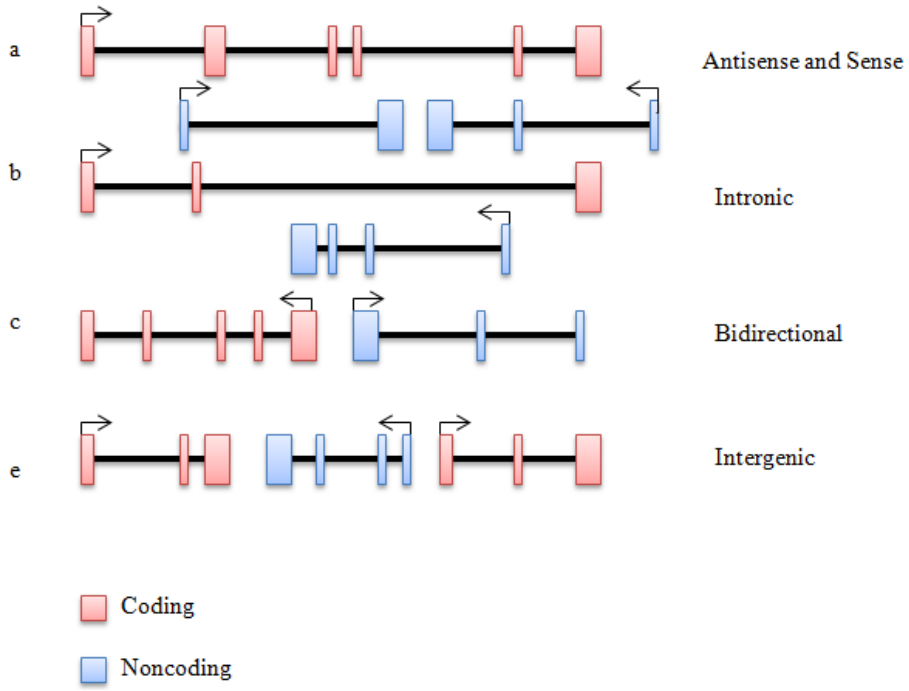

Figure 1: classification of long non-coding RNAs (lncRNAs) based on their placement. LncRNAs can be found harbored in a:sense or antisense; b:intronic; c:bidirectional and c:intergenic regions.

LncRNAs mechanisms of action

The functional roles of lncRNAs are largely elusive despite the substantial progress in other aspects of lncRNAs analysis such as sequencing and mapping. More recently, a pile of functional examples have shown the implication of lncRNAs in numerous cellular processes including chromatin modification, transcription, and posttranscriptional processing(Birney et al., 2007; van Bakel and Hughes, 2009). Although the largest transcript class in human transcriptomes is identified as lncRNAs, the questions like how lncRNAs could exert a function or even whether all lncRNAs are functional remained largely without answer. Several mechanistic themes of lncRNAs' functions have been shown so far that many of possible lncRNAs mechanisms of action can be encompassed into three main themes.(Mercer et al., 2009; Rinn and Chang, 2012). These modes of actions which are not mutually exclusive are included: decoy; guide and sacffold.

Serving as decoys is the simplest function of lncRNAs. In this mode of action, regulatory proteins cannot access to DNA recognition elements.

As decoy mode of actions, lncRNAs can compete with mRNAs for miRNA target sites. PANDA identified as a recent lncRNA decoy example (Wang and Chang, 2011). In order to prevent p53-mediated apoptosis, PANDA associates with the transcription factor NF-YA(Hung et al., 2011). Normally, several key genes for apoptosis are transactivated by NF-YA, however the association of PANDA with NF-YA titrates this transcription factor away from target gene chromatin. Second mechanistic theme of lncRNAs' functions is guide. According to this fundamental, lncRNAs can guide changes in gene expression either in *trans* (distantly located genes).or in *cis* (on neighboring genes).(Lee, 2009). (Jeon and Lee, 2011; Schmitz et al., 2010; Wang et al., 2011).

