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Review article

Very long non-coding RNA and human disease

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ABSTRACT

A role for non-coding RNAs (ncRNAs) in the development of disease has been well documented in the case of miRNAs. Recent studies have shown that long non-coding RNAs (lncRNAs), greater than 200 nt in length, are also implicated in various diseases. In this review, we focus on these lncRNAs, the very long non-coding RNAs (vlncRNAs), which are more than 5 kb long and for which detailed information is available. These studies have demonstrated that vlncRNAs have important biological functions, and that their aberrant expression may result in various cancers. Future investigations in this exciting field are needed to explore the role of vlncRNAs in pathogenesis and, in particular, to further understand their functional mechanisms.

1. Introduction

Classically, proteins are recognized as having the main responsibility for biological function, with RNA merely a messenger that transfers protein-coding information from DNA [1,2]. This concept has changed in recent years, however—whereas only 2% of the genome encodes protein, more than 80% of the genome produces non-protein coding RNA transcripts [1–5], and these non-coding RNAs (ncRNAs) have important biological functions including gene regulation [6,7], imprinting [8–12], epigenetic regulation [13,14], cell cycle control [15], regulation of transcription, translation, and splicing [7,16–20].

There are two major classes of ncRNAs, grouped according to size: small RNA, which includes microRNA (miRNA), PIWI-interacting RNA (piRNA), endogenous short interfering RNA (endo-siRNA), and other ncRNAs less than 200 nt; and long non-coding RNA (lncRNA), which is larger than 200 nt and is transcribed from intergenic, intragenic, or around protein-coding regions. miRNAs are involved in post-transcriptional regulation of mRNA through the RNA-induced silencing complex [16],

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whereas piRNAs and siRNAs maintain genomic integrity by suppressing transposable elements [17] or other unknown factors in cell nucleus [18]. The lncRNAs are involved in various levels of genome regulation and related fundamental epigenetic processes [19–25].

The importance of lncRNAs in gene regulation has become apparent in recent years [6,20–30], but the key sequences of lncRNA that determine regulatory function remain unknown. Thus, although the rules of translation via the genetic code are well understood and a mutation in a protein-coding gene that contributes to a given disease can be attributed to the resultant change in amino acid sequence [6,20–30], there is no equivalent code for lncRNA function. Genetic studies on lncRNA could help us identify their regulatory sequences and understand their mechanism of action more clearly. In this review, we focus on a specific group of lncRNAs, those more than 5000 nt long, which we call very long non-coding RNAs (vlncRNAs), and explore their roles in the development of disease.

2. vlncRNA annotation and relevant databases

High-throughput technologies such as Tiling Chip or Deep Sequencing data, combined with computational approaches, have identified long, abundantly expressed non-coding transcripts associated with various cancers [13,28,29,31–37]. Currently, ncRNAs are curated by a variety of public databases, such as lncRNAdb (http://lncrnadb.com/), a database of eukaryotic lncRNAs validated by experimental data [38]; RNAdb (http://research.imb.uq.edu.au/rnadb/), a lncRNA set conserved between human and mouse that was used in a high-throughput functional screen [39]; fRNAdb (http://www.ncrna.org/frnadb/index.html), a database hosting a large collection of ncRNA sequence data from public non-coding databases [40]; NONCODE (http://www.noncode.org/NONCODERv3/), a database of non-coding RNAs [41], together with annotation of potential function, based on a coding–non-coding coexpression network [34]; and NRED (http://jsm-research.imb.uq.edu.au/nred/), a database of expression data of human and mouse lncRNAs with various gene expression profiles [31]. Moreover, the Encyclopedia of DNA Elements consortium is annotating lncRNAs using a combination of RNA-seq data, chromatin state maps, and computational approaches [42]. In this review, we survey the vlncRNAs, collected from various ncRNA databases by filtering for sequence length greater than 5000 nt.

3. Function of vlncRNAs

vlncRNAs originate from intronic, exonic, intergenic, intragenic, and promoter regions, and from 3′- and 5′-UTRs and enhancer sequences; they are sometimes bidirectional transcripts [30]. In particular, a large group of vlncRNAs, referred to as natural antisense transcripts, is antisense to known protein-coding genes [43,44]. In the following sections, we will discuss various vlncRNAs with respect to their functions in epigenetic regulation, transcriptional and post-transcriptional regulation, as well as in tumorigenesis (Fig. 1).