The final lncRNAs' mechanism of action is scaffold. The major players in various scaffolding complexes were traditionallly assumed to be proteins. In order to bring together multiple proteins, lncRNAs can serve as adaptors and form lncRNA-RNPs.. A central platform is provided by lncRNAs which upon relevant molecular components are assembled. Prime examples of lncRNA scaffold are the telomerase RNA (TERC) and

Table 1: various types of lncRNAs based on their pathogenicity source:(Hauptman and Glavač, 2013)

Types of lncRNAs	Examples	Types of cancer	Reference
Oncogenic	Steroid receptor RNA activator (SRA)	Breast;Uterus; Ovary (down-regulated	(Foulds et al., 2010; Novikova et al., 2012)
	HOX antisense intergenic RNA (HOTAIR)	Breast; Hepatocellular	(Bhan et al., 2013; Nie et al., 2013; Schorderet and Duboule, 2011)
	Antisense ncRNA in the INK4 locus (ANRIL)	Leukemia; Prostate	(Congrains et al., 2013; Wan et al., 2013)
	Metastasis-associated lung adenocarcinoma transcript 1 (MALAT-1)	Breast; Prostate; Colon; Uterus; Liver	(Gutschner et al., 2013; Lai et al., 2012; Tano et al., 2010)
Tumor suppressor	Maternally expressed gene 3 (MEG3)	Brain (down-regulated)	(Johnson, 2012; Mercer et al., 2010)
	Growth arrest-specific 5 (GAS5)	Breast (down-regulated)	(Mourtada-Maarabouni et al., 2008; Tani et al., 2012)
	CCND1/Cyclin D1	Inhibition of the cyclin D1 gene expression	(Faust et al., 2012; Yoshida et al., 2003)
	LincRNA-p21	Repressed p53 pathway; induces apoptosis	(Clark et al., 2012; Huarte et al., 2010)
Oncogenic and tumor suppressor	H19	Bladder; Liver; Lung; Colon; Esophagus; Breast; Choriocarcinoma	(Gabory et al., 2010; Tsang et al., 2010)

HOTAIR. TERC assembles the telomerase complex while; HOTAIR binds by specific domains of the RNA structure to PRC2 and the LSD1-CoREST complex (Tsai et al., 2010; Zappulla and Cech, 2006). H3K27 methylation and H3K4me2 demethylation are the result of this combination of interactions which leads to gene silencing. Many of the recently discovered lncRNAs act under one of these three modes of action.

Structure of lncRNAs

The lncRNAs are generally expressed in lower amounts compared to their protein-coding counterparts, hence it is difficult to detect robustly and assemble complex transcript structures of them. Fundamentally, there are many distinctions between lncRNAs and mRNA, structurally and functionally. However, there are mutual ground between these two types of transcripts including: introns; exons; polyadenylation; and alternate splice variants (Mitra et al., 2012). One of the most fascinating features of RNAs is that their

functional performance typically driven by secondary and tertiary structures.

Although some well-defined lncRNAs have very low sequence conservation which implies the possible lineage-specific adaptive evolution (Ponting et al., 2009), new studies identified several large, intervening ncRNAs (lincRNAs) (>1500) that showed some evolutionary conservation (Mitchell Guttman et al., 2009). The current hypothesis that lncRNAs are not generally evolutionary conserved is challenged by this discovery.

A structural understanding of different lncRNAs has come from structural studies and classic chemical probing (Steitz, 2008). A long linear sequence has the potential to form multiple RNA structures. Basically, RNA structures can experience various conformational changes based on their solvent conditions; hence they have a frequently dynamic structure. Variance in temperature; changes in salt and ligand concentrations; and differences in protein binding are all the variables that RNAs can react to and result in alterations in gene expression.. Acknowledging all of these difficulties, genome-scale approaches have been developed to recognize RNA secondary structures which also applicable to lncRNAs (Wan et al., 2011).

Genome-scale approaches apply either specific enzymes that cleave structured and unstructured regions of RNAs or chemical probes to acylate flexible RNA bases that are not participating in structural interactions.

Having such technologies, it will be possible to gain an in-depth knowledge about the importance of lncRNAs structure and function. Perhaps modern bimolecular approaches will be helpful to uncovered the common motifs of RNA structure that result in specific protein interactions.

Steroid Receptor RNA Activator (SRA):

Human RNAs originating from the steroid receptor RNA activator (SRA) characterized initially to act as a regulatory non-coding RNA (as a coactivator for several nuclear receptors) (Colley and Leedman, 2009; Foulds et al., 2010). However later on, it was shown that SRA is bifunctional gene and it encodes for the SRA protein (SRAP) (Leygue, 2007; Novikova et al., 2012). The length of SRA gene is 0.87 kB (Novikova et al., 2012) which among lncRNAs, has the advantage of being short enough for mechanistic studies; and yet long enough to carry many of the lncRNAs characteristics. SRA lncRNA and SRAP Protein are conserved in phylum Chordata (Chooniedass-Kothari et al., 2004; Leygue, 2007). Having large number of isoforms that majority of them share a central core region is another characteristic of SRA. It is noticeable that only some isoforms have the ability of encoding SRAP protein. One mechanism of generating coding and non-coding isoforms of SRA is assumed to be differential splicing (Hube et al., 2006; Leygue, 2007).