4. vlncRNAs control transcription by mediating changes in chromatin structure

The structure of chromatin determines the accessibility of DNA to polymerase II and transcription factors, and is integral to transcriptional control. Chromatin structure can be altered by specific post-translational modification, such as trimethylation of histone H3 lysine 4 (H3K4me3) at gene promoters, whereas H3K36me3 in transcribed regions is linked to gene activation, and H3K9me3, H3K27me3, and H4K20me3 are linked to repression [45] (Fig. 1A–C). There is substantial evidence for an important role of lncRNAs in these processes, and

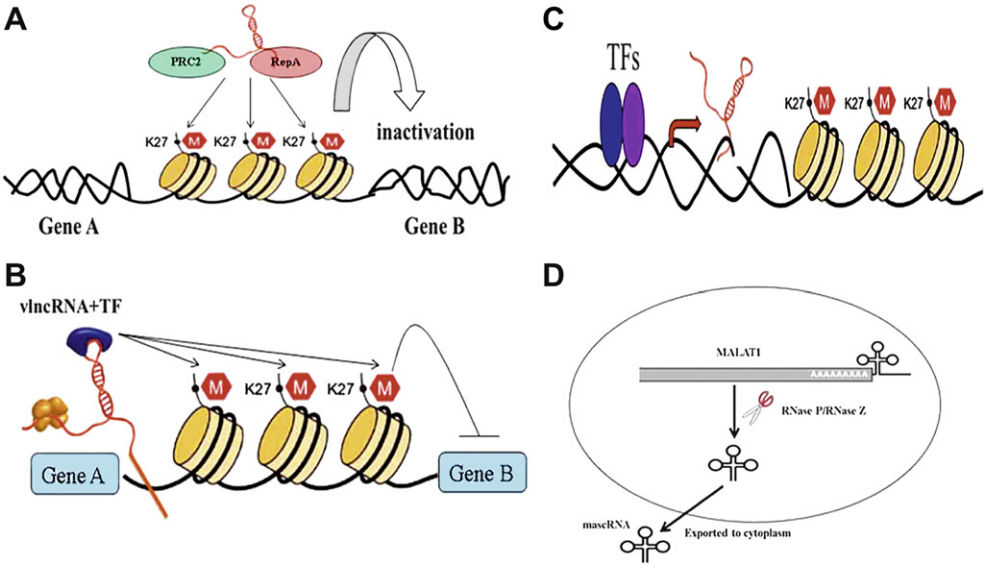

Fig. 1 – Mechanisms for regulation of epigenetics and gene expression by vlncRNAs. (A) vlncRNA regulates histone modification in *cis* and in *trans*. (B) Promoter-associated vlncRNA as an inhibitor of transcription. (C) Promoter-associated vlncRNA as an activator of transcription. (D) vlncRNA generation of sRNA regulatory transcript.

approximately one-third of long intergenic non-coding RNA (lincRNA) is associated with chromatin-modifying complexes [13]. In addition, many intronic and intergenic ncRNAs have been found by different methods [14], suggesting that lncRNAs are key participants in controlling the chromatin structure. Similar to lncRNAs, vlncRNAs are also associated with chromatin-modifying complexes and can affect gene expression. The following examples describe vlncRNAs that mediate changes in chromatin structure and control transcription.

4.1. *XIST control of X-chromosome inactivation*

On X-chromosome inactivation (XCI), one of the two X chromosomes in female mammals is inactivated to achieve comparable expression levels of X-chromosome genes in males and females. A number of vlncRNAs including *XIST* and *TSIX* participate in this process [46–49]. There are data suggesting that *XIST* recruits chromatin modeling complexes to silence the X chromosome (resulting in an inactive X chromosome, denoted Xi). Zhao et al [50] discovered a 1.6-kb ncRNA (*RepA*) transcribed from the 5′ region of *XIST*, which binds polycomb repressive complex 2 (PRC2) to bring about silencing (Fig. 1A). In pre-XCI cells, *RepA* initially recruits PRC2 to the future Xi and inhibits the interaction of *TSIX* by binding PRC2. During initiation of the silencing process, *TSIX* is down-regulated on the future Xi, and *RepA* can engage PRC2 resulting in the activation of full-length *XIST* transcription (Fig. 1B and C). The up-regulated *XIST*, in turn, preferentially binds to PRC2 through its *RepA* sequence, resulting in the spread of *XIST* along Xi and the distribution of PRC2 and trimethylated histone H3K27 throughout the Xi [46,47,50]. Therefore, *RepA* and *XIST* are capable of recruiting PRC2 to establish the local chromatin modification required for the initiation and spread of XCI, resulting in the suppression of expression of genes on the Xi.