Functionality of SRA lncRNA depends on a number of functional motifs, with predicted secondary structures.(Lanz et al., 2002). SRA lncRNA structural analysis showed that overall architecture of the ribosome is similar to secondary structure of this lncRNA. Figure 2 represents the secondary structure of SRA. There are four domains, with numbers of helices and loops in structure of SRA which reflects complexity of the structure and makes it comparable (in proportional terms) to a ribosome subunit (Novikova et al., 2012). The SRA lncRNA and SRAP involved in similar estrogen-signaling pathway and their functions often overlapped. They act as co-activator for several human sex hormone receptors such as androgen receptor (AR), estrogen receptor (ER) and glucocorticoid receptor (GR). The SRA lncRNA, apart from increasing the activity of a range of steroid receptors, can enhances myogenic differentiation 1 (MyoD)-mediated transcription. Furthermore, the SRA lncRNA functions as a scaffold for specific corepressor complexes (Leygue, 2007). The SRA is under influence of alternative splicing of the first intron regarding contribution to either SARP or lncRNA (Hubé et al., 2011). Functional similarities between SRA lncRNA and SRAP have been identified by showing the ability of SARP to regulate receptors and bind to promoter regions regulated by nuclear receptors (Chooniedass-Kothari et al., 2010). Hyperplasia and morphological abnormalities in steroid hormone responsive tissues caused by transgenic expression of SRA *in vivo*; and also higher apoptosis was a result of hyperplasia but tumourigenesis was not

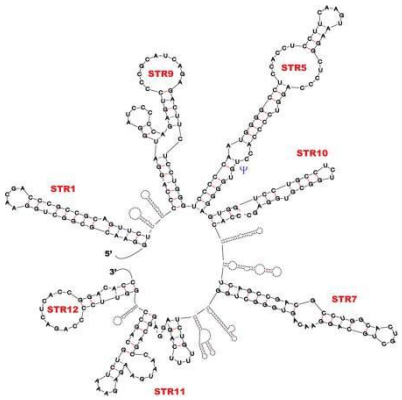

Figure **2**: using Mfold software, secondary structure of human core SRA lncRNA was predicted (Zuker, 2003).

occurred (Lanz et al., 2003). In human, expression level of SRA in tumours of steroid hormone responsive tissues such as breast, uterus and ovary has been found to be upregulated; and the assumption is that alteration the steroid receptors' actions is causative agent of tumorigenesis (Lanz et al., 2003). This characteristic supports the idea of applying SRA as a potential biomarker of steroid-dependent tumors. Also the association of SRA lncRNA with cardiomyopathy in humans has been shown (Friedrichs et al., 2009). Zhao et al. (2007) showed pseudouridylation regulates SRA activity.

Several substructures in SRA secondary structure are predicted by low-resolution RNA modeling (Zuker, 2003) (Figure 2).. The functional importance of SRA structural features and potential role(s) of SRA in modulating other molecules were highlighted by these observations.

HOX Antisense Intergenic RNA (HOTAIR)

In the human genome, the newly identified HOTAIR is located between HoxC11 and HoxC12 (chromosome 12q13.13) and regulates HoxD expression in multiple tissues(He et al., 2011; Rinn et al., 2007). It is the first lncRNA discovered to be involved in tumorigenesis with a length of 2.2 kb; and it is transcribed in antisense manner (Wang et al., 2008). HOTAIR, as an epigenetic regulator in gene expression is deregulated in number ofcancers; and also expressed in posterior and distal fibroblasts (Gupta et al., 2010; Kogo et al., 2011; Niinuma et al., 2012; Rinn et al., 2007; Yang et al., 2011).

In breast cancer (both primary and metastatic) the expression of HOTAIR is up regulated ; hence, an efficient predictor of metastasis is the expression level of HOTAIR (Gupta et al., 2010). Kogo et al. (2011) monitored the expression of HOTAIR in patients with stage IV colorectal cancer (CRC) who have liver metastases and a poor prognosis.