4.2. *vlncRNAs involved in imprinting*

Just as vlncRNAs play important roles in X-inactivation, similar mechanisms have also been observed during genomic imprinting [8–10]. *AIR*, a 108-kb-long vlncRNA, is required for allele-specific silencing of the *cis*-linked *SLC22A3*, *SLC22A2*, and *IGF2R* genes [11]. *AIR* interacts with the *SLC22A3* promoter chromatin and the H3K9-specific histone methyltransferase G9a in placenta [10]. Depletion of G9a fails to silence *SLC22A3* and results in nonimprinted transcription. When truncated, *AIR* does not accumulate at the *SLC22A3* promoter, resulting in reduced G9a recruitment and biallelic transcription [10]. Similarly, the 90.5-kb vlncRNA *KCNQ1OT1* has been linked to the bidirectional silencing of about 10 paternally imprinted genes in the *KCNQ1OT1* domain, and the mechanism involves the interaction between *KCNQ1OT1* and both G9a and PRC2 in a lineage-specific manner [12].

4.3. *vlncRNAs involved in epigenetic silencing*

The *INK4b/ARF/INK4a* locus in human cells contains three important tumor suppressors, whose expression is controlled in part by PRC1, PRC2, and histone methylation [51]. A vlncRNA called *ANRIL* (antisense non-coding RNA in the INK4 locus) is transcribed in an antisense direction to the protein-coding genes in this locus, and is up-regulated in some cancer tissues [52]. *ANRIL* plays an important role in controlling the epigenetic state of the *INK4b/ARF/INK4a* locus through interactions with subunits of PRC1 and PRC2. In brief, *ANRIL* binds to and recruits PRC1 and PRC2, resulting in trimethylation of H3K27 and repression of the *INK4b/ARF/INK4a* locus, facilitating oncogenesis [52] (Fig. 1A).

5. vlncRNA regulates splicing

The vlncRNA *MALAT1* (metastasis-associated in lung adenocarcinoma transcript 1) was identified in an attempt to characterize transcripts associated with early-stage non-small cell lung cancer (NSCLC) [53]. Two recent studies found that *MALAT1* regulates alternative splicing through its interaction with the serine/arginine-rich (SR) family of nuclear phosphoproteins involved in the splicing machinery [7,54], and *MALAT1* has been suggested to serve as a fine-tuning mechanism to modulate the activity of SR proteins.

MALAT1 is an abundant vlncRNA transcribed from chromosome 11q13 and primarily localized in nuclear speckles. It modulates the distribution of pre-mRNA splicing factors to nuclear speckles and particularly affects the phosphorylation state of SR proteins [54]. In *MALAT1*-depleted cells, levels of mislocalized and unphosphorylated SR proteins increase, resulting in a higher number of exon inclusion events [7]. Therefore, *MALAT1* contributes to a broad post-transcriptional gene-regulatory mechanism by coordinating a specific mRNA patterning in distinct cell types.

6. vlncRNA is involved in a wide variety of other biological processes

Apart from their roles in nuclear processes discussed above, vlncRNAs have also been implicated in the regulation of a number other biological processes. For example, some vlncRNAs can act as precursors for small RNAs, either by an RNase III-like cleavage from the sense and antisense duplexes, such as *XIST/TSIX*, or by a tRNA-like 3′-end processing of *MALAT1* [43,44] (Fig. 1D). Another example is the vlncRNA *DLEU2* (deleted in lymphocytic leukemia 2), which is frequently deleted in malignancy and functions as a critical host gene of the cell cycle inhibitory miR-15/16 [55]. Finally, *P15AS* (P15-antisense), which overlaps a protein-coding gene but is transcribed in the opposite direction, facilitates cancer progression by silencing its parental gene in *cis* and in *trans* through the formation of a type of heterochromatin [52,56].

7. vlncRNAs and diseases

The data gathered to date strongly implicate vlncRNAs in the basal regulation of protein-coding genes, including those central to normal development and oncogenesis, at both the transcriptional and post-transcriptional levels, and an increasing number have been functionally validated as affecting different cellular and developmental pathways [57,58]. It is not surprising, therefore, that the dysregulation of vlncRNAs appears to be a primary feature of many complex human diseases, including cancer.