Their results showed that HOTAIR expression levels were higher in cancerous tissues than in corresponding noncancerous tissues. HOTAIR is reported to reprogram chromatin organization in cooperation with polycomb repressive complex 2 (PRC2). The HOXD locus on chromosome 2 is the target of PRC2 where this complex causes the transcriptional silencing of many metastasis suppressor genes in association with HOTAIR (Tsai et al., 2010). Basically, PRC2 repressive activity will be enhanced by alteration in expression level of HOTAIR (Hauptman and Glavač, 2013; Wapinski and Chang, 2011). It is noticeable that HOTAIR serves as a molecular scaffold for two distinct chromatin modification complexes. The 5' domain of HOTAIR binds with PRC2 and this biologic bond is responsible for H3K27 trimethylation (H3K27Me3) whereas the 3' domain of HOTAIR binds the LSD/CoREST/REST complex which mediates enzymatic demethylation of H3K4 (H3K4Me0) (Eilebrecht et al., 2013; Kotake et al., 2010; Nie et al., 2012; Tsai et al., 2010; Yap et al., 2010). Consequently, HOTAIR has the ability to attach two distinct complexes enables RNA-mediated assembly of PRC2 and LSD1 and coordinates targeting of PRC2 and LSD1

to chromatin for coupled histone H3 lysine 27 methylation and lysine 4 demethylation. Deletion of the HoxC cluster in mouse which contains the cognate HOTAIR transcript showed a small phenotypic effect with slightly change in expression of H3K27me3(Schorderet and Duboule, 2011). HOTAIR promoter contains multiple functional estrogen response elements (EREs); and it transcriptionally induced by estradiol (E2). Different estrogen receptors co-regulators such as CREB-binding protein/p300; histone methylases MLL1 (mixed lineage leukemia 1); and MLL3 along with estrogen receptors (ERs) bind to the promoter of HOTAIR in an E2-dependent manner. HOTAIR promoter in the presence of E2 increases the level of RNA polymerase II recruitment; histone H3 lysine-4 trimethylation; and histone acetylation.

Similar to protein-coding gene transcription, E2-induced transcription of antisense transcript HOTAIR is coordinated via ERs and ER coregulators; and that is why knockdown of ERs and MLLs downregulated the E2-induced HOTAIR expression (Bhan et al., 2013). Although HOTAIR exists in mammals with poor sequence conservation (He et al., 2011; Rinn et al., 2007), structure prediction of HOTAIR showed two fragments with an invariable structures in the 5' end exon 1 and the 3' end domain B of exon 6 (A 239 bp domain).(He et al., 2011).

HOTAIR's level of expression has the potential to apply as an indicator for the existence of lymph node metastasis in HCC(Gutschner and Diederichs, 2012; Morey and Helin, 2010; Qiu et al., 2013). Despite all of the studies, the precise mechanism by which these lncRNAs affect multiple genes is still unclear.

Antisense ncRNA in the INK4 locus (ANRIL)

This lncRNA, also known as CDKN2B-antisense RNA 1 (CDKN2B-AS1) or P15 antisense RNA (P15AS) encodes in the chromosome 9p21 region; and it transcribed by RNA pol II (Folkersen et al., 2009; Gibb et al., 2011; Yap et al., 2010). It detected as an unspliced transcript of 34.8 kb known as p15AS. The level of expression of the sense transcripts which some of them (such as p15/CDKN2A) are tumor suppressors can be altered by ANRIL(Kim and Sharpless, 2006; Yu et al., 2008). ANRIL is located upstream of the CDKN2A; and it splices into multiple linear isoforms such as CDK2BAS (Folkersen et al., 2009; Pasmant et al., 2007).

These splicing isoforms are mostly polyadenylated but also some circular non-polyadenylated variants have also been reported (Burd et al., 2010). An intriguing characteristic of the splicing variants is their tissue-specific feature however only in very few tissues the regulatory mechanisms of ANRIL have been evaluated(Burd et al., 2010). This locus has been associated with cardiovascular disease (CDV) (Broadbent et al., 2008; Burton et al., 2007). Also, it has been highlighted as the strongest genetic susceptibility locus for other conditions such as glaucoma; Alzheimer disease; periodontitis disease; type 2 diabetes; and endometriosis (Burdon et al., 2011; Cugino et al., 2011; Emanuele et al., 2011; Ramdas et al., 2011; Schaefer et al., 2009; Uno et al., 2010). Aside from all of these impairments, in context of oncogenic transcript, there are several cancers such as ovarian cancer; glioma; basal cell carcinoma; melanoma; pancreatic carcinoma; leukemia; and breast cancer which have been associated with misregulation of this transcript.(Chen et al., 2007; Gayther et al., 2007; Kumar et al., 2001; Rajaraman et al., 2012; Sherborne et al., 2010; Stacey et al., 2009; Turnbull et al., 2010; Yeh and Bastian, 2009). In patients carrying the atherosclerosis risk haplotype expression, including in mononuclear cells ;peripheral blood; whole blood and atherosclerotic plaque tissue overexpression of ANRIL has been found; and the severity of atherosclerosis directly linked to level of expression (Holdt et al., 2010). As the potential disease-associated haplotype block three genes including methyl-thioadenosine phosphorylase (MTAP), CDKN2A and CDKN2B are presented in this region. For instance, it was shown that deletion and inactivation of MTAP result in to cancerogenesis (Hellerbrand et al., 2005; Schmid et al., 1998). Furthermore, CDKN2A or B are identified as tumor suppressors and have a well-established role in senescence and aging; apoptosis and cell proliferation(Cánepa et al., 2007; Matheu et al., 2009).

Based on the aforementioned evidences, it is possible that expression of these genes would be regulated by the disease-associated

single nucleotide polymorphisms (SNPs). However, in several reports, the majority of the disease-associated polymorphisms are linked directly to the expression of ANRIL rather than MTAP or CDKN2A/B (Cunnington et al., 2010; Holdt et al., 2010; Sherborne et al., 2010). Although there are many undiscovered details about ANRIL functionality, it is obvious that the 9p21 locus contains manytranscription factor binding sites and regulatory elements. Transcription factor binding sites might be impaired by these disease-associated alleles and response to different stimuli result in alteration of ANRIL; CDKN2A/B expression (and possibly other loci) which eventually will lead to development of disease. Structural analysis showed that there are many hair-pin structures in ANRIL exons. These hair-pin structures attach to CBX7, and also they are participated in CBX7 recognition of histone methylated lysine (H3K27)(Yap et al., 2010). In order to induce silencing, evidence has suggested ANRIL interacts with polycomb proteins which is a common mechanism of epigenetic regulation among lncRNAs such as HOTAIR; RepA; and Kcnq1ot1 (Pandey et al., 2008; Tsai et al., 2010; Zhao et al., 2008). Two polycomb repressor complexes including PRC1 (CBX7) and PRC2 (SUZ12) reported to be activated by ANRIL in order to regulate histone modification in the CDKN2A/B locus (Cunnington et al., 2010; Jarinova et al., 2009; Popov and Gil, 2010; Yap et al., 2010). As several studies show, ANRIL affects mechanism of epigenetic regulation in three different ways. Firstly, by building complex with SUZ12, ANRIL can initiate long term repression of CDKN2B locus. In this mechanism, ANRIL binds SUZ12 subunit and this complex induce methylation of histone 3 in the lysine 27 (H3K27) by which the CDKN2A/B locus will be silenced (Kotake et al., 2010). Secondly, through interaction with chromobox 7 (CBX7) in the polycomb repressive complex 1 (PRC1), ANRIL can be contribute in maintenance of chromatin silencing of the CDKN2A/B locus. . Finally , it shown in differentiated cells that ANRIL has the ability to change DNA methylation of the locus (Yu et al., 2008). Apparently, these functions are sensitive to physiological changes and rely on cell type. It is not clear whether other chromatin-modifying proteins mediate these regulatory effects or other mechanisms such as DNA methylation or the ANRIL circular isoforms are responsible. Overall, although the characteristics of the ANRIL have remained mostly unexplored, it is clear that ANRIL is an interesting target for new therapies for a wide range of human diseases (Congrains et al., 2013).

Metastasis-Associated Lung Adenocarcinoma Transcript 1 (MALAT-1)