Here, we describe some of the better characterized vlncRNAs that have been associated with cancer biology (Table 1).

7.1. Involvement in various cancers

XIST expression levels are correlated with outcome in some cancers [59,60], such as the therapeutic response in ovarian cancer [61], and it is frequently implicated in breast cancer [62–64]. Notably, however, because *XIST* is not expressed in males, such correlations are only of value in samples obtained from females [65].

7.2. Involvement in metastasis

The *MALAT1* gene was associated with high metastatic potential and poor patient prognosis during a comparative screen of NSCLC patients with and without metastatic tumors [53]. Another report indicated that up-regulated *MALAT1* contributes to bladder cancer cell migration by inducing epithelial–mesenchymal transition-associated genes [66].

7.3. Cancer type-specific vlncRNA expression

Many studies describe vlncRNA expression in various cancers, but a few vlncRNAs are specifically expressed in a particular type of cancer. For example, the vlncRNAs *PCA3* (prostate cancer antigen 3), *PCGEM1* (prostate-specific transcript 1), and *PCNCR1* (prostate cancer non-coding RNA 1) are associated with prostate cancer [67–70]. Indeed, *PCA3* is a very sensitive and specific molecular marker for the diagnosis of prostate cancer [71]. Likewise, expression of *PCGEM1*, a prostate-specific gene with a function in the regulation of apoptosis, is associated with high-risk prostate cancer patients [70]. The vlncRNA *PCNCR1* is also involved in prostate cancer progression [68].

8. Perspectives

As in the case of lncRNAs, vlncRNAs do not have protein-coding capacity, but nevertheless have functions relating to the programming and regulation of the mammalian genome. There have been recent rapid advancements in the understanding of these functions, but several important problems remain to be solved. For example, vlncRNAs frequently exhibit sequence divergence but have conserved functions, perhaps indicating the importance of secondary structure. Moreover, although a number of vlncRNAs are associated with PRC2 complexes, they do not interact exclusively with these proteins. Therefore, it will

Table 1 – Identification of tumor-associated vlncRNAs.

vlncRNA	Molecular mechanism	Tumor	Reference
P15AS/ANRIL	Antisense, transcription regulation	Prostate cancer	[52,56]
BA318C17.1	Unknown	Colon cancer	[72]
GNAS-AS1	Unknown		[73]
His-1 RNA	Unknown		[74]
KCNQ1OT1	DNMT1 interaction and transcription gene silencing	Colon cancer	[8,12]
DLEU2	Primary miRNA, other	Chronic lymphocytic leukemia	[55,75]
LOC285194	Unknown	Osteosarcoma	[76]
MALAT1	RNA splicing, small RNA Production, protein interaction	Multiple cancers	[44,53,66,77]
MEG3	Unknown	Multiple cancers	[78,79]
NCRMS	Unknown		[80]
NTT sense/antisense	Unknown		[81,82]
p53 mRNA	RNA protein binding	Multiple cancers	[83]
p53int1	unknown		[84]
PCA3/DD3	Unknown	Prostate cancer	[67]
PCGEM1	Unknown	Prostate cancer	[70]
PCNCR1	Unknown	Prostate cancer	[68]
PR Antisense	Regulation of gene expression		[85]
PRINS	Unknown		[86,87]
SRA RNA	RNA–protein binding, transcription factor coactivator	Breast cancer	[88,89]
TSIX	Antisense of Xist		[62,90]
SNHG14/UBE3A-AS1	Unknown		[91,92]
UCA1	Unknown	Bladder cancer	[93,94]
XIST	X inactivation	Multiple cancers	[59,60,62,95]
ZNFX1-AS1	Unknown	Breast cancer	[96]

be of great interest to unravel the sequences and structural motifs in vlncRNAs that determine their function.

Another challenging unanswered question is how protein partners interact with vlncRNAs to bring about their specialized functions. vlncRNAs, similar to lncRNAs, may recruit and then guide their protein partners to the correct chromosomal destinations. Specific sequences within vlncRNAs could recognize particular chromatin regions via sequence complementarity, thereby bringing the associated proteins to the targeted region. For example, *XIST* recruits PRC2 to establish local chromatin modification on Xi [50]. In the case of vlncRNAs recruiting proteins at a distance [34,35] or in *trans*, the higher-order, tertiary structure of chromatin might help bring distant chromosomal regions together. Alternatively, vlncRNAs might induce allosteric structural modifications of their protein partners to either enhance or suppress their normal activities.

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