Another classic oncogenic lncRNA is metastasis-associated lung adenocarcinoma transcript 1 (MALAT-1) also known as nuclear enriched abundant transcript 2 (Neat-2).
MALAT-1 is a highly conserved lncRNA originally identified as a transcript overexpressed in many cancers (Ji et al., 2003). In normal human tissues MALAT-1 is widely transcribed and expressed, particularly it is highly abundant in neurons (Hutchinson et al., 2007; Wilusz et al., 2008). According to Hutchinson et al.(2007) MALAT-1 is an intergenic single exon transcript with ~7kb in length. A unique characteristic of MALAT-1 is to create two ncRNAs from the one original transcript during post transcriptional process. The primary transcription product of the MALAT-1 locus is a 6.7 kb nuclear-retained lncRNA followed by a cytoplasmic 61-nt tRNA-like ncRNA known as mascRNA (MALAT1-associated small cytoplasmic RNA (Wilusz et al., 2008). The long MALAT-1 transcript has been localized to nuclear speckles (interchromatin granule clusters [IGCs] or SC35 domains) which are highly dynamic subnuclear domains enriched with pre-mRNA splicing/processing (Clemson et al., 2009; Hall et al., 2006; Lamond and Spector, 2003; Tripathi et al., 2010). The nuclear speckles do not considered as sites of transcription or pre-mRNA splicing; instead they are thought to be storage; modification or assembly sites (Lamond and Spector, 2003). The MALAT-1 locus at 11q13.1 has been associated with cancer (Davis et al., 2003) such as hepatocellular carcinoma, breast, pancreas, colon, osteosarcoma, uterus and prostate cancers (Fellenberg et al., 2007; Guffanti et al., 2009; Lin et al., 2006; Yamada et al., 2006). Increasing expression of MALAT-1 can be used as an indicator for HCC patients following liver transplantation (Lai et al., 2012). Although the vital roles of MALAT-1 in human has been identified, it is possible that it has not any significant role in living animals under normal physiological

conditions (Eißmann et al., 2012; Nakagawa et al., 2012). The regulatory role of MALAT-1 toward the serine/arginine-rich (SR) proteins (a family of nuclear phosphoproteins which are involved in the splicing machinery) has been identified. Primary location of SR proteins is in the nucleus where they are enriched in speckles. According to the structural studies, SR proteins share a modular structure with one or two N-terminal RNA recognition motifs (RRMs) and an RS domain composed of arginine-serine repeats. The RS domain is important for the activity of SR proteins in splicing and this domain is a target for extensive phosphorylation, and the phosphorylation status. SRSF1 which is one of the SR proteins has tendency for specific binding to MALAT1 via its RRM. Within the 5' half of both human and mouse MALAT-1, there is a significant enrichment for SRSF1 (SF2/ASF) binding sites. This direct interaction has been demonstrated and is dependent on its canonical RRM (RRM1) or the pseudo RRM (RRM2) domains (Sanford et al., 2009). Distribution of MALAT-1 to nuclear speckles and the recruitment of SRSF1 is influenced by Independent sequence elements in MALAT-1 (Tripathi et al., 2010). Aberrant mitosis, with a large fraction of cells accumulating at G2/M boundary, and increased cell death are resulted from MALAT-1 depletion (Tripathi et al., 2010). Furthermore, in neuroblastoma cells, depletion of MALAT-1 result in synapse function and dendrite development (Bernard et al., 2010). In cells and tissues, SR proteins are abundantly and ubiquitously expressed however, their level of cellular expression are tightly regulated. Therefore, alternative splicing patterns can be influenced even by slightly perturbations in the concentration of SR proteins (Lin and Fu, 2007). Nevertheless, in what way the concentration or activity of SR proteins is regulated in cells is not fully understood.

CONCLUSION

In the past decade, current conceptions of transcriptome complexity have been completely changed by the discovery of hundreds of genomic regions that do not contain protein-coding genes; and yet strongly associated with a wide spectrum of human diseases. It seems researchers were specifically looking for RNAs that code proteins; and that is why ncRNAs were overlooked in the past. Identification of lncRNAs not only has revitalized the old dogma of biology but it has expanded immensely the prospect of controlling expression of specific genes. Through underscoring the importance of lncRNAs' regulatory roles these transcripts emerged as key players in the etiology of several diseases particularly cancer (Tsai et al., 2011; Wapinski and Chang, 2011). The entire spectrum of cancer is characterized by dysregulation in lncRNA expression. Mostly, by facilitating epigenetic repression of downstream target genes, lncRNAs function induces cancer through disruption of normal cell processes. Recently, lncRNAs represent the leading edge of oncology research. Clinical interpretation of lncRNAs may land on the production a new class of gene-specific medical therapies in the near term. Apart from RNA-based therapies which could be a viable option for clinical oncology, lncRNAs have the potential to apply as biomarker in cancer biology. Despite all of the progress in identification of lncRNAs and analysis their dysregulation in cancer, there are many questions unanswered.

Future studies will need to pinpoint the nature of lncRNA-chromatin interactions; and discern the sequence and or structural basis of RNA-protein and RNA-DNA interactions. Evidently, the abundance and scale of lncRNAs expression changes in cancer is just beginning to come to light.

